Textbook of Neuroanesthesia and Neurocritical Care

Volume I - Neuroanesthesia

Hemanshu Prabhakar
Zulfiqar Ali
Editors

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Foreword

Neuroanaesthesia and neurocritical care continue to evolve and develop as specialities, presenting those of us responsible for patient care with ever more challenges. Within the operating theatre, technological advances in surgical techniques and imaging have necessitated changes both in the way we work and also where we work. Advances in interventional neuroradiology have led to a greater demand for anaesthetic and critical care input outside of the operating theatre, often in remote sites, with all the associated challenges. An ever-increasing number of surgical procedures of greater complexity alongside an aging population have led to increased demands on the neurocritical care unit. Fortunately, advances in neuroanaesthesia, neurocritical care and neuromonitoring have recognised and facilitated these changes.

It has often been said that neuroanaesthesia is a speciality where the knowledge and skill of the anaesthetist directly influences patient outcome. This remains true today. To this end, the *Textbook of Neuroanaesthesia and Neurocritical Care* edited by Hemanshu Prabhakar covers all aspects of patient care. Volume I rightly begins with the fundamentals of neuroanaesthesia including anatomy, physiology and pharmacology, an understanding of which is essential to underpin good care. There is detailed guidance on the process of anaesthesia for neurosurgery including coexisting problems, special considerations, pain management and near misses. A special topics section includes recent innovations such as robotic surgery, gene delivery and expression, intra-arterial drug delivery and simulation in neuroanaesthesia. In volume II, the complexities of critical care are thoroughly addressed, starting with the fundamentals of neurocritical care through to the intensive care management of specific conditions, neuromonitoring, pain management, ethical considerations and near misses. Again, there is a special topics section on recent advances including research and evidence-based practice.

This comprehensive textbook is an authoritative and practical clinical text. It covers the breadth and depth of the complex specialities of neuroanaesthesia and critical care and includes chapters by many leading names in neuroanaesthesia who have lent their expertise to this work. It will be essential reading for trainees, clinicians and researchers involved in neurosciences. Despite the ever-increasing challenges facing us, this book should provide the reader with the necessary knowledge to enhance their practice and provide optimal neuroanaesthesia and neurocritical care.

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Preface

The editors feel pleased to present the first edition of *Textbook of Neuroanesthesia and Neurocritical Care*. This book has tried to cover the basic concepts of neuroanaesthesia and neurocritical care along with the major changes that have evolved in the field of neurosciences in the last decade. An attempt has been made by the authors to present an updated presentation of the subject. The book is available in two volumes: volume I focuses on the foundation of neuroanaesthesiology, and volume II focuses on the understanding of the neurocritical care. We hope that this book will be of immense use for readers, who are more focused on gaining an advanced understanding in the field of neurosciences.

We thank the authors for doing an outstanding job of producing authoritative chapters. We feel privileged to have compiled this first edition and are enthusiastic about everything it offers to our readers. We learned much in the process of editing this textbook and hope that you will find this textbook a valuable source of educational resource in the field of neurosciences.

New Delhi, India — Hemanshu Prabhakar
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Part I

Fundamentals of Neuroanesthesia

Neuroanatomy

1

Ravi K. Grandhi and Alaa Abd-Elsayed

1.1 Overview

The nervous system is made up of two parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The brain and spinal cord form the majority of the CNS. The CNS integrates, processes, and coordinates incoming sensory data and outgoing motor functions that alter the activities of the end organs or muscles. The brain is also the part of the body where higher cognitive activities occur, while the cranial and spinal nerves form the majority of the PNS. The PNS delivers sensory information to the CNS and carries motor commands from the CNS to the peripheral tissues and systems. The two systems are in close communication with each other. And when one of the two systems is altered in any fashion, the other one may be affected. This chapter will review the significant anatomical considerations in each of the two systems (Fig. 1.1).

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1.2 Central Nervous System

1.2.1 Brain

The brain can be divided into the supratentorial and the infratentorial compartments. The supratentorial compartment contains the cerebral hemispheres and the diencephalon (thalamus and hypothalamus). The infratentorial compartment is made up of the brain stem and the cerebellum.

1.2.1.1 Supratentorial Compartment

Cerebrum

The cerebrum makes up the largest part of the brain. It is made up of a right and left hemisphere. The hemispheres are made up of numerous sulci or fissures and gyri or folds. The two sides of the brain are connected via the corpus callosum, which is a collection of white matter fibers. Based on functional differences, the cerebrum is divided into four lobes: frontal, parietal, temporal, and occipital lobes. The frontal lobe is separated from the parietal lobe via the central sulcus (Rolandic fissure). The frontal lobe is separated from the temporal lobe via the lateral sulcus (Sylvian fissure). The frontal and parietal lobes are separated from the temporal lobe via the lateral sulcus. And finally, the parieto-occipital sulcus divides the parietal lobe from the occipital lobe.

The cerebrum is made up of numerous functional areas that each provide a particular activity

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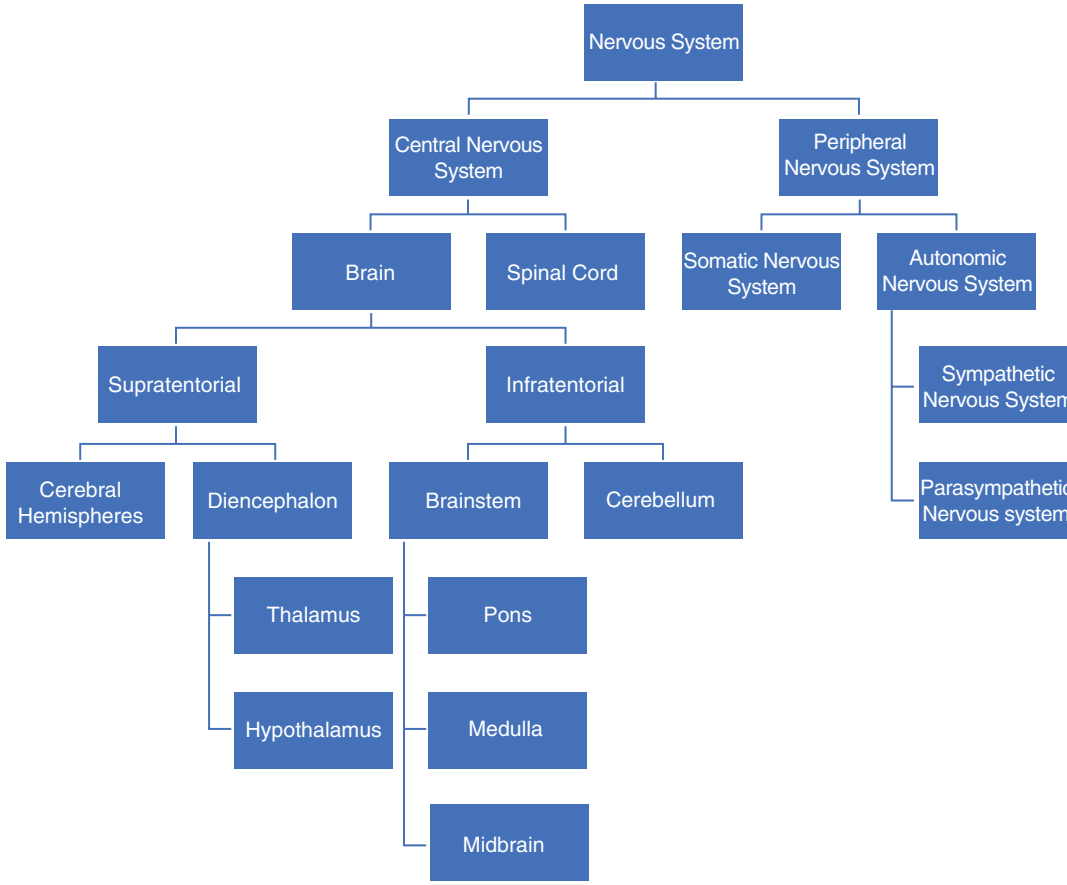

Fig. 1.1 Overall anatomical organization of the nervous system

essential to survival. The frontal lobe, which is made up of primary motor cortex, executes actions. Adjacent to this cortex is also the premotor cortex and other supplementary motor areas, which are involved in selecting voluntary movements. There are also sensory areas within the cortex, which help integrate the different stimuli from the senses. These areas work closely with the thalamus. Each of the hemispheres receives information about the contralateral side of the body. The primary somatosensory cortex located in the lateral parietal lobe, which integrates the touch signal, is often illustrated as a homunculus. The homunculus is a deformed human, where there are different sized body parts reflecting the relative density of their innervation. Areas with lots of innervation such as the fingertips and lips require more cortical processing compared to other areas. Also, within the cerebrum are Broca's and Wernicke's areas, which are responsible for speech and comprehension. Broca's area is located in the frontal lobe, while Wernicke's is located at the temporoparietal junction. These two areas are closely linked by arcuate fibers. Damage to any one of these parts can cause problems either with speech or comprehension. The cerebrum also works closely with the hippocampus to form memories. Neurodegenerative diseases such as Alzheimer's affect the cerebrum.

Cortex

The outermost surface of the cerebrum is the cortex that has a grayer appearance and, as a result, is called gray matter. The cortex is a folded structure, and each one of these folds is referred to as a gyrus. Each one of the grooves is called a

sulcus. These folds allow the brain to occupy a smaller cranial volume and store increased functional areas [1]. Below the cortex are myelinated axons, which give the characteristic appearance and often referred to as white matter.

Limbic System

The limbic system is the medial portion of the temporal lobe. It is vital in forming memories, emotions, and behaviors. The limbic system coordinates actions between different parts of the brain including the cortex, brain stem, thalamus, and hypothalamus. The limbic system is made up of the amygdala, hippocampus, fornix, mammillary bodies, cingulate gyrus, and parahippocampal gyrus. These structures communicate with each other via the Papez circuit. The amygdala is a collection of the nuclei that receives multiple sensory nerve signals. The amygdala integrates this information, ignores some stimuli, and creates outputs via the hypothalamus, thalamus, hippocampus, brain stem, and cortex. The amygdala also plays a role in mediating emotional responses associated with memories particularly the fear response [2]. The hippocampus is most important to memory formation, particularly declarative memory. Declarative memory is the ability to recall previous life events. Overtime, certain declarative memories can be independently recalled without the hippocampus [3]. The hippocampus is also important in learning [4].

Basal Ganglia

The basal ganglia (or basal nuclei) are made up of the caudate nucleus, putamen, globus pallidus, nucleus accumbens, olfactory tubercle, ventral pallidum, subthalamic nucleus, and substantia nigra [5]. The basal ganglia work with the motor cortex, premotor cortex, and motor nuclei of the thalamus. It modulates voluntary movements, procedural learning, and routine behaviors or habits [6]. The substantia nigra forms the dopamine necessary for basal ganglia function. The subthalamic nucleus is the only part of the basal ganglia to produce the excitatory neurotransmitter glutamate. A number of motor-related diseases have pathology in the basal ganglia, including Parkinson's and Huntington's disease.

Diencephalon

The diencephalon is made up of the thalamus, epithalamus, subthalamus, and hypothalamus.

Thalamus

The thalamus integrates sensory and motor inputs and transmits the information to the ipsilateral cerebral cortex. There is reciprocal feedback that projects to the thalamic subnuclei. It receives significant inputs from all the senses except for smell. The thalamus may also serve as a filter, trying to simplify the information received and process it to convey the best overall impression. There are a number of nuclei in the thalamus that play key roles in the functioning of the body. The anterior thalamic nuclei work closely with the limbic system, which is also connected with the cingulate gyrus and mammillary bodies. Medial nuclei are associated with the frontal association cortex and premotor cortex. Ventral anterior and lateral nuclei have inputs from the globus pallidus and project to the motor cortex. Ventral posteromedial and ventral posterolateral nuclei function as sensory transmitters associated with the face and body, respectively. Another part of the thalamus is the medial and lateral geniculate bodies, which process auditory and visual information [7]. Finally, the thalamus is also the primary entrance through which additional information from the reticular formation reaches the cerebral cortex. Animals with a damaged thalamus often suffer in a permanent coma.

Epithalamus

The epithalamus connects the limbic system to the rest of the brain. The pineal gland is a part of the epithalamus. The pineal gland secretes melatonin, which is involved in the regulation of the circadian rhythm.

Subthalamus

The subthalamus has efferent connections to the striatum (caudate nucleus and putamen), dorsal thalamus, substantia nigra, and red nucleus. It also has afferent connections from the substantia nigra and striatum. It is often involved in movement control.

Hypothalamus

The hypothalamus mediates the endocrine, autonomic, visceral, and homeostatic functions. It is the highest center for regulation of visceral functions. The hypothalamus connects the nervous system to the endocrine system via the pituitary gland. The hypothalamus is made up of a number of nuclei, each of with particular nuclei that function to regulate the body. Anterior nuclei include preoptic, supraoptic, and paraventricular. Anterior nuclei function in thermoregulation via sweating or panting, vasopressin release, oxytocin release, thyroid-releasing hormone release, and corticotropin-releasing hormone release. Middle nuclei include infundibular, tuberal, dorsomedial, ventromedial, and lateral. They function in the regulation of blood pressure, heart rate, gastrointestinal stimulation, satiety, growth hormone-releasing hormone release, and feeding. Posterior nuclei include supramammillary, mammillary, intercalate, and posterior. They function in arousal, learning, memory, energy balance, and sleep. Lateral nuclei are the location where hypocretin is released, which functions in arousal, temperature regulation, blood pressure, hunger, and wakefulness. Anterior and medial nuclear groups provide parasympathetic control, whereas sympathetic control is performed by the posterior and lateral nuclei. The hypothalamus is also connected with other areas in the brain to help coordinate different functions.

Pituitary

Pituitary gland is located below the hypothalamus at the base of the brain. The hypothalamus works closely with the pituitary to initiate endocrine responses. The pituitary regulates the majority of body functions, including blood pressure, water balance, thyroid levels, breast milk production, sexual organ function, and growth. The pituitary has three parts: anterior, intermediate, and posterior. The anterior pituitary synthesizes and secretes prolactin, growth hormone, adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone. The anterior and intermediate pituitary together release melanocyte-releasing hormone. The posterior pituitary does not synthesize but secretes antidiuretic hormone and oxytocin.

1.2.1.2 Infratentorial Compartment

The infratentorial compartment is the area under the tentorium cerebelli. The primary component is the cerebellum. Nerves C1–C3 innervate this area.

Cerebellum

The cerebellum is made up of tightly folded layer of the cortex, with several deep nuclei embedded in the white matter underneath and a fluid-filled ventricle in the middle. Signals in the cerebellum flow in a unidirectional fashion. The cerebellum plays a major role in motor functions, in particular coordination, posture, and balance [8]. Damage to the cerebellum leads to motor disturbances. There is decreased muscle tone ipsilateral to the lesion site. The cerebellum is an anatomically distinct portion from the cerebrum. It is made up of fine grooves, with several different types of neurons in a very regular distribution. The most important types of cells in the cerebellum are the Purkinje and granule cells. All of the output from the cerebellum passes through a couple of small deep nuclei lying within the white matter.

The three lobes of the cerebellum are flocculonodular lobe, anterior lobe, and posterior lobe. The latter two lobes are also split into the midline cerebellar vermis and lateral cerebral hemispheres. The flocculonodular lobe regulates balance and eye movements. It receives vestibular input from both the semicircular canals and the vestibular nuclei and sends fibers back to the medial and lateral vestibular nuclei. It also receives visual input from the superior colliculi and from the visual cortex.

The cerebellar vermis and paravermis regulate body and limb movements. It receives proprioception input from the dorsal columns of the spinal cord and trigeminal nerve, as well as visual and auditory systems. It also sends fibers to the deep cerebellar nuclei which in turn project to both the cerebral cortex and brain stem, thus providing modulation of the descending motor systems. This area also has sensory maps because it

receives data on the position of various body parts in space. This information is also used to anticipate the future position of the body (also known as "feed forward").

The lateral hemispheres are involved in the planning movement and evaluating sensory information for action. It receives input from the cerebral cortex particularly the parietal lobe via the pontine nuclei and dentate nucleus and sends fibers to the ventrolateral thalamus and red nucleus. This area is also involved in planning the movement that is about to occur.

Blood Supply

Cerebral blood flow to the brain makes up about 15% of cardiac output. The brain is vulnerable to factors that acutely decrease perfusion; as a result the brain has many safeguards including autoregulation and redundancy within the blood supply. Autoregulation is the phenomenon of maintaining a constant blood flow despite a change in perfusion pressure. The consequence of a compromise in blood flow, which is known as a stroke, can be devastating [9]. The arterial blood supply is divided into anterior and posterior portions. The anterior part is via the left and right internal carotid arteries, while the posterior portion is the vertebrobasilar artery. The anastomosis of these systems forms the circle of Willis and helps to create a redundant system of blood supply to help protect against ischemia. However, it is important to note that the system doesn't always protect against ischemia and is not completely redundant. Once the internal carotid arteries enter the cranial vault, they branch into the anterior cerebral artery (ACA) and eventually form the middle cerebral artery (MCA). The anterior cerebral arteries are connected via the anterior communicating artery (ACOM). The ACA supplies the majority of the midline portions of the frontal and superior medial parietal lobes. The MCA supplies most of the lateral portions of the hemispheres. The ACA, MCA, and ACOM form the anterior circulation of the circle of wills. The posterior circulation begins when the basilar artery, which is formed from the right and left vertebral arteries, branches into the left and right posterior cerebral artery (PCA). The vertebral arteries are formed from the subclavian artery. The posterior communicating arteries (PCOM) connect the PCAs and also connect to the anterior circulation. The PCA supplies most of the blood to the occipital lobe and inferior portion of the temporal lobe [7].

Three arteries perfuse the cerebellum: superior cerebellar arteries (SCA), anterior inferior cerebellar artery (AICA), and posterior inferior cerebellar artery (PICA). The SCA branches off the lateral portion of the basilar artery, just inferior to its bifurcation into the posterior cerebral artery. It also supplies blood to the pons before reaching the cerebellum. The SCA supplies blood to most of the cerebellar cortex, the cerebellar nuclei, and the superior cerebellar peduncles. The AICA branches off the lateral portion of the basilar artery, just superior to the junction of the vertebral arteries.

Symptoms associated with infarctions vary based on the artery infarcted in the brain and the area of the brain supplied by that particular artery. MCA infarctions or strokes are the most common. MCA infarctions present with sensory and motor disturbances of the contralateral face, arm, and leg. They can also present with aphasias if the dominant hemisphere is affected. If the ACA is infarcted, it can present with leg weakness more than arm weakness. If the PCA is infarcted, then it presents with visual field abnormalities. Lacunar strokes present with pure sensory or pure motor abnormalities. Vertebrobasilar infarctions present with brain stem dysfunction, which can include vertigo, ataxia, and dysphagia.

The venous drainage system helps remove the blood from the brain. It is made up of two parts: the superficial and deep sinuses. The superficial system is composed of the sagittal sinuses and cortical veins that are located on the surface of the cerebrum. The most prominent of these sinuses is the superior sagittal sinus, which is located midline along the fal x cerebri. The deep venous drainage system is composed of the lateral sinuses, sigmoid sinuses, straight sinus, and draining deep cerebral veins. All the veins in the deep venous drainage system combine to form the vein of Galen. Both of these systems combine to drain into the internal jugular veins.

Brain Stem

The brain stem is considered the most ancient part of the brain. It is made up of three parts: the medulla oblongata, pons, and midbrain. The brain stem primarily provides motor and sensory innervation to the face and neck via the cranial nerves. It also plays a key role in connecting the motor and sensory systems of the brain, which includes the corticospinal tract, posterior column-medial lemniscus pathway, and the spinothalamic tract. Finally, the brain stem plays a key role in the regulation of cardiac and respiratory function. It also regulates the CNS helping to maintain consciousness and regulating the sleep cycle [10].

Medulla Oblongata

The medulla oblongata is a structure that is located superior to the cervical spinal cord. On the external surface, the prominent structure is the anterior median fissure. On either side of this are the medullary pyramids. The pyramids are made up of the corticospinal and corticobulbar tracts originating from the spinal cord. At the caudal part of the medulla, these tracts cross over to form the decussation of the pyramids. The anterior external arcuate fibers lie on top of this. The area between the anterolateral and posterolateral sulcus is the olivary bodies. These bodies are formed by the inferior olivary nuclei. The posterior medulla contains the gracile fasciculus and the cuneate fasciculus. Together, they make up the posterior funiculi. Just above these tubercles is the triangular fossa, which forms the lower floor of the fourth ventricle. The fossa is bound by the inferior cerebral peduncle, which connects the medulla to the cerebellum.

The medulla plays an important role in controlling the autonomous nervous system. The medulla regulates respiration via interaction with the carotid and aortic bodies. These receptors detect changes in pH; thus, if the blood is acidic, the medulla sends signals to the respiratory musculature to increase the respiratory rate to reoxygenate blood. The medulla also plays an important role in regulating the parasympathetic and sympathetic nervous systems, which play a key role in the cardiovascular system [11]. It also plays as a baroreceptor. And finally, the medulla is important in managing the reflex centers of vomiting, coughing, sneezing, and swallowing [12].

Pons

The pons is located between the medulla and midbrain. The pons contains the tracts that carry signals that travel from the cerebrum to the medulla and on to the cerebellum. It also contains the tracts that carry important sensory signals up to the thalamus. Posteriorly, there are cerebellar peduncles that connect the pons to the cerebellum and midbrain. The pons also has the respiratory pneumotaxic center and apneustic centers, which are vital in maintaining respiration and transitioning from inspiration to expiration. The pons also has the nuclei that coordinate with sleep, swallowing, respiration, and bladder control. The pons also coordinates the activities of the cerebral hemispheres. It also plays an important role in control of cranial nerves of 5–8, which includes hearing, equilibrium, taste, and facial sensations.

Midbrain

The midbrain is made up of four parts: tectum, cerebral peduncles, tegmentum, and cerebral aqueduct. The tectum forms the upper border of the midbrain. It is comprised of the superior and inferior colliculi. The inferior colliculi are the principal midbrain nuclei of the auditory pathway. Above the inferior colliculi are the super colliculi, which are involved in vision, in particular the vestibulo-ocular reflex. Together they form the corpora quadrigemina. These structures help to decussate the fibers of the optic nerve. Of note, the trochlear nerve comes out of the posterior midbrain below the inferior colliculi. The dorsal covering of the cerebral aqueduct is also part of the midbrain.

The tegmentum, which forms the floor of the midbrain, is made up of several nuclei, substantia nigra, and reticular formation. The ventral tegmentum is composed of cerebral peduncles, which serve as the transmission axons of the upper motor neurons. The reticular formation is a large area of the midbrain that has multiple regulatory functions. It plays a key role in arousal,

sleep-wake cycling, and maintaining consciousness [13, 14]. It also contains the locus coeruleus, which is involved in alertness modulation and autonomic reflexes. Serotonin is also made in the reticular formation, which is a key regulator of mood. The reticular formation also plays a key role in regulation of the cardiovascular system, along with the medulla. Finally, the reticular formation is important in habituation, which is the process by which the brain begins to ignore repetitive meaningless stimuli, but remains vigilant to new sounds. The red nucleus is closely involved in motor coordination. Another important part of the tegmentum is the substantia nigra, which is closely associated with the basal ganglia. Dopamine produced in the substantia nigra and ventral tegmental area plays a role in excitation, motivation, and habituation. Dysfunction is associated with Parkinson's disease.

The cerebral aqueduct is involved with the movement of CSF. It is surrounded by gray matter, which is known as the periductal gray. In this area, there are neurons involved in the pain desensitization pathway that interact with the reticular activating system. When the neurons here are stimulated, they cause activation of the nucleus raphe magnus. The neurons project into the posterior gray column of the spinal cord and prevent pain sensitization transmission [15].

Development

In utero, the brain starts to develop at the beginning of the third week as the ectoderm forms the neural plate. By the fourth week, the neural plate has widened to give a broad cephalic end and a narrower caudal end. The swellings represent the beginning of the forebrain, midbrain, and hindbrain. Neural crest cells make up the lateral edge of the plate at the neural folds. By the end of the fourth week, the neural plate folds and closes to form the neural tube, which brings together the neural crest cells. Cells at the cephalic end give rise to the brain, while cells at the caudal end give rise to the spinal cord. With time the tube flexes giving rise to the crescent-shaped cerebral hemispheres. These cerebral hemispheres first appear on day 32. During this fourth week, the cephalic part bends forward forming the cephalic flexure, which becomes the forebrain. The forebrain divides into two parts: the telencephalon and diencephalon. The telencephalon goes on to form the cerebral cortex, basal ganglia, and other structures. The diencephalon forms the thalamus and hypothalamus. The hindbrain goes on to develop into the metencephalon and myelencephalon. The metencephalon forms the cerebellum and pons. The myelencephalon forms the medulla oblongata [7]. The developing brain is more vulnerable to injury in comparison to the developed or adult brain. When the development of the brain is delayed by an external influence or toxin, there is virtually no regeneration or repair. This can lead to lifelong disability. As a result, minimizing exposures to a developing brain is vital.

One of the most defining features of the brain is the gyri that define the outer surface. In womb, the brain starts off smooth, but with time the fissures start to form. The fissures form because of the rapidly growing hemispheres, which rapidly increase in size due to the expansion of the gray matter. The underlying white matter does not grow at the same rate as the hemispheres [7].

1.2.1.3 Spinal Cord

The spinal cord is a bundle of nervous tissue that extends from the medulla oblongata in the brain stem to the lumbar region of the vertebral column. The spinal cord connects the brain to the peripheral nervous system. The spinal cord is encased in a bony shell made up of the cervical vertebrae. The spinal cord transmits nerve signals from the motor cortex to the musculature and from the afferent fibers of the sensory neurons to the sensory cortex. The spinal cord also plays a key role in coordinating reflexes and contains numerous reflex arcs (ankle jerk, knee jerk, biceps jerk, forearm jerk, triceps jerk). The spinal cord is made up of 31 segments; at each level there are 1 pair of sensory nerve roots and 1 pair of motor nerve roots.

The spinal cord and brain are covered by three protective layers of the meninges. The dura mater is the outermost layer and forms a tough protective coating. Between the vertebrae and dura mater is the epidural space. The epidural space is

made up of adipose tissue and has numerous blood vessels. The arachnoid mater is the middle layer that is located underneath the dura mater. The arachnoid mater is named for its open, spiderlike appearance. The space between the arachnoid mater and pia mater is the subarachnoid space. The subarachnoid space has cerebrospinal fluid (CSF), which is accessed in neuraxial anesthesia. The CSF is made in the brain's lateral ventricles and flows through the foramen of Monro into the third ventricle and through the cerebral aqueduct to the fourth ventricle. It passes into the subarachnoid space through three openings in the roof of the fourth ventricle. The two lateral openings are the foramen of Luschka and a median opening called the foramen of Magendie. The CSF then flows through the subarachnoid space around the brain and drains into the superior sagittal sinus through the arachnoid granulations [7].

The pia mater is tightly adhered to the spinal cord. The cord is stabilized within the dura mater by connecting denticulate ligaments, which extend from the enveloping pia mater laterally between dorsal and ventral roots. The dural sac ends at the level of the second sacral vertebrae.

Spinal Cord Segments

The gray column (matter) at the center of the spinal column is shaped like a butterfly and consists of cell, bodies of interneurons, motor neurons, neuroglia cells, and unmyelinated axons. The gray matter consists of longitudinal columns of cells, with a segmental relationship to the spinal nerve fibers. These columns are grouped into the dorsal (posterior) horn, ventral (anterior) horn, and intermediate gray. The dorsal roots are afferent fascicles, receiving sensory information. The roots terminate in dorsal root ganglia, which are made up of the respective cell bodies. The ventral nerve roots are made up of efferent fascicles that arise from motor neurons whose cell bodies are found in the ventral horns of the spinal cord [7]. The ventral horn also includes interneurons, which are involved in the processing of motor information. The intermediate gray contains the interneurons for primitive connections.

The white matter is located adjacent to the gray matter and is made up of myelinated motor and sensory axons. The columns of white matter carry information up or down the spinal cord [7]. The white matter is made up of the dorsal white matter, ventral white matter, and lateral white matter. The dorsal white matter has the ascending tracts, while the ventral white matter has the descending tracts. The dorsal column below T6 has the gracile fasciculus, which has input from the lower body. And above T6, there is both input from the lower body and upper body, which is also known as the cuneate fascicle. The lateral white matter has both and is mainly involved with pain and movement. The absolute amount of white matter decreases as you progress caudally through the spinal cord. Lesions at the dorsal and ventral roots present as strictly sensory or motor deficits; while lesions at the peripheral nerves more often present with deficits in both the sensory and motor pathways.

The spinal cord terminates at the conus medullaris, while the pia mater continues via the filum terminale, which anchors the spinal cord to the coccyx. The cauda equina is a collection of nerves below the conus medullaris that travel in the vertebral column to the coccyx. The cauda equina forms because the spinal cord stops elongating at about age 4, even though the vertebral column continues to lengthen until adulthood.

There are 31 spinal cord segments in the spinal cord – 8 cervical segments, 12 thoracic segments, 5 lumbar segments, 5 sacral segments, and 1 coccygeal segment. In the fetus, vertebral segments correspond with spinal cord segments. In adults, the spinal cord ends around the L1/L2 vertebral level, which corresponds to the conus medullaris. As a result, the spinal cord segments do not correspond with the vertebral segments especially in the lower spinal cord. The cervical enlargement, stretching from the C5 to T1 vertebrae, is the location for the sensory and motor output associated with the arms and trunk. This enlargement corresponds with the brachial plexus. The lumbar enlargement, located between L1 and S3, handles sensory input coming from and going to the legs. This corresponds with the lumbosacral enlargement [7].

Development

There are four stages of spinal cord development: neural plate, neural fold, neural tube, and spinal cord. At the end of the third week, the ectoderm located at the midline of thickens to form the neural plate. Slowly, the lateral edges of the neural plate began to move dorsally and medially. When the edges meet, they form the neural tube. As the neural tube begins to develop, the notochord begins to secrete sonic hedgehog (SHH) [16]. This helps to establish the ventral pole in the developing fetus [16]. As a result, the floor plate also begins to secrete SHH, which induces the basal plate to develop motor neurons. During the maturation of the neural tube, lateral walls thicken and form the longitudinal groove of the sulcus limitans. This extends the length of the spinal cord into dorsal and ventral portions. At the same time, the ectoderm secretes bone morphogenetic protein (BMP). These two opposing gradients help the cells divide along the dorsal ventral axis [17]. This release of the BMP also induces the roof plate to secrete BMP, which leads to the formation of the sensory neurons. Simultaneously, the lumen of the neural tube begins to narrow to help form the central canal of the spinal cord. Further, the floor plate secretes netrins. The netrins act as chemoattractants, which lead to the decussation of pain and temperature sensory neurons in the alar plate across the anterior white commissure. These fibers ascend toward the thalamus. Once the caudal neuropore and formation of the brain's ventricles with the choroid plexus is completed, the central canal of the caudal spinal cord is filled with CSF. Closure of the neural tube progresses both cranially and caudally. Malformations of the neural tube closure can lead to abnormal development of the central nervous system. Failure of the cranial tube to close completely at the cranial end may manifest as exencephaly, anencephaly, or cranioschisis. The complete closure of the lumbar region of the neural tube may lead to rachischisis or myeloschisis, which is where the spinal cord is exposed to the outside. More mild defects may present as spina bifida, which is the result of an incomplete vertebral arch.

Over the course of the cell division process, groups of cells break off from the neural plate and become a part of the mesoderm. Slowly, these neural crest cells migrate away from the neural tube and form a number of different tissues including the neurons of the dorsal root ganglion and postsynaptic cells of the sympathetic and parasympathetic nervous systems. When these cells fail to appropriately migrate, it forms diseases such as Hirschsprung's disease. Hirschsprung's occurs when there is a portion of the digestive system that can't perform peristalsis.

Blood Supply

The blood supply of the spinal cord is made of three longitudinal arteries, which are the anterior spinal artery, right posterior spinal artery, and left posterior spinal artery. The anterior spinal artery provides blood flow to the anterior 2/3 of the spinal cord [7]. These arteries travel in the subarachnoid space and send branches into the spinal cord. They form connections via the anterior and posterior segmental medullary arteries, which enter the spinal cord at various points. The blood flow through these arteries provides sufficient blood supply primarily to the cervical spinal cord. Beyond that region, the spinal cord derives much of its blood supply from the anterior and posterior radicular arteries, which run into the spinal cord alongside the dorsal and ventral nerve roots. The largest of the anterior radicular arteries is the artery of Adamkiewicz, which usually arises between L1 and L2. Impaired blood flow to these radicular arteries can result in spinal cord infarction and paraplegia [18].

Somatosensory Organization

The somatosensory system is primarily concerned with transmitting the sensory information from the integumentary and musculoskeletal systems of the body. This system can be divided into the dorsal column-medial lemniscus (DCML) and the anterolateral system (ALS). The DCML plays the main role in the touch, proprioception, and vibration, while the ALS plays the key role in pain and temperature. Both sensory pathways use three different nerves to transmit the information from the sensory receptors in the periphery to the

cerebral cortex. In both pathways, the primary sensory neuron cell bodies are found in the dorsal root ganglion and their central neurons project into the spinal cord.

In the DCML, a primary neuron's axon enters the dorsal column of the spinal cord. If the primary axon enters below level T6, the axon travels in the fasciculus gracilis, which is the medial part of the cord. If the primary axon enters above level T6, it travels in the fasciculus cuneatus, which is located more lateral. Through both these pathways, the primary axon ascends to the caudal medulla, where it leaves the fasciculi and synapses with a secondary neuron in one of the dorsal column nuclei, either the nucleus gracilis or nucleus cuneatus, respectively. The first processing of discriminative touch information occurs in the caudal medulla. The secondary axons synapse with these nuclei. These secondary axons are known as the internal arcuate fibers. The internal arcuate fibers decussate and ascend as the contralateral medial lemniscus. Axons from the medial lemniscus terminate in the ventral posterolateral nucleus of the thalamus. In the thalamus, neurons synapse with tertiary neurons, which eventually ascend in the posterior limb of the internal capsule to the primary sensory cortex. Further, the axons that enter the dorsal columns also give rise to collaterals that terminate in the spinal cord. These collaterals play an important role in modulating simple motor behaviors.

The ALS has a different anatomical pathway compared to the DCML. The primary axons of the ALS enter the spinal cord and ascend 1–2 levels ipsilaterally before synapsing with the substantia gelatinosa. Once synapsing, the secondary axons decussate in the ventral white commissure and ascend as a part of the anterolateral spinothalamic tract. This tract travels through the medulla and eventually synapses in the thalamus and further similar to the DCML. In syringomyelia with pathologic cavitation, there is often bilateral loss of pain and temperature sensations in the dermatomes at the level of the lesion because of the proximity of the ventral white commissure to the central canal of the spinal cord.

It is important to note that some of the pain fibers in the ALS deviate away from this pathway to the reticular formation in the midbrain. The reticular formation is connected with the hippocampus to create memories and centromedian nucleus to create diffuse non-specific pain sensation. Further, the ALS axons help inhibit the initial pain signal via projections to the periaqueductal gray in the pons and nucleus raphe magnus.

Motor Component

The corticospinal tract is the motor pathway for the upper motor neurons (UMN) coming from the cerebral cortex and from the primitive brain stem motor nuclei. The cortical upper motor neurons originate from Brodmann areas 1, 2, 3, 4, and 6. Majority originate from Brodmann area 4, which is premotor frontal area. They descend down the posterior limb of the internal capsule, into the cerebral peduncles, and then into the medullary pyramids, where about 90% of axons cross to the contralateral side at the decussation of the pyramids. Then the neurons descend as the lateral corticospinal tract. The axons synapse with lower motor neurons (LMN) in the ventral horns. Most of the axons will cross to the contralateral side of the cord before they synapse. The midbrain nuclei include four motor tracts that send UMN axons down the spinal cord to LMN. These four tracts are the rubrospinal tract, vestibulospinal tract, tectospinal tract, and reticulospinal tract. Damage to the UMN of the corticospinal tract can lead to paralysis, paresis, hypertonia, hyperreflexia, or spasticity.

The LMN have two divisions: the lateral corticospinal tract and the anterior corticospinal tract. The lateral tract contains fibers that are involved with distal limb control. Thus, these neurons are only found at the cervical and lumbosacral enlargements. There is no decussation of the lateral corticospinal tract after decussation at the medullary pyramids. The lateral corticospinal tract forms the majority of connections in the corticospinal tract. The anterior corticospinal tract descends ipsilaterally in the anterior column and synapses ipsilaterally in the ventromedial nucleus. These nerves control the large postural muscles of the trunk and axial skeleton.

Spinocerebellar Tract

Proprioceptive information, which are the stimuli that affect muscle joints or other deep tissues, travel in the spinal cord via three tracts based on the spinal cord level. These receptors are responsible for the perception of motion and position of the body. They carry unconscious proprioceptive information about the body position from the periphery to the cerebellum. Above T1, proprioceptive primary axons enter the spinal cord and ascend ipsilaterally until synapsing in the accessory cuneate nucleus. The secondary axons pass into the cerebellum via the inferior cerebellar peduncle, where they synapse with the cerebellar deep nuclei. This is part of the cuneocerebellar tract [19]. From the levels of T1–L2, proprioceptive information enters the spinal cord and ascends ipsilaterally until synapsing with Clarke's nucleus (nucleus dorsalis). Below the level of L2, proprioceptive information travels via the fasciculus gracilis and DCML, until reaching Clarke's nucleus. Neurons within Clarke's nucleus give rise to second-order sensory fibers that ascended the ipsilateral dorsal part of the lateral funiculus of the spinal cord. At the medulla, these fibers enter the cerebellum via the inferior peduncle. Lesions or deficits to the cerebellum manifest with ataxia of the extremities on the same side of the lesion. It is often hard to damage just the spinocerebellar tracts.

1.2.1.4 Peripheral Nervous System

The peripheral nervous system (PNS) is made up of the nerves and ganglia that are located outside of the brain and spinal cord. The primary function of the peripheral nervous system is to connect the CNS to the limb and organs. However, unlike the CNS, the PNS is not protected by the vertebral column and skull or by the blood-brain barrier. Thus, the nerves are more exposed to toxins, mechanical injuries, and other pathological processes. The peripheral nervous system is divided into the somatic nervous system and autonomic nervous system. The somatic nervous system is involved with voluntary control of the muscles. Of note, the sensory nervous system is part of the somatic nervous system. In the somatic system, the cranial nerves are part of the PNS except for the optic nerve. The optic nerve is considered a tract of the diencephalon [5]. However, the remaining ten cranial nerves extend outside of the brain and are considered a part of the PNS. The autonomic nervous system is involved in involuntary self-regulation via the sympathetic and parasympathetic nervous systems. The sympathetic and parasympathetic systems are antagonists.

1.2.1.5 Somatic Nervous System

The somatic nervous system (SoNS) is made up of the sensory and somatosensory nervous system. The SoNS is made up of afferent neurons (sensory) and efferent nerves (motor). The afferent nerves relay information from the body to the CNS, while the efferent nerves are responsible for stimulating muscle contraction. The efferent nerves include all the non-sensory neurons connected with the skeletal muscles and skin. The efferent SoNS involves an initial signal that begins in the upper cell bodies of motor neurons within the precentral gyrus. Stimuli from the precentral gyrus are transmitted down the corticospinal tract to control the skeletal muscles. These stimuli are conveyed from the upper motor neurons (UMN) through the ventral horn of the spinal cord and across synapses to be received by the sensory receptors of alpha motor neuron, which are large lower motor neurons, of the brain stem and spinal cord. UMN release acetylcholine from their axonal terminal knobs, which are received by the nicotinic receptors of the lower motor neurons. These signals are further relayed to the end organ. In contrast to this pathway, the SoNS is also made up of reflex arcs. The reflex arc is a shorter neuronal circuit creating direct connections between the sensory input and a specific motor output. Reflex arcs have various levels of complexity; some involve just two nerves, while others have three nerves, with the addition of an interneuron. Some of the reflexes are protective, while others contribute to regular behavior [10]. This leads to a shorter response time.

In the head and neck, 12 cranial nerves carry somatosensory data. Ten of the cranial nerves originate from the brain stem and also control the anatomic functions in the head. The nuclei of the

Table 1.1 Cranial nerves

Cranial nerve	Location of exit	Structures supplied
I: Olfactory nerve	Cribriform plate	Olfactory mucosa
II: Optic	Optic foramen	Rods and cones of the retina
III: Oculomotor	Superior orbital fissure	Superior rectus, medial rectus, inferior rectus, inferior oblique, and sphincter oblique
IV: Trochlear	Superior orbital fissure	Superior oblique
V: Trigeminal	Superior orbital fissure, foramen rotundum, foramen ovale	Muscles of mastication, tensor tympani, tensor palati
VI: Abducens	Superior orbital fissure	Lateral rectus
VII: Facial	Internal auditory canal	Posterior external ear canal, anterior 2/3 of the tongue, facial muscles, salivary glands, lacrimal glands
VIII: Vestibulocochlear	Internal auditory canal	Cochlea and vestibule of the inner ear
IX: Glossopharyngeal	Jugular foramen	Posterior 1/3 of the tongue (sensory and taste), middle ear, carotid body/sinus, stylopharyngeus, parotid gland
X: Vagus	Jugular foramen	External ear, aortic arch/body, epiglottis, soft palate, pharynx, larynx, lungs
XI: Accessory	Jugular foramen	Trapezius, sternocleidomastoid
XII: Hypoglossal	Hypoglossal canal	Muscles of the tongue

olfactory and optic nerves lie in the forebrain and thalamus. The vagus nerve receives sensory information from the organs in the thorax and abdomen. The cranial nerves are summarized in Table 1.1.

1.2.1.6 Cervical Spinal Nerves (C1–C4)

Spinal nerve C1 (suboccipital nerve) provides innervation to the nerves at the base of the skull. C2 and C3 form many nerves in the neck, providing both motor and sensory controls. These nerves include greater occipital nerve, lesser occipital nerve, greater auricular nerve, and lesser auricular nerve. The phrenic nerve is a nerve, which arises from C3, C4, and C5, that is vital to survival by supplying the thoracic diaphragm enabling breathing. It is important to note that if the cervical spine is transected above C3, then the patient will not be able to spontaneously breathe.

1.2.1.7 Brachial Plexus (C5–T1)

The brachial plexus, which is made up of the last four cervical nerves (C5–C8 and T1), innervates the upper limb and upper back. It is made up of five roots, three trunks, six divisions (three anterior and three posterior), three cords, and five branches [20]. The five roots come together to form five trunks (superior trunk, middle trunk, and inferior trunk). The dorsal scapular nerve comes from the superior trunk and innervates the rhomboid muscles which retract the scapula. The subclavian nerve, which branches from C5 and C6, innervates the subclavius muscle that lifts the ribs during respiration. The long thoracic nerve, which originates from the C5, C6, and C7, innervates the serratus and is vital in lifting up the scapula [20].

The trunks split into divisions and then form cords, which are named in relation to their positon with the axillary artery. The three cords are the posterior, lateral, and medial cords. The cords lead to the formation of the terminal branches. The terminal branches are musculocutaneous nerve, axillary nerve, radial nerve, median nerve, and ulnar nerve. Because both the musculocutaneous and median nerve originate from the lateral cord, they are well connected. The musculocutaneous nerve innervates the skin of the anterolateral forearm along with the brachialis, biceps brachii, and coracobrachialis [20]. The median nerve innervates the skin of the lateral 2/3 of the hand and the tips of digits 1–3. It also innervates the forearm flexors, thenar eminence, and lumbricals of the hand 1–2 [20]. The axillary nerve innervates the sensory portion of the lateral shoulder and upper arm and also plays a role innervating the deltoid and teres minor muscles [20]. The radial nerve innervates the sensory portion of the

posterior lateral forearm and wrist. It also innervates the triceps brachii, brachioradialis, anconeus, and extensor muscles of the posterior arm and forearm [20]. The ulnar nerve innervates the skin of the palm and medial side of the hand and digits 3–4. It also innervates the hypothenar eminence, some forearm flexors, the thumb adductor, lumbricals 3–4, and the interosseous muscles [20]. Brachial plexus injuries affect the cutaneous sensation and the muscular motions depending on the nerve that has been affected.

1.2.1.8 Lumbosacral Plexus (L1-Coccygeal Nerve)

The lumbosacral plexus is made up of three key parts: lumbar plexus, sacral plexus, and pudendal plexus. Often times bone injuries in the pelvic region can affect these nerves.

1.2.1.9 Autonomic Nervous System (ANS)

The ANS controls involuntary responses to regulate physiologic functions, in particular those that have smooth muscle [21]. This includes the heart, bladder, and other exocrine or endocrine organs via ganglionic neurons [21]. The ANS is always active. Depending on the situation, either the sympathetic or parasympathetic system dominates. This leads to the release of neurotransmitters, which affect the organs in different ways. The other division of the ANS is the enteric nervous system [22]. The enteric nervous system surrounds the digestive tract and, as a result, allows for local control of the gastrointestinal system [22]. However, the sympathetic and parasympathetic provide input.

The sympathetic system is involved in "flight or fight," which is a stress response mediated by norepinephrine and epinephrine [21]. This often occurs when the body feels that it is under great stress. The norepinephrine and epinephrine increase the heart rate and blood flow to certain areas such as the muscles while also decreasing the activities of noncritical functions such as digestion [22].

The parasympathetic system is in many ways the opposite of the sympathetic system. The primary neurotransmitter involved is acetylcholine, which allows the body to "rest and digest." As a result of the parasympathetic system, there is decreased heart rate and other sympathetic response, while there is increased digestion, urination, and defecation. Humans have some control over the parasympathetic system.

1.3 Conclusion

The nervous system is made up of two key parts: CNS and PNS. The relationship and interaction between the two are as important as each individual part. Damage to one area can be minor or devastating for the welfare of the individual. Disturbances during development in utero can be particularly profound affecting a number of different areas of the nervous system. Anatomy plays a key role in determining function and pathology. Clearly identifying the different structures and function can help predict the deficiency found upon damage.

Key Points

- The nervous system is made up of two parts: the central nervous system and peripheral nervous system. The two systems work closely together to coordinate function.
- Pathology in one portion can lead to dysfunction in the end organs. Stresses or dysfunction during development can lead to diffuse debility.
- Some of the pathological changes are amenable to correction, while others are not.

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Physiology for Neuroanesthesia

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2.1 Cerebral Metabolism

2.1.1 Introduction

The primary function of the brain is to develop action potentials in response to stimulation to allow the propagation of neuronal transmission [1]. In order to maintain this function, the brain requires considerable energy supply, together with the effective removal of waste products. Energy is primarily used for the maintenance of functioning ion channels, such as the Na^+/K^+ ATPase ion pump, to maintain the resting membrane potential and therefore neuronal function. In addition, energy is required for the maintenance of cellular structure and integrity and for the production of neurotransmitters. Under normal conditions supply of energy substrate exceeds demand, but under certain conditions supply fails to meet demand, and neuronal damage can occur. This section will look at cerebral metabolism under aerobic and anaerobic conditions and adaptations during periods of stress and ischemia.

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2.1.2 Aerobic and Anaerobic Metabolism

The main energy substrate of the brain is glucose, accounting for 25% of the total glucose consumption within the body (30 mg/100 g/min) [1]. In addition to acting as an energy substrate, glucose is a precursor for the neurotransmitters γ-aminobutyric acid (GABA), acetylcholine, and glutamate. Glucose initially crosses the blood-brain barrier by facilitated diffusion using GLUT1 glucose transporter system before uptake into cells occurs via GLUT1 into astrocytes, GLUT3 into neurons, and GLUT5 into microglial cells.

Around 70% of glucose entering the cells undergoes oxidation using the glycolytic and citric acid cycle, with the remaining 30% being converted to amino acids, proteins, and lipids [2]. The glycolytic pathway converts glucose to pyruvic acid, a process that generates two molecules of adenosine triphosphate (ATP). In the presence of oxygen, pyruvic acid enters the mitochondria and is oxidized within the citric acid cycle to carbon dioxide and water, a process that generates the coenzymes reduced nicotine adenine dinucleotide (NADH), flavin adenosine dinucleotide, and guanosine triphosphate (GTP). These coenzymes then undergo oxidative phosphorylation within the electron transport chain, allowing the generation of a maximum of 38 molecules of ATP for each molecule of glucose metabolized.

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In the absence of adequate oxygen supply, anaerobic glycolysis occurs with the conversion of pyruvic acid to lactic acid, yielding two molecules of ATP. Although less energy efficient than aerobic metabolism, the lactic acid generated acts as a key energy substrate during periods of high metabolic activity and stress. It is hypothesized that within astrocytes, lactate produced by glycolysis is exported via the monocarboxylate transport protein and taken up by adjacent neurons for oxidation and further energy production, a process termed astrocyte-neuron lactate shuttle [3, 4].

2.1.3 Cerebral Metabolic Changes During Periods of Stress

While the brain has considerable energy expenditure, the metabolic reserves are very limited, and periods of dysglycemia are tolerated poorly, in particular, hypoglycemia. Glycogen stores within the brain are exhausted after 2–3 min [2]. Blood sugar levels <4 mmol/L result in glycogenolysis and gluconeogenesis attempting to restore blood glucose levels. However, if the blood glucose level falls to <3 mmol/L, these compensatory mechanisms fail, and neuronal function deteriorates [5]. This manifests clinically as altered level of consciousness and impairment of cognition. In these acute periods of hypoglycemia, the brain adapts through the utilization of lactate, organic acids, and amino acids for energy production, in an attempt to prevent irreversible neuronal damage.

During prolonged fasting, the brain adapts to utilize ketone bodies. Ketone bodies are produced by the metabolism of fatty acids. Their conversion to acetyl Co-A allows energy production through the citric acid cycle. In addition, during starvation the brain also uses gluconeogenesis for the regeneration of glucose and utilizes alternative energy sources such as glutamine, glycine, and glycerol.

Ischemic and hypoxic insults are tolerated poorly by neuronal tissue principally through the impairment of energy production. In the absence of oxygen delivery, oxidative phosphorylation is blocked, and ATP production falls by around 95% [6]. This results in ion channel disruption and altered ionic homeostasis and leads to neuronal depolarization and the release of intracellular calcium and excitatory neurotransmitters such as glutamate. During these periods, lactate utilization from anaerobic metabolism acts as an alternative energy source to ensure ATP production continues.

2.1.4 Cerebral Metabolic Rate and Flow-Metabolism Coupling

Cerebral metabolic rate (CMR) is the rate at which the brain utilizes metabolic substrates (oxygen ($CMRO_2$), glucose (CMR_{glu})) or generates by-products (CMR_{lact}) [7]. Oxygen consumption of the brain is considerable, accounting for 20% of basal oxygen consumption (50 mL/min) at rest:

$$CMRO_2 = CBF \times (A - V)O_2 \text{Content Difference} \quad (2.1)$$

where $CMRO_2$ is the cerebral oxygen consumption, CBF is cerebral blood flow, V is the cerebral veins, and A the cerebral arteries.

Flow-metabolism coupling ensures that areas of the brain with increased metabolic requirements receive increased oxygen and nutrient delivery, to allow aerobic metabolism to continue. Neuronal activation within neural and glial tissue leads to the production of metabolic by-products such as adenosine, nitric oxide (NO), H^+, K^+, Ca^{2+}, and lactate [8]. These act locally to cause cerebral vasodilatation and hyperemia, thereby increasing regional blood flow to metabolically more active tissue. Astrocytes, with their abundance and anatomical location surrounding cerebral blood vessels, play an important role in flow-metabolism coupling through their Ca^{2+}-dependent release of neurotransmitters in response to neuronal activity [8, 9].

In conditions leading to a reduction in cerebral metabolic oxygen demand, such as hypothermia, coma, and in general anesthesia, cerebral blood flow is therefore reduced. Conversely an increase in cerebral metabolic demand, for example, in

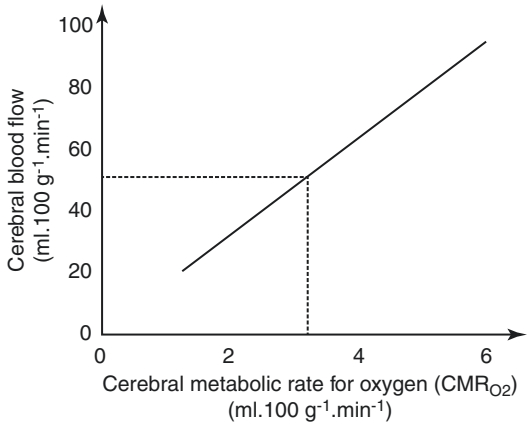

Fig. 2.1 Cerebral flow-metabolism coupling. Areas of brain tissue with increased $CMRO_2$ produce increased amounts of vasoactive metabolites, causing local vasodilatation and hyperemia, leading to increased CBF. The dotted line demonstrates normal values for $CMRO_2$ (3.3 mL/100 g/min) and CBF (50 mL/100 g/min). (Reproduced with permission from Cross M, Plunkett E. Flow-metabolism coupling. In: Physics, Pharmacology and Physiology for Anaesthetists: Key Concepts for the FRCA. Cambridge: Cambridge University Press; 2014. pp. 316–8. doi:10.1017/CBO9781107326200.132)

seizures and hyperthermia, will lead to an increase in cerebral blood flow (Fig. 2.1).

When these protective autoregulatory processes fail, cerebral flow-metabolism uncoupling occurs, leading to mitochondrial dysfunction, oxidative stress, neuronal death, and brain tissue atrophy [8]. This is seen most often in ischemic stroke, where changes in chemical mediator release and alteration in cerebral flow dynamics lead to flow-metabolism uncoupling and disruption of the blood-brain barrier [8]. In addition, conditions such as traumatic brain injury, diabetes mellitus, increased age, hypertension, and dementia can all lead to loss of cerebral metabolic autoregulation [8].

2.1.5 Waste Removal and Water Homeostasis

The high metabolic demands of cerebral parenchyma require an efficient system for waste removal to prevent toxin build up and maintain ionic homeostasis. The macroscopic glymphatic pathway uses perivascular spaces to allow the continuous exchange of waste products and toxins between the intracellular and cerebrospinal fluids. Using convective flow facilitated by glial aquaporin 4 (AQP4) water channels, waste products are removed from the cerebral parenchyma, entering the perivenous space before draining into the cervical lymphatic system [10].

2.2 Cerebral Blood Flow and Cerebral Perfusion Pressure

The brain accounts for 20% of the body's resting oxygen consumption, despite weighing only 2% of the total body mass (1400 g). This coupled with relying heavily on aerobic metabolism for ATP production, and with very limited glycogen stores, makes it vulnerable to ischemic insults from hypoperfusion. It therefore requires an efficient blood supply to deliver oxygen and glucose to meet its high metabolic demands. The brain receives 15% of cardiac output (700 mL/min or 50 mL/100 g/min). Grey matter receives a higher proportion of the arterial blood supply (70 mL/100 g/min) than white matter (20 mL/100 g/min) due to its higher metabolic requirements.

The cerebral arterial supply arises from the anterior and posterior cerebral circulations, supplied by the internal carotid arteries and the vertebral arteries, respectively. These coalesce to form the circle of Willis, providing a protective collateral blood supply in the event of a unilateral interruption to arterial supply. Venous drainage occurs via the dural venous sinuses and cerebral veins which drain into internal jugular veins.

CBF can be described by the Hagen-Poiseuille equation for laminar flow:

$$\mathrm{CBF} = \frac{\Delta P \pi r^4}{8 \mu l} \tag{2.2}$$

where CBF is cerebral blood flow, ΔP is the driving pressure gradient, r is the radius of the vessel, l is the length of the vessel, and μ is the viscosity of blood.

CBF can therefore be affected by:

1. Changing the driving pressure (ΔP—the cerebral perfusion pressure (CPP))

   Perfusion pressure is the difference in the pressures between the arterial and venous circulation which dictates blood flow to the organ [7]. Mean cerebral venous pressure is hard to measure, and therefore ICP is used as a surrogate:

$$\text{Cerebral Perfusion Pressure}(\text{CPP}) = \text{Mean Arterial Pressure}(\text{MAP}) - \text{ICP} \quad (2.3)$$

   Therefore, to increase CPP, MAP can be increased or ICP decreased. CPP values of <50 mmHg lead to cerebral hypoperfusion and ischemia. Maintaining an adequate CPP is a fundamental principle in the neurocritical care management of traumatic brain injury (TBI), with current guidelines recommending targeting a CPP of 60–70 mmHg [11]. Further discussion on management of TBI is beyond the scope of this chapter.
2. Altering the cerebral blood vessel radius (r)

   This occurs through autoregulation, neurohumoral effects, respiratory gas effects, and cerebral flow-metabolism coupling and will be discussed in more detail below.

2.3 Cerebral Autoregulation

Cerebral autoregulation is the process by which the cerebral vasculature maintains a constant CBF across a range of systemic blood pressures or CPPs [7, 12]. This concept was introduced initially by Lassen in the 1950s [13]. Lassen initially produced a biphasic curve (Fig. 2.2) with low-pressure limits and a plateau, with a high-pressure limit introduced later [14].

For MAP, the low and high limits are 60 and 160 mmHg, respectively, with 50 and 100 mmHg, respectively, for CPP. At first it was thought that cerebral blood flow varied passively with perfusion pressure, but other work revealed that the changes in vascular diameter were an active process [15].

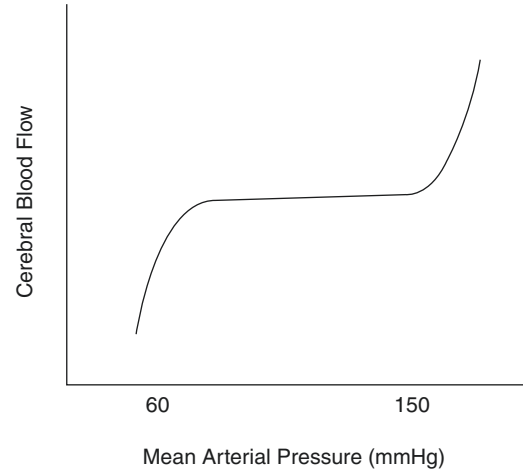

Fig. 2.2 Lassen curve demonstrating constant cerebral blood flow between the low (60 mmHg) and high (160 mmHg) mean arterial pressure limits due to cerebral autoregulation. (Reprinted by permission from Springer Nature: Eur J App Physiol. Blood Pressure regulation IX: cerebral autoregulation under blood pressure challenges. Tzeng Y-C, Ainslie PA. 2014;114(3): 545–59)

We now know that CBF is determined by several factors: autoregulatory, neurogenic, chemical, systemic, and metabolic. CBF is most heavily influenced by changes in $PaCO_2$ [16].

2.3.1 Mechanism of Autoregulation

There have been many proposed mechanisms for autoregulation. There is interplay between the mechanisms at any given time, but as previously described, carbon dioxide (metabolic) appears to have the most direct effects on CBF.

The four central mechanisms researched have been:

1. Neurogenic
2. Myogenic
3. Endothelial
4. Metabolic

2.3.1.1 Neurogenic

The cerebral blood vessels are under both sympathetic and parasympathetic control. The sympathetic nerve supply arises from the superior cervical ganglion, utilizing neuropeptide Y

and norepinephrine. This causes cerebral vasoconstriction. In chronic disease states such as hypertension, the prolonged sympathetic activity causes a rightward shift of the autoregulation curve.

Parasympathetic innervation arises from the otic and sphenopalatine ganglia, vasoactive intestinal peptide, and acetylcholine-mediated cerebral vasodilatation. The parasympathetic system does not appear to have any control over the position of the autoregulation curve.

During seizure and hypertension, the third group of sensory fibers may come into action. These arise in the trigeminal ganglion and are responsible for the release of calcitonin gene-related peptide and substance P, with a subsequent increase in CBF due to vasodilatation.

2.3.1.2 Myogenic

If CBF were directly proportional to the pressure gradient across the vessel, there would be no plateau on the Lassen curve and by definition no autoregulation. This would be a purely passive response; since this does not happen in vivo clearly, there has to be some active mechanism at play. This leads to the investigation of a myogenic response to pressure changes, controlling vascular tone to maintain the CBF. Increases in the MAP lead to increased transmural pressure, this brings about depolarization of vascular smooth muscle, and the precapillary resistance vessels become constricted, maintaining a constant CBF (Fig. 2.3). Conversely these vessels dilate to promote CBF when the MAP and therefore transmural pressure drop. These changes occur almost instantaneously via nitric oxide (NO).

Changes in MAP will produce varying degrees of vascular tone depending on the nature of the blood vessel. Arterioles have a high proportion of smooth muscle fibers compared to their venous counterparts and therefore respond more to the MAP changes; their principal role is to control CBF where the venous vessels act more like capacitance vessels and elicit an effect on the cerebral blood volume (CBV).

2.3.1.3 Endothelial

NO plays a vital role in the control of vascular tone. NO is formed from the precursor L-arginine within the inner layer of the blood vessel (endothelium). It passes by diffusion into the smooth muscle cells and triggers production of cGMP. cGMP promotes the uptake of Ca^{2+} via protein kinase G; the subsequent decrease in Ca^{2+} levels causes reduced vascular tone. Agents that block the nitric oxide synthase enzymes reduce NO levels and cause vasoconstriction. The endothelium also produces the vasodilators endothelial-derived hyperpolarizing factor (EDHF) and prostacyclin (PGI_2) and endothelin, which brings about vasoconstriction.

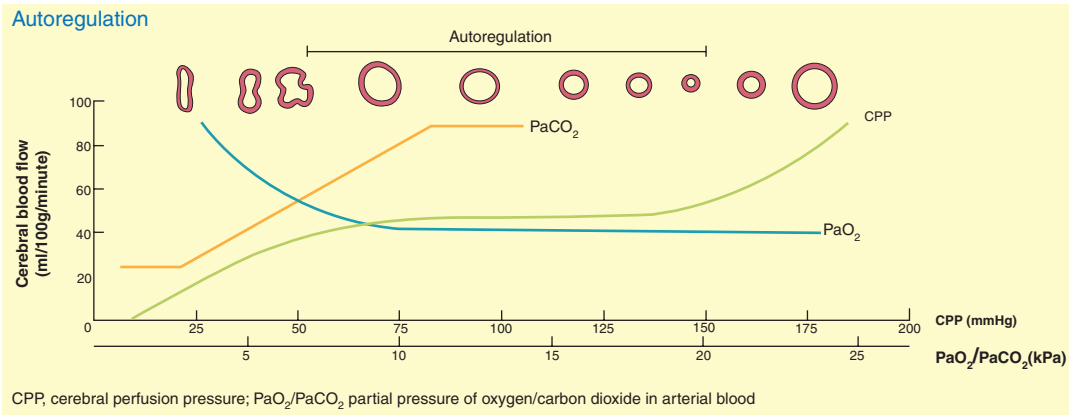

Fig. 2.3 Autoregulation curves. (Reprinted from Anesthesia and Intensive Care Medicine, 12(5), Sharlow E, Jackson, A. Cerebral blood flow and intracranial pressure, pp. 220–2, copyright 2011, with permission from Elsevier)

2.3.1.4 Metabolic

Carbon Dioxide Reactivity

As previously described CBF is extremely sensitive to changes in CO_2, a mechanism known as CO_2 reactivity [17, 18]. Hypocapnia causes cerebral vasoconstriction, and hypercapnia, conversely, causes vasodilatation. Hypocapnia lowers the autoregulation plateau with a small change in the lower limit of autoregulation (LLA), but so far there is no evidence to suggest any effect on the upper limit of autoregulation (ULA). Hypercapnia causes an upward shift in the plateau of autoregulation with a rightward shift of the LLA and a leftward shift of the ULA.

The manipulation of CO_2 levels can produce a profound effect with an increase or decrease of 4% CBF for each 1 mmHg change in $PaCO_2$. It is this reactivity which is the basis for hyperventilation, leading to a relative hypocapnia with subsequent vasoconstriction, as a temporizing measure in the management of acutely raised ICP.

Arterial Oxygen Tension

CBF increases vasodilatation in response to falling PaO_2 to compensate for reduced oxygen delivery (Fig. 2.3). The activation of oxygen-sensitive ion channels leads to release of vasoactive substances such as NO, adenosine, and prostacyclin that facilitate the compensatory vasodilatation. Clinically loss of consciousness may occur when the PaO_2 is ≤30 mmHg.

2.3.2 Cerebral Flow-Metabolism Coupling

As previously discussed, CBF is variable across the brain and significantly influenced by neuronal activity. Global or regional increases in activity lead to a proportional increase in blood flow. "Flow-metabolism coupling" is the term used to describe the matching of oxygen or glucose delivery to metabolic demand; this was described by Roy and Sherrington in 1890. Vasoactive metabolites are released in areas that have seen an increase in neuronal activity. The effect of these substances is to promote CBF by vasodilatation [19]. The substances that have been most closely investigated include adenosine, nitric oxide, and carbon dioxide, as well as histamine, potassium, and prostaglandins.

Table 2.1 Reference ranges for the constituents of CSF and plasma

	CSF	Plasma
Sodium (Na^+)	144–152 mmol/L	135–145 mmol/L
Potassium (K^+)	2.0–3.0 mmol/L	3.8–5.0 mmol/L
Glucose (fasting)	2.5–4.5 mmol/L	3.0–5.0 mmol/L
Calcium (Ca^{2+})	1.1–1.3 mmol/L	2.2–2.6 mmol/L
Magnesium (Mg^{2+})	1.2–1.5 mmol/L	0.8–1.0 mmol/L
Chloride (Cl^-)	123–128 mmol/L	100–110 mmol/L
Phosphate (PO_4^-)	0.4–0.7 mmol/L	0.81–1.45 mmol/L
Urea	2.0–7.0 mmol/L	2.5–6.5 mmol/L
Bicarbonate (HCO_3^-)	24–32 mmol/L	24–32 mmol/L
Protein	200–400 mg/L	60–80 g/L
pH	7.28–7.32	7.35–7.45
Osmolality	280–300 mmol/kg	275–295 mmol/kg
Specific gravity	1.006–1.008	1.010–1.020

2.4 Cerebrospinal Fluid

Cerebrospinal fluid (CSF) is a clear aqueous solution produced by the ependymal cells of the choroid plexus in the lateral, third, and fourth ventricles. It is produced at a rate of 0.35–0.40 mL/min (500–600 mL/day). Relative to plasma, CSF contains a higher concentration of Na^+, Cl^-, and Mg^{2+} ions, and a lower concentration of K^+, amino acids, uric acid, Ca^{2+}, PO_4^{2-}, and glucose (Table 2.1) [20].

The lower specific gravity of CSF (1.007) relative to brain tissue (1.040) reduces the effective mass of the brain from 1400 g to only 47 g, enabling it to support the brain and protect against acceleration and deceleration forces against the skull [20]. In addition, CSF also acts to supply neuronal tissue with nutrients such as glucose

and simple amino acids, maintains ionic homeostasis through active and passive transport of ions, and acts as an intracerebral transport system for neurotransmitters. CSF production within the choroid plexus occurs by ultrafiltration of plasma through fenestrated capillaries, with the addition of water and other dissolved substances by active transport across the blood: CSF barrier. As a result, production is partly dependent on CPP, with a pressure below 70 mmHg causing a reduction in CSF production due to the reduction in cerebral and choroid plexus blood flow [21].

CSF is circulated from the lateral ventricles to the third ventricle via the foramen of Monro. It then enters the fourth ventricle via the aqueduct of Sylvius, before passing into the subarachnoid space through the medial foramen of Magendie and the lateral foramina of Luschka in the roof of the fourth ventricle. CSF reabsorption occurs across arachnoid villi and arachnoid granulations, down a pressure gradient of ~6 cmH_2O between the CSF (mean pressure ~15 cmH_2O) and superior sagittal sinus (mean pressure ~9 cmH_2O). The low-pressure cerebral sinuses, together with their high blood flow velocity, create a "suction pump" effect that is thought to facilitate continued CSF reabsorption despite the normal fluctuations in CSF pressure that occur with movement and posture [20].

2.5 Intracranial Pressure

2.5.1 Introduction

Maintenance of adequate cerebral perfusion pressure (CPP) and control of intracranial pressure (ICP) are fundamental pillars of neuroanesthesia and neurocritical care. With correlation between raised ICP and worse outcomes demonstrated in patients with traumatic brain injury, perioperative and critical care control of ICP is a core skill of the neuroanesthetist [11, 22]. This section will address the anatomy of the intracranial compartment, pressure-volume relationships within the intracranial vault, and clinical features and causes of raised ICP.

2.5.2 Intracranial Pressure and the Pressure-Volume Relationship

Intracranial pressure is the pressure within the intracranial cavity relative to atmospheric pressure [23]. Normal ICP ranges from ~5 to 15 mmHg, with a significant variation between individuals and with posture.

ICP is a dynamic pressure waveform, with variation in amplitude due to cardiac and respiratory cycles. Within each wave there are three distinct phases, P1, P2, and P3, together known as the "vascular pulse." P1, the percussion wave, represents transmitted cerebral arterial pulsation from the choroid plexus. P2, the tidal wave, represents intracranial compliance, and P3, the dicrotic wave, represents aortic valve closure. During the respiratory cycle, there is variation in amplitude between consecutive waves, known as the "respiratory pulse" (Fig. 2.4). Pathological ICP waveforms are beyond the scope of this chapter.

The mean intracranial vault volume in an adult male is 1473 mL and consists of three main components: brain parenchyma (~85% of total intracranial volume), cerebral blood, and CSF [24]. Intracranial cerebral blood volume at any one time is ~100–130 mL (~10% of intracranial volume). Of the cerebral blood, 15% is arterial, 40% is venous, and 45% is within the microcirculation. Intracranial CSF accounts for ~75 mL (~5% of intracranial volume) [25]. ICP is therefore dictated by the volume of the components within the closed skull vault.

The Monro-Kellie doctrine, first described in the eighteenth century, and refined by Harvey Cushing in the twentieth century, hypothesizes that since the intracranial contents are contained within the rigid skull vault, any increase in the volume of one component must be offset by a reduction in the volume of the other component if the pressure is to remain the same [26–28]. The initial compensatory mechanism that ensures ICP remains controlled during intracranial volume increase occurs through volume buffering. Blood contributes most significantly to volume buffering, particularly in acute rises

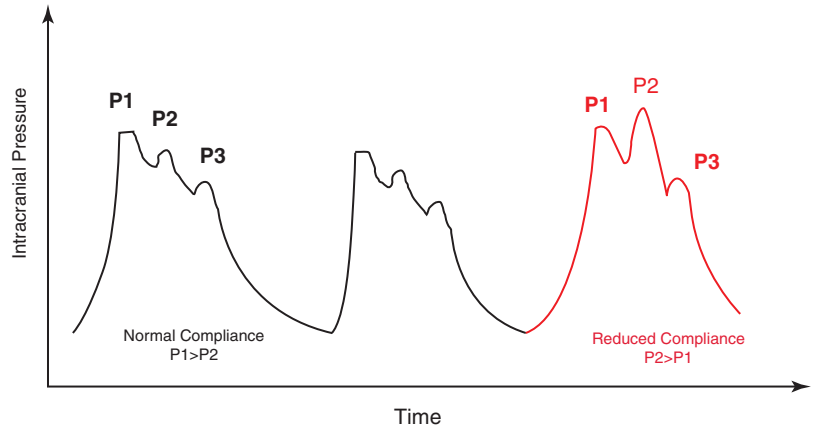

Fig. 2.4 Graph showing the three distinct phases of the ICP vascular pulse waveform. Within normal individuals P1 > P2 > P3. A reduction in intracranial compliance, for example, in brain injury, can be seen as a reversal of the P1:P2 ratio with P2 > P1 (shown in red)

in ICP, such as in traumatic brain injury. Compensatory mechanisms occur through increased cerebral venous outflow, decreased cerebral blood flow (CBF), and compression of intracranial venous sinuses. CSF volume buffering occurs through "spatial compensation," whereby intracranial CSF is displaced into the spinal canal. This occurs more slowly and is significant in slow increases in ICP such as intracranial tumor growth.

Once these compensatory mechanisms are exhausted, ICP increases rapidly. This decompensation phase leads to a reduction in CPP and focal brain compression. This can lead to cerebral ischemia, foramen magnum herniation, and brain stem death (Fig. 2.5).

Historically CSF and cerebral blood volume compensation have been given equal weighting within the Monro-Kellie doctrine, but this may be misleading to the dynamic reality, due to the disproportionately large cerebral blood flow (700 mL/min, 14% of cardiac output) in comparison to CSF production (0.35–0.40 mL/min) [25]. Afferent cerebral arterial inflow has traditionally been the focus of ICP management, through CPP manipulation. However, the contribution of the cerebral venous efferent drainage is significant and undervalued. Failure of adequate venous drainage to match afferent arterial inflow can lead to large increases in ICP. Causes of venous obstruction can be classified into focal intracranial causes (skull fracture, venous sinus thrombosis, cerebral edema, idiopathic intracranial hypertension) and extracranial causes (cervical and thoracoabdominal venous obstruction) [25]. Extracranial causes are of particular relevance to the neuroanesthetist. Cervical spine flexion and rotation cause a significant increase in ICP [29], and raised intrathoracic (e.g. positive pressure ventilation) and intra-abdominal pressure (e.g., prone positioning, abdominal compartment syndrome) will also increase cerebral venous pressure, thereby increasing ICP.

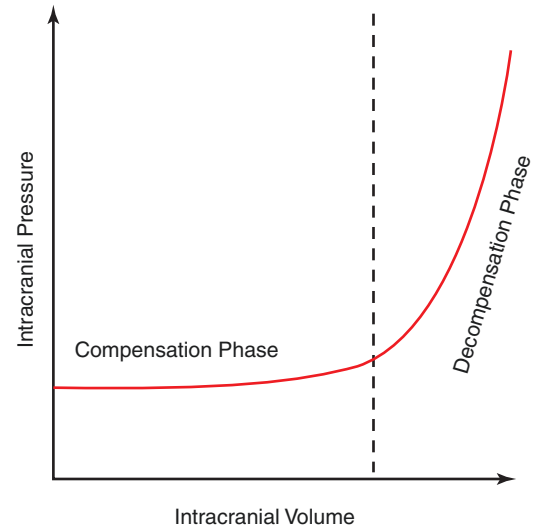

Fig. 2.5 Intracranial pressure-volume curve. Initial compensatory mechanisms ensure intracranial compliance ($\Delta V/\Delta P$) remains high. Once these compensatory mechanisms are exhausted, decompensation occurs as compliance reduces and intracranial pressure rapidly increases

Table 2.2 Causes of raised intracranial pressure

A. Increase in brain parenchyma volume	B. Increase in cerebral blood volume	C. Increase in CSF volume
Cerebral edema – Vasogenic – Cytotoxic – Interstitial	Increased cerebral arterial blood flow – Hypoxia – Acidosis – Hypercarbia	Reduced CSF reabsorption at arachnoid villi – Subarachnoid hemorrhage – CNS infection
Hemorrhagic lesions – Subdural, extradural and subarachnoid – Cerebral contusions	Decreased cerebral venous drainage – Intracranial: skull fracture, venous sinus thrombosis – Extracranial: cervical and thoracoabdominal venous obstruction	Obstructive hydrocephalus – Trauma – Neoplasm
CNS infection – Cerebral abscess – Subdural empyema		Increased CSF production – CNS infection

Classification based on changes to each of the three principle components of the intracranial vault: brain parenchyma, blood, and CSF

2.5.3 Causes of Intracranial Hypertension

Causes of raised ICP can be classified based on changes to each of the contributing component parts of the intracranial vault: brain parenchyma, blood, and CSF (Table 2.2).

2.5.4 Clinical Features of Raised Intracranial Pressure and Cushing's Reflex

Intracranial hypertension in the awake patient may manifest with headache, nausea and vomiting, abnormal posture, and reduced Glasgow Coma Score (GCS). As intracranial hypertension progresses, symptoms of brain herniation may occur. These can be supratentorial or infratentorial with reference to the tentorium cerebelli. Uncal herniation, an example of supratentorial herniation, occurs when the uncus of the temporal lobe descends across the temporal incisura, causing brain stem and posterior cerebral artery compression. The oculomotor nerve and corticospinal tracts are compressed, manifesting as unilateral papillary dilatation and contralateral hemiplegia. Progression of intracranial hypertension will eventually cause cerebellar tonsillar herniation, an example of infratentorial herniation, through the foramen magnum. This leads to lower brain stem and upper cervical spinal cord compression and can progress to brain stem death.

The cardiorespiratory effects of the brain stem compression manifest clinically as Cushing's triad. Cushing's triad describes the association of hypertension, bradycardia, and abnormal respiration (Cheyne-Stokes respiration) due to raised intracranial pressure [30]. Cushing's triad occurs due to Cushing's reflex. Critical intracranial hypertension causes brain tissue ischemia as the CPP falls. This leads to a hypothalamic mediated sympathetic hypertensive response in an attempt to maintain CPP. Hypertension-induced baroreceptor activation then results in a vagus nerve-mediated bradycardia. The bradycardia response however may not occur as frequently in mechanically ventilated patients [31]. Cushing's triad is a sign of impending brain stem herniation, and attempts to control the ICP should be undertaken rapidly. Management of raised ICP is beyond the scope of this chapter.

2.6 Pituitary Gland Physiology

The pituitary gland is the principle neuroendocrine organ of the body. The physiological effects of the pituitary gland are wide reaching and fundamental to hormonal homeostasis and reproduction. Situated outside the blood-brain barrier in the sella turcica of the sphenoid bone in the middle cranial fossa, the gland is divided embryologically and functionally into two distinct parts: the anterior pituitary (adenohypophysis) and the posterior pituitary (neurohypophysis). The average size of the gland in an adult is approximately 15 × 10 × 6 mm, weighing 500–900 mg [32]. The anterior pituitary is derived embryologically from Rathke's pouch and is further divided anatomically into the pars distalis, pars tuberalis, and pars

intermidia, occupying two-thirds of the total volume of the pituitary gland. Blood supply to the anterior pituitary is principally from the superior hypophyseal artery, a branch of the internal carotid artery. In addition, the hypothalamic-hypophyseal portal system, consisting of portal veins formed from capillaries of the inferior hypophyseal artery, connects the hypothalamus directly to the anterior pituitary gland. The posterior pituitary is derived from neural crest cells and is divided into the pars nervosa and the infundibulum. It occupies the remaining one-third of the pituitary gland and receives its blood supply from the inferior hypophyseal artery, another branch of the internal carotid artery.

The anterior pituitary gland secretes six peptide hormones. Their release is principally under the control of the hypothalamus, with hypothalamic trophic hormones stimulating the anterior pituitary directly via the hypothalamic-hypophyseal portal system. The posterior pituitary secretes two hormones and is stimulated by the hypothalamus via hypothalamic axons that synapse directly with the gland. In addition to hypothalamic stimulation, secretion from the pituitary gland is also under control of circulating hormones from the peripheral circulation. These act via negative feedback loops, which act to stimulate or inhibit hormone release from the pituitary gland and hypothalamus (Table 2.3).

Table 2.3 Site of action and metabolic effects of the pituitary hormones

	Site of action and metabolic effect	Release stimulated by	Release inhibited by
Anterior pituitary			
Adrenocorticotrophic hormone (ACTH)	Adrenal cortex: stimulates glucocorticoid and mineralocorticoid synthesis	Corticotrophin-releasing hormone (CRH), stress	Glucocorticoid (−ve feedback loop)
Growth hormone (GH)	Widespread effects on musculoskeletal system: stimulates lipolysis and gluconeogenesis and inhibits action of insulin	Growth hormone-releasing hormone (GHRH), stress, exercise, dopamine, hypoglycemia, glucagon	GH (−ve feedback loop), somatostatin
Thyroid-stimulating hormone (TSH)	Thyroid gland: stimulates thyroid hormone synthesis	Thyrotropin-releasing hormone (TRH)	Thyroid hormones (−ve feedback loop), somatostatin
Follicle-stimulating hormone (FSH)	Males: testes stimulates spermatogenesis Females: ovaries stimulates ovarian follicle growth	Gonadotrophin-releasing hormone (GnRH)	Testosterone (males), estrogen (females)
Luteinizing hormone (LH)	Males: testes stimulates testosterone production Females: ovaries stimulates luteinization of follicles and ovulation	GnRH, estrogen	Testosterone (males), estrogen and progesterone (females)
Prolactin (PL)	Mammary glands: stimulates milk production Ovaries: inhibits action of gonadotrophins	Prolactin-releasing hormone (PRLH), dopamine antagonists, stress, nipple stimulation/suckling, prolactin	Dopamine
Posterior pituitary			
Antidiuretic hormone (ADH)	Renal: distal tubule and collecting duct causing water reabsorption Vascular: arteriole vasoconstriction	Increase in extracellular fluid osmolality, thirst, activation of renin-angiotensin-aldosterone system, pain, hemorrhage	Decrease in extracellular fluid osmolality, alcohol
Oxytocin	Uterus: uterine contraction Breasts: lactation Kidneys: water retention	Nipple stimulation/suckling	Dopamine

Pituitary tumors most commonly present clinically in three distinct ways. Macroadenomas (>10 mm diameter) cause local mass effects (headache, visual disturbance, vomiting). Microadenomas (<10 mm diameter) typically present with hormone hypersecretion syndromes (e.g., acromegaly from excess GH production, Cushing's disease from excess ACTH production) or hormone hyposecretion syndromes (e.g., pituitary-related hypothyroidism). Due to the widespread systemic effects of hormonal excess or deficiency, it is vital that these patients are managed with close liaison between neuroanesthesia, endocrinology, and neurosurgery teams to ensure safe perioperative and postoperative care.

The pituitary gland is of particular relevance to the neuroanesthetist due to the complex endocrine challenges that patients requiring surgery for pituitary tumors present. In addition, dysnatremias, including cerebral salt-wasting syndrome and diabetes insipidus, are common after pituitary surgery and can be complex to manage in the neuro-intensive care unit.

2.7 Spinal Cord Physiology

This section is aimed at giving a brief overview of the fundamental anatomy and physiology of the spinal cord relevant to the neuroanesthetist, in particular physiological changes occurring with spinal cord injury.

2.7.1 Spinal Cord Anatomy

The spinal cord extends from the medulla oblongata at the foramen magnum to the conus medullaris and cauda equina at the level of L1/2 in an adult (L2/3 in a neonate) [33]. Thirty-one pairs of spinal nerves exit the spinal cord, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal. The function of the spinal cord is to carry motor and sensory information between the body and the brain. These pathways can be divided functionally into the somatic nervous system and the autonomic nervous system. The spinal cord in cross section shows a central "H"-shaped grey matter region surrounded by white matter. Grey matter contains neuron cell bodies and unmyelinated fibers and is divided functionally into ten laminae of Rexed (I to X) [34]. White matter contains the ascending and descending fiber tracts of the somatic nervous system.

The major motor pathway of the somatic nervous system is the corticospinal tract, which descends in the lateral and ventral white matter, as the lateral corticospinal tract and the anterior corticospinal tracts, respectively, before exiting the spinal cord in the ventral root of the spinal nerves. Two major sensory pathways ascend within the spinal cord white matter. The posterior columns, consisting of the fasciculus cuneatus and the fasciculus gracilis, transmit information concerning fine touch, proprioception, and vibration from the ipsilateral side of the body. The spinothalamic tracts, consisting of the anterior and lateral spinothalamic tracts, transmit sensory information concerning pain, temperature, and touch from the contralateral side of the body.

Intraoperative neurophysiologic monitoring (IONM) is now commonly used in spinal surgery to minimize the risk of iatrogenic damage to the spinal cord and spinal nerves during high-risk spinal surgery. Using various combinations of transcranial motor-evoked potentials, somatosensory-evoked potentials, and stimulated and spontaneous electromyelogram (EMG), IONM allows continual assessment of the sensory and motor somatic pathways while a patient is under general anesthesia [35]. It is essential the neuroanesthetist is aware of the effects that anesthesia and drugs have on IONM. Further discussion on this topic is beyond the scope of this chapter.

The arterial supply to the spinal cord is from the single anterior spinal artery, the paired posterior spinal arteries, branches of the vertebral and posterior inferior cerebellar arteries, respectively, and arterial vasocorona formed from anastomoses between the spinal arteries [36]. The anterior spinal artery supplies the anterior two-thirds of the cord, the posterior spinal arteries supply the posterior one-third of the cord, and the arterial vasocorona supplies the lateral aspect of the cord. In addition, the spinal cord receives

an extensive collateral supply from segmental arteries. These are formed from ascending cervical arteries, deep cervical arteries, posterior intercostal arteries, lumbar arteries, and lateral sacral arteries [36]. These segmental arteries form anastomoses with the spinal arteries to reinforce the blood supply to the cord. The most dominant thoracolumbar segmental artery is the artery of Adamkiewicz, also known as the arteria radicularis anterior magna. Pathology affecting the aorta (e.g., abdominal aortic aneurysm, aortic dissection, trauma) can lead to interruption of the artery of Adamkiewicz, causing cord ischemia and infarction. Venous drainage of the spinal cord broadly follows the arterial supply, draining into the internal vertebral plexus within the epidural space, before further drainage into the dural venous sinuses and cerebral veins and the external vertebral plexus [36].

2.7.2 Spinal Cord Perfusion Pressure

In addition to early operative intervention to realign the vertebral bodies and improve spinal cord perfusion, management of acute traumatic spinal cord injury (TSCI) also focuses on maintenance of adequate spinal cord perfusion pressure to prevent secondary cord injury. Analogous to cerebral perfusion pressure in traumatic brain injury, spinal cord perfusion pressure can be defined as:

$$\begin{aligned}&\text{Spinal Cord Perfusion Pressure}(\text{SCPP})\\&= \text{Mean Arterial Pressure}(\text{MAP})\\&\quad - \text{Intraspinal Pressure}(\text{ISP})\end{aligned} \tag{2.4}$$

Previously there has been a weak evidence to support augmenting the MAP to maintain SCPP [37]. While recognizing the paucity of high-quality evidence, the joint guidelines of the American Association of Neurological Surgeons and Congress of Neurosurgical Surgeons recommend maintaining a MAP of 85–90 mmHg for 5–7 days after TSCI [38]. There is now increasing evidence to advocate the use of intraspinal pressure probes in acute TSCI to individualize SCPP [39]. This approach is analogous to using ICP monitoring for CPP-guided management in TBI. Inserted subdurally at the site of injury during operative stabilization, the probes allow direct measurement of ISP. This allows an individualized approach to maintaining an adequate SCPP through augmenting MAP with vasopressors or inotropes or reducing ISP through laminectomy. Recent data suggests that maintaining a SCPP above 50 mmHg is a strong predictor of improved neurologic recovery following spinal cord injury [40].

2.7.3 The Autonomic Nervous System

The autonomic nervous system controls involuntary visceral functions of the body and consists of the sympathetic and parasympathetic nervous system. The actions of the sympathetic and parasympathetic nervous systems are functionally antagonistic, with the sympathetic nervous system controlling the "fight-or-flight" visceral response and the parasympathetic nervous system the "rest and digest" response [34]. The autonomic nervous system relies on reflex arcs. These consist of an afferent limb, which relays information from sensory receptors (e.g., baroreceptors in the carotid sinus) to the central integration point, which then relays information to the efferent limb, consisting of preganglionic and postganglionic fibers and autonomic ganglion [41]. This efferent limb is anatomically and functionally divided into the sympathetic and parasympathetic nervous systems. All preganglionic fibers within the autonomic nervous system are myelinated, while postganglionic fibers are unmyelinated.

Preganglionic fibers of the sympathetic nervous system originate in the lateral horns of the grey matter of the spinal cord between T1 and L2/L3, known as the thoracolumbar outflow, and synapse with postganglionic neurons in the ganglia of the paravertebral sympathetic chain [41]. Postganglionic adrenergic neurons join visceral or spinal nerves, releasing predominantly noradrenaline to stimulate adrenergic receptors in target organs. The preganglionic fibers of the

parasympathetic nervous system arise from the "craniosacral" outflow, consisting of cranial nerves III, VII, IX, and X, and sacral nerves from the S2 to S4 sacral segments of the spinal cord [41]. These release acetylcholine to act at nicotinic and muscarinic acetylcholine receptors in target organs.

Pathophysiology affecting the autonomic nervous system of particular relevance to the neuroanesthetist is neurogenic shock in acute spinal cord injury and autonomic hyperreflexia.

2.7.4 Neurogenic Shock

Neurogenic shock describes a type of distributive shock that occurs in spinal cord trauma due to interruption of the thoracolumbar sympathetic outflow in cervical and high thoracic spinal cord injuries. Damage to the cord above T6 leads to loss of cardiac sympathetic nervous system innervation and loss of sympathetic vasomotor tone. Neurogenic shock manifests clinically as a triad of hypotension, bradycardia (due to unopposed vagal stimulation), and peripheral vasodilatation and may persist for 1–6 weeks after injury [42]. Diagnosis should only be considered after exclusion of hemorrhagic shock in the trauma patient, and hypotension should be corrected to prevent end-organ damage and secondary spinal cord ischemia.

2.7.5 Autonomic Dysreflexia

Autonomic dysreflexia (also known as autonomic hyperreflexia) occurs in 50–70% of patients with spinal cord injuries above T6 [43]. Severe hypertension and bradycardia occur due to a disorganized sympathetic response to noxious stimuli below the level of injury [44]. Eighty percent of episodes are triggered by bladder distension. Additional causes include bowel distension, pressure sores, and surgical noxious stimuli [43]. Management is focused on removal of the stimulus and control of hypertension to prevent end-organ damage.

Key Points

- The brain relies heavily on aerobic metabolism for ATP production and has very limited glycogen stores. Ischemic insults are tolerated poorly.
- Cerebral autoregulation is the process by which the cerebral vasculature maintains a constant cerebral blood flow across a range of cerebral perfusion pressures. This occurs through four principle mechanisms: neurogenic, myogenic, endothelial, and metabolic. Carbon dioxide has the greatest direct effect on cerebral blood flow.
- Compensatory mechanisms occur to maintain ICP during intracranial volume changes. Once these mechanisms are exhausted, ICP rises rapidly, leading to a reduction in cerebral perfusion pressure and focal brain compression.
- Patients with pituitary gland disease can present a number of challenges to the neuroanesthetist and require a multidisciplinary approach to management.
- Neurogenic shock and autonomic dysreflexia occur in spinal cord injury. Attention should be paid to MAP after traumatic spinal cord injury to maintain an adequate spinal cord perfusion pressure.

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3 Pharmacological Considerations in Neuroanesthesia

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3.1 Introduction

Anesthetic agents and their adjuncts help to provide sedation, immobility, adequate analgesia, and amnesia in patients undergoing surgical interventions. In neurosurgical patients, special consideration should be made for facilitating intraoperative neurophysiological monitoring, optimizing cerebral hemodynamics, and allowance for rapid emergence from anesthesia to allow for timely evaluation of a neurological exam. In addition, some procedures require active participation from the patient to isolate specific areas of the brain for targeted manipulation. This situation requires a lighter level of sedation while still addressing pain control and some level of amnesia. Taking advantage of drug-specific pharmacokinetic and pharmacodynamic parameters allows anesthesiologists to achieve these goals during surgery. However, certain disease states and conditions may alter kinetic profiles of anesthetic agents resulting in oversedation and prolonged emergence from anesthesia.

The ideal anesthetic agent would be quick in onset, rapidly metabolized with minimal dependence on hepatic or renal function, have no active metabolites, have minimal drug interactions, and have minimal side effects such as nausea or vomiting which can increase intracranial pressure (ICP). The ideal agent would also have minimal effects on mean arterial pressure (MAP) while still allow optimal cerebral perfusion pressure (CPP) and cerebral blood flow (CBF). While there is no such ideal agent, the use of multiple agents customized to the patient's needs and type and length of surgery can achieve many of these goals.

This chapter will review some considerations for anesthesia in neurosurgical procedures beginning with some conditions that may affect drug dosing, followed by drug class-based considerations, and then periprocedural considerations. Information regarding specific anesthetic procedures and agents will be discussed in future chapters.

3.2 Obesity

Many drugs have fixed dosing that is determined by healthy hepatic and renal function and average weight. Obesity can be defined as a body mass index (BMI) >30 kg/m^2, while morbid obesity is defined as a BMI >40 kg/m^2. These conditions can have significant implications for dosing

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highly lipophilic medications. Unfortunately, many drug studies exclude the obese patient population, making dosing in these patients very challenging. Certain physiological parameters are increased in obesity such as gastric emptying, cardiac output, and hepatic blood flow which can affect drug delivery and distribution factors [1]. Hepatic and renal clearances are affected to various degrees in obesity making it difficult to provide dosing recommendations. Although the volume of distribution (V_d) of lipophilic drugs may be expected to increase with weight, it also is dependent on other factors such as ionization properties and protein binding. For certain anesthetic agents, specific scalars have been recommended for use when dosing in obese patients (see Table 3.1). The most commonly used equation for LBW:

$$\text{MALE}(\text{kg}):\left[9.27\times10^{3}\times\text{TBW}\right]/\left[6.68\times10^{3}+216\times\text{BMI}\right]$$

$$\text{FEMALE}(\text{kg}):\left[9.27\times10^{3}\times\text{TBW}\right]/\left[8.78\text{X}10^{3}+244\times\text{BMI}\right]$$

where TBW is total body weight and BMI is body mass index (defined as [TBW in kg]/[height in meters]^2).

3.3 Hypothermia

Targeted temperature management (TTM) has been used in a variety of clinical settings and ranges from therapeutic hypothermia (often seen after cardiac arrest) to intraoperative cooling [4]. Hypothermia has been reported to protect the brain from ischemia during vascular neurosurgery [5], although this is seldom performed in current practice. A recent review found no benefit on mortality or neurological disability with induced hypothermia in neurosurgical procedures. However, considerations should be made for patients undergoing various forms of targeted temperature management (TTM) who require neurosurgical interventions.

Decreasing the body temperature to 32–34 °C has significant effects on the pharmacokinetic parameters of many anesthetic agents. Cardiac output is typically decreased, and the distribution of lipid soluble drugs into fat can be diminished. Hepatic blood flow and intrinsic enzyme activity are typically decreased in hypothermia resulting in decreased bioactivation and metabolism of many drugs. High extraction drugs (e.g., propofol, fentanyl) are dependent on hepatic blood flow for clearance from the blood and will require smaller cumulative doses. Renal clearance is not well understood, and therefore renal drug disposition for anesthetics in the setting of hypothermia is unknown.

3.4 Opioids

Morphine is the main opioid used in clinical practice with all others compared to it as the standard. It provides mainly analgesia and sedation through its agonist effects at the mu receptor (μ). Its half-life is approximately 2–4 h after a single dose making it useful in controlling pain, especially in the intensive care unit (ICU). Several synthetic variants of morphine have been created for use in surgery that have shorter half-lives, allowing for more rapid emergence from anesthesia. Alfentanil, fentanyl, and sufentanil have about 2-h half-lives, while remifentanil has a half-life of 3–10 min. All the opioids are renally excreted, but morphine and fentanyl have recommendations for adjustment in patients with renal dysfunction to prevent oversedation. Morphine has an active metabolite which may be decreased in patients with hepatic dysfunction, but may accumulate in renal dysfunction.

Considerations must be made in dosing anesthetic agents in obese patients since the proportion of fat to lean body tissue does not increase linearly with increasing weight [6]. Many anesthetic agents are lipophilic and will readily enter into the central nervous system causing sedation or analgesia but also redistribute to other fatty tissues, making dosing in obesity somewhat challenging. The use of lean body weight (LBW) or

Table 3.1 Drugs used in neuroanesthesia—pharmacokinetic parameters and dosing considerations

Drug	Intracranial effects	Half-life	Metabolism	Elimination	Dosing in obesity [2, 3]	Effect of hypothermia
Morphine	↔ CMR ↔ CBF ↑ ICP	2–4 h	Hepatic > active metabolite	Renal (2–12% unchanged) Bile/feces (7–10%)		Increased half-life; decreased systemic clearance
Fentanyl	↔ CMR ↔ CBF ↑ ICP	3.7 h	Hepatic (CYP3A4 substrate) > inactive metabolites	75% renal (10% unchanged) 9% feces	Use LBW	Increased serum concentration
Alfentanil	↔ ICP	1.5–1.8 h	Hepatic (CYP3A4 substrate)	Renal (1% unchanged)	Use LBW	
Sufentanil	↔ ICP	2.7 h	Hepatic (CYP3A4 substrate) Small intestine	Renal (<2% unchanged)	Use IBW	
Remifentanil	↔ CBF ↔ ICP	3–10 min	Blood Tissues Hepatic	Renal	Use IBW	Decreased systemic clearance
Midazolam	↓ CMR ↓ CBF ↓ ICP	3 h	Hepatic > active metabolite	Renal (<1% unchanged	TBW (loading dose) IBW (maintenance dose)	Decreased systemic clearance
Propofol	↓ CMR ↓ CBF ↓ ICP	Initial: 25–56 min Terminal: 184–309 min	Hepatic (CYP2B6 substrate)	Renal	TBW	Increased serum concentration
Thiopental	↓ CMR ↓ CBF ↓ ICP	3–26 h	Hepatic	Renal	LBW	

ideal body weight (IBW) is recommended for alfentanil, sufentanil, and remifentanil to avoid overdosing and unnecessary prolonged sedation. Because these agents are highly lipophilic, their pharmacodynamic effects (i.e., sedation) may be achieved without regard to plasma concentrations which tend to be higher when dosed based on total body weight (TBW).

Therapeutic hypothermia can decrease the metabolic activity of the liver and kidneys, reducing their ability to metabolize and eliminate active drug and metabolites [7]. Hypothermia has been found to decrease the total body clearance of morphine and fentanyl [8], requiring a decrease in infusion rates. Upon rewarming, serum concentrations were reported to decrease, indicating restoration of normal total body clearance, primarily via phase II glucuronidation [9].

3.5 Benzodiazepines

Of all the benzodiazepines, midazolam is used most often in anesthesia due to its short half-life compared to diazepam and lorazepam. However, midazolam has an active metabolite that is renally cleared, so caution must be taken when dosing in patients with renal dysfunction to avoid unnecessary accumulation and prolonged sedation. In obese patients, midazolam clearance does not seem to differ compared to nonobese patients. However, volume of distribution (V_d) and half-life are increased significantly in obese patients. As a result, bolus dosing (i.e., for induction) should be performed using total body weight to adjust for the higher V_d. During therapeutic hypothermia, midazolam clearance decreases [7] but returns to normal upon rewarming [10].

3.6 Propofol

Propofol is an intravenous anesthetic agent that has also been used for sedation in intensive care units. It has multiple mechanisms of action including antagonistic effects at the NMDA receptor. It has been used for induction and maintenance of total IV anesthesia in many cases due to its rapid onset of action and short duration of action, primarily due to its lipophilicity. Current dosing is based on total body weight, even in obese patients. Therapeutic hypothermia results in an increase in serum propofol concentrations [11] as a result of a decrease in total body clearance by about 30%.

One of the rare fatal complications seen with propofol therapy is propofol-related infusion syndrome (PRIS) which is characterized by acidosis, acute heart failure, and rhabdomyolysis [12]. Although PRIS is seen mostly in the ICU with prolonged (>48 h) or high doses (>75 μg/kg/min), it has been described postoperatively [13, 14]. Lipemic blood during or after a lengthy surgery may indicate potential adverse effects from prolonged use of propofol and should be addressed [15]. Liver function tests, triglycerides, and arterial blood gases should be monitored postoperatively.

3.7 Volatile Anesthetics

Inhalational anesthetics can be used during induction or maintenance of anesthesia in neurosurgical procedures where they are associated with an increase in cerebral blood flow due to vasodilation [16]. This may result in an increase in intracranial pressure, although they also produce a decrease in cerebral metabolic rate of oxygen consumption (CMRO2). Their mechanisms of action include inhibition at acetylcholine and glutamine receptors and enhancement of excitatory $GABA_A$ and glycine receptors [17]. Agents available for use include enflurane, isoflurane, desflurane, and sevoflurane. Mean arterial pressure, cardiac output, and systemic vascular resistance are typically unaffected (or reduced) with inhaled anesthetics, although arrhythmias have been reported with enflurane. Sevoflurane seems to cause the least issues with ICP and cerebral autoregulation and may be considered a preferred anesthetic agent in neurosurgery [18, 19] Consideration should be given to monitoring for malignant hyperthermia

and postoperative nausea and vomiting which are highly associated with volatile anesthetics. In terms of drug interactions, concomitant administration of opioids and benzodiazepines can effectively lower the requirements of an inhalational agent in a patient.

For certain procedures, inhaled agents may not be optimal when compared to intravenous regimens. One study of craniotomy for brain tumors found that a propofol-containing regimen resulted in lower ICPs and higher CPPs when compared to regimens containing either isoflurane or sevoflurane [20]. Propofol may have additional benefits in faster recovery, lower incidence of postoperative nausea and vomiting, and neuroprotection when compared to volatile anesthetics [21].

3.8 Paralytics

Neuromuscular blockade can facilitate endotracheal intubation, promote ventilator synchrony, and ensure a fixed and immobile surgical field. They may also slow recovery and wakefulness after surgery where they can obtund the neurological exam and are not appropriate for functional procedures. Two classes of paralytics are available—depolarizing (succinylcholine) and non-depolarizing (vecuronium, atracurium, cisatracurium, rocuronium). Succinylcholine may cause increases in intracranial pressure that can be minimized by premedication with lidocaine or a defasciculating dose of rocuronium. Of the non-depolarizing agents, only cisatracurium has a non-organ-dependent method of metabolism via serum esterases (Hofmann elimination). The others are hepatically metabolized and renally cleared to varying extents. Hypothermia has been reported to decrease the clearance of cisatracurium [22], rocuronium [23], and vecuronium [24], extending their duration of action by two-fold and potentially delaying postoperative recovery. Increased dosing of paralytics may be necessary in patients on concomitant phenytoin due to possible hepatic induction or effects at the neuromuscular junction [21].

3.9 Anticonvulsants

Patients undergoing neurosurgery are often given or are receiving anticonvulsant medications for seizure prophylaxis or to treat epilepsy. The two most commonly prescribed are phenytoin and levetiracetam. Phenytoin can be loaded intravenously before surgery (15–18 mg/kg) with maintenance dosing (5 mg/kg/day) starting 12 h afterward if needed. The rate of infusion must not exceed 50 mg/min due to hypotension. Fosphenytoin, a prodrug of phenytoin, can be infused three times as fast (150 mg phenytoin equivalents/min) or given intramuscularly. Levetiracetam loading is not necessary due to the relatively fast onset of action after a single maintenance dose. However, large single doses of 60 mg/kg have been well tolerated when given intravenously [25]. Unlike phenytoin, it must be adjusted for patients with renal disease. It has very few cardiorespiratory side effects and drug interactions.

3.10 Premedications

Induction agents such as barbiturates and narcotics may cause respiratory depression with a resultant increase in $PaCO_2$, which causes an increase in cerebral blood flow (CBF) and cerebral blood volume and ultimately may lead to increases in intracranial pressure (ICP) [26]. Premedication must be cautiously used or even avoided in procedures requiring strict ICP control.

3.11 Positioning

During the process of positioning for a surgical procedure, one may encounter many changes in blood pressure that may require treatment. Specifically, when headpins are being inserted, the provider should be ready to treat any rapid changes in heart rate or blood pressure to avoid complications such as intracranial hemorrhage or increases in ICP. The anesthesiologist may choose to deepen the anesthetic plane or administer additional boluses of IV agents that act rapidly (e.g., remifentanil, esmolol, propofol).

3.12 Induction and Airway Management

Intravenous induction is the preferred route and any of the short-acting induction agents (e.g., propofol, etomidate) and can be administered provided these agents are carefully titrated to avoid sudden changes in blood pressure [27]. Short-acting opioids like fentanyl or alfentanil are also used in induction.

Airway management/instrumentation in neurosurgical patients is critical, especially in those with an unstable cervical spine or raised intracranial pressure. Part of successful airway management involves careful selection of pharmacologic agents. In order to blunt laryngoscopic response to intubation, agents such as high-dose narcotics (e.g., fentanyl, 5–10 μg/kg), β-adrenergic antagonists (e.g., esmolol, 0.5 mg/kg), labetalol (10–20 mg), IV (1.5–2.0 mg/kg) or topical lidocaine [28], a second dose of propofol (0.5–1 mg/kg), or a deep level of an inhalation anesthetic such as isoflurane or sevoflurane are considerations.

3.13 General Anesthesia

Various anesthetic agents have unique systemic and cerebral pharmacodynamic effects and specific pharmacokinetic profiles. Several factors including patient characteristics, underlying neurologic pathology, anticipated surgical intervention, and use of intraoperative neuromonitoring will determine the choice of pharmacologic agents. Often a balanced anesthetic technique is implemented which combines potent, short-acting opioids with volatile agents or intravenous hypnotic agents. The ideal anesthetic agent should not increase the ICP and must be well controllable in order to achieve rapid postoperative emergence and to facilitate extubation of the patient. Despite the lack of strong evidence, pharmacologic burst suppression is frequently used to provide intraoperative neuroprotection in the setting of global and focal cerebral injury and in cases of cerebrovascular disease. Agents such as propofol, thiopentone, or etomidate are often used to achieve this goal and are titrated using continuous electroencephalography (EEG).

3.14 ICP Management

Intraoperative management of intracranial pressure includes osmotherapy, hyperventilation, appropriate positioning, drainage of cerebrospinal fluid, maintaining hemodynamic stability, and adequate depth of anesthesia. With acute life-threatening intracranial hypertension, one can initiate hyperventilation prior to implementing osmotic diuretics or deepening the anesthetic. If the ICP is elevated preoperatively, it is wise to avoid volatile agents, since these have vasodilating properties and can lead to further increases in ICP. Another reason to avoid volatile agents is if the surgical area of interest is deep or difficult to access to improve operating conditions for the surgeon. In patients with a history of postoperative nausea and vomiting (PONV), avoidance of inhalational anesthetics and use of total intravenous anesthesia (TIVA) can be beneficial since vomiting can increase ICP.

3.15 Emergence/Post-op

Postoperatively it is the key to diagnose complications such as intracranial hemorrhage or cerebral edema in the awake patient in a timely manner; therefore, we use controllable anesthetic agents such as propofol, sevoflurane, or desflurane.

3.16 Conclusion

Various pharmacological considerations should be made with agents used in neuroanesthesia as a result of changes in metabolism or elimination, presence of drug interactions, obesity, or targeted cerebrovascular activity. Adjustments to dosing or use of alternative agents can ensure timely and rapid recovery to allow for a proper neurological examination in the postoperative period.

Key Points

- Renal and hepatic dysfunction may prolong effects of many anesthetic and paralytic agents, requiring dosage adjustments.
- Shorter-acting opioids and benzodiazepines are used to facilitate postoperative emergence and allow an earlier neurological assessment.
- Volatile anesthetic agents may increase intracranial pressure (ICP) due to vasodilation, whereas parenteral anesthetics such as propofol can lower ICP as well as provide burst suppression.

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Part II

Neuromonitoring

4 Intraoperative Monitoring of the Brain

Hironobu Hayashi and Masahiko Kawaguchi

4.1 Introduction

Intraoperative brain monitoring is a standard of care in order to minimize neurological morbidity in a variety of neurosurgeries such as resection of tumor and vascular malformations, aneurysm clipping, microvascular decompression, and epilepsy surgery. As of today, different possible modalities of intraoperative brain monitoring include intracranial phenomenological monitoring (e.g., intracranial pressure, cerebral perfusion pressure, and cerebral blood flow) and more advanced monitoring such as brain oxygenation, metabolism, and function during neurosurgical procedures with a risk of postoperative brain complications (Table 4.1). Since the specific modalities of brain monitoring have a direct interaction with anesthetic agents and physiologic parameters, the anesthesiologist needs to achieve the goals of anesthesia including unconsciousness, amnesia, immobility, antinociception, muscle relaxation, and physiological stability while allowing effective monitoring. This chapter will review the outline and recent evidence of intraoperative brain monitoring (intracranial pressure, transcranial Doppler, near-infrared spectroscopy, electroencephalography, somatosensory evoked potential, myogenic motor evoked potential, auditory brainstem response, and visual evoked potential) and the interactions between the anesthetic agents and the specific brain monitoring modalities to be monitored.

Table 4.1 Multimodalities of intraoperative brain monitoring

	Clinical practicability	Temporary resolution	Invasiveness
Monitoring of the neurological function			
Electroencephalography	++	High	–
Evoked potential	+++	High-low	±
Monitoring of cerebral oxygen delivery			
Regional cerebral saturation	+++	High	–
Mixed venous oxygen saturation	+	High	+
Monitoring of cerebral blood flow			
Transcranial Doppler	±	Low	–
Monitoring of driving pressure			
Intracranial pressure monitoring	±	Low	+

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4.2 Intracranial Pressure

Intracranial pressure (ICP) is the pressure in the brain tissue or supratentorial cerebrospinal fluid. The intracranial cavity is a closed space surrounded by the skull and contains brain parenchyma (70% of the intracranial volume), blood (15%), and cerebrospinal fluid (15%). Changes in ICP are dependent on volume changes in one or more of the intracranial components. In compensatory phase, ICP is maintained within a normal range by volume distribution and elasticity of the intracranial components even though the intracranial volume of one or more intracranial components increases. When the compensatory mechanism collapses (non-compensatory phase), ICP rises and causes intracranial hypertension. ICP monitoring allows early detection of cerebral edema and initiation of immediate therapeutic intervention.

Elevated ICP is seen in patients with traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, malignant brain tumor, hydrocephalus, meningitis, and encephalitis. ICP monitoring can be used for evaluation and treatment of intracranial hemodynamics in such cases. The presence of ICP monitoring allows calculation of cerebral perfusion pressure (CPP), which is important. CPP is calculated by subtracting ICP from the mean arterial blood pressure. Monitoring ICP and CPP is fundamental in management, especially for traumatic brain injury [1, 2]. In severe cases of traumatic brain injury, decreased CPP resulted from elevated ICP is associated with mortality or poor clinical outcome. While ICP monitoring is frequently used in the intensive care unit, implementation of ICP monitoring during surgery enables anesthetic management based on CPP. In emergency craniotomy for removal of hematoma, intraoperative evaluation of CPP may lead to prediction of outcome [3].

4.2.1 Methodology of Intracranial Pressure Monitoring

For ICP catheter placement site, the ventricle, brain parenchyma, subdural space, and subarachnoid space are available, but the accuracy and risk of complications are different among the placement sites (Table 4.2). ICP monitoring using intraventricular catheter or brain parenchymal microtransducer device is more accurate and frequently used. Intraventricular monitoring allows therapeutic cerebrospinal fluid drainage, but it has a risk of placement-related hemorrhage and catheter-associated ventriculitis. When the ventricle is deviated, excluded, or narrowed, ventricular catheter insertion can be difficult. Brain parenchymal monitoring is easy to insert, but it has a risk of hemorrhage and infection and high medical expense of the use of microtransducer. Subdural space monitoring is low-invasive with no risk of brain hemorrhage, but the catheter may be occluded due to its thinness and cause malfunction. Moreover, insertion may be difficult in patients with elevated ICP. Subarachnoid space monitoring is also low-invasive with no risk of brain hemorrhage, and collection of cerebrospinal fluid is possible, but observation of pressure waveforms is likely to be difficult because the catheter is thin. The common consensus for normal range of ICP is 5–15 mmHg. ICP of 15–25 mmHg may be considered tolerable, 25–40 mmHg is severely elevated, and over 40 mmHg cannot be tolerated for extended duration of time.

Table 4.2 Intracranial pressure sensor insertion site, complication, reliability, and cost

Placement site	Bacterial infection	Brain hemorrhage	Occlusion and dysfunction	Reliability	Cost
Ventricle	10–17%	1.1%	6.3%	High	Low price
Brain parenchyma	14%	2.8%	9%		High price
Subdural space	4%	0%	10%		High price
Subarachnoid space	5%	0%	16%	Low	Low price

Partial modification from J Neurotrauma 2007; 24: S1–106

4.2.2 Intracranial Pressure Monitoring in Patients with Severe Traumatic Brain Injury

The Fourth Edition of the *Brain Trauma Foundation's Guideline for the Management of Severe Traumatic Brain Injury* recommends an ICP threshold >22 mmHg for initiation of ICP-lowering treatment in patients with severe traumatic brain injury and management target CPP of 60–70 mmHg [1]. Blood pressure management is also described, in which maintenance of systolic blood pressure ≥100 mmHg and ≥110 mmHg are recommended for 50–69 years old and 15–49 years old or 70 years or older, respectively. In the BOOST-II study, survival and neurological outcomes of severe traumatic brain injury patients were more favorable in those with multimodal ICP management and brain tissue oxygenation monitoring than those with ICP monitoring alone [4].

4.2.3 Intracranial Pressure Monitoring in Patients with Nontraumatic Brain Injury

ICP may be elevated by subarachnoid hemorrhage, brain hemorrhage, malignant brain tumor, hydrocephalus, meningitis, encephalitis, ischemic brain injury, and metabolic encephalopathy. Although no standardized guidelines, indication, or target of treatment have been established, unlike those for traumatic brain injury, a Glasgow Coma Score (GCS) ≤8, imaging findings of cerebral edema, aggravation of neurological symptoms, and mass effect are considered the indications of ICP monitoring for nontraumatic brain injury [5]. Basically, the condition is managed to maintain ICP <20 mmHg and CPP >60 mmHg.

ICP monitoring is frequently used for high-grade subarachnoid hemorrhage. Since ICP elevation (>20 mmHg) is often associated with acute hydrocephalus after subarachnoid hemorrhage, for ICP measurement, ventricular monitoring is preferable to enable cerebrospinal fluid drainage [6]. ICP <20 mmHg is associated with a favorable outcome after 6 months [7], and ICP >20 mmHg has been reported to increase the risks of death and poor outcomes [7, 8].

4.3 Transcranial Doppler

Transcranial Doppler (TCD) is a noninvasive method capable of continuously monitoring cerebral circulation at bedside. Low-frequency (2 MHz) ultrasound used for TCD monitoring transcranially propagates in the brain, but TCD is not used for monitoring of the brain tissue structures but used only for monitoring of cerebral blood vessels because the spatial resolution of TCD is insufficient. By measuring blood flow in the intracranial major arteries, the blood flow velocity as a cerebral circulatory index and microembolic signals (MES) associated with the stroke risk can be monitored. Mainly, the middle cerebral artery is monitored through the transtemporal approach. The biggest difference from other monitoring of cerebral circulation is that MES can be evaluated. Actually, the importance of TCD can be understood from the fact that most postoperative neurological complications are due to embolization, and a smaller percentage are due to hemodynamic factors. In neurosurgery, TCD is used during carotid artery and cerebral vascular bypass surgeries. In the postoperative management and intensive care fields, TCD is used to measure the cerebral blood flow velocity to detect vasospasm and hyperperfusion syndrome.

4.3.1 Methodology of Transcranial Doppler Monitoring

The frequency best suited for TCD application is on the order of 2 MHz. Although a versatile probe for echocardiography may be used, for monitoring of time-course changes in cerebral blood flow and microembolic signals during surgery, which requires prolonged monitoring, fixation of the probe is easy using a device exclusive for TCD, facilitating highly reliable TCD monitoring.

Table 4.3 Characteristics of cerebral blood vessels detected by transcranial Doppler

Window	Blood vessel	Depth (mm)	Blood flow velocity (cm/s)	Direction of blood flow
Temporal bone	Middle cerebral artery	45–55	60 ± 12	Toward
	Anterior cerebral artery	55–75	50 ± 12	Away
	Posterior cerebral artery	65–80	40 ± 11	Toward/away
Orbit	Ophthalmic artery	30–50	30 ± 10	Toward
	Internal carotid artery	55–70	50 ± 15	Toward/away
Foramen ovale	Vertebral artery	65–85	40 ± 10	Away
(Suboccipital)	Basilar artery	>85	40 ± 10	Away

Toward: Blood flow direction toward the probe, away: blood flow direction leaving the probe

The cerebral blood vessel is identified based on the window (region to which the probe is attached), direction of the probe, depth of the blood vessel, blood flow velocity, and direction of blood flow (Table 4.3). For example, when the depth is set at about 50 mm beforehand, the probe is placed on the patient's temple vertically to slightly anterior upward, and blood flow toward the probe is detected, it is the middle cerebral artery. However, the vessels cannot be properly identified in up to 10–30% of cases because ultrasound cannot sufficiently penetrate from the window due to the thickened skull. Especially, TCD monitoring is difficult in the elderly due to the thickened skull.

4.3.2 Transcranial Doppler Monitoring During Carotid Endarterectomy and Postoperative Management

When a large decrease in the cerebral blood flow velocity is detected on the operation side during cross-clamping of the carotid artery by TCD monitoring, shunt placement and countermeasures against cerebral ischemia elevating blood pressure are considered to maintain cerebral blood flow [9]. In addition, the occurrence of postoperative stroke can be predicted by evaluating reduction of the cerebral blood flow velocity and by evaluation of MES during surgery. In a systematic review, the diagnostic odds ratio of postoperative stroke was 4.0 (95% CI: 2.2–7.5) when changes in TCD (either the middle cerebral artery velocity or MES) were observed during surgery, compared with that with no changes in TCD [10]. Furthermore, TCD can be used to diagnose and predict cerebral hyperperfusion syndrome in which headache, convulsion, intracranial hemorrhage, and local neurologic manifestation develop several days after or within 4 weeks after carotid endarterectomy. Cerebral hyperperfusion is typically detected by postoperative TCD monitoring when >100% increase of baseline value (the blood flow velocity of the middle cerebral artery on the ipsilateral side before surgery). Besides the commonly used intraoperative TCD monitoring, additional TCD measurement in early postoperative phase (within 2 h after surgery) is useful to more accurately predict cerebral hyperperfusion after carotid endarterectomy under general anesthesia [11].

4.3.3 Transcranial Doppler Monitoring in Subarachnoid Hemorrhage

Cerebral vasospasm after aneurysmal subarachnoid hemorrhage is a poor prognostic factor. Normally, cerebral vasospasm occurs 4–14 days after aneurysmal subarachnoid hemorrhage, but it occurs within 48 h in 13% of patients [12]. Cerebral vasospasm is predicted from a high mean flow velocity on TCD and strongly associated with delayed cerebral ischemia and cerebral infarction. Normally, the mean flow velocity and Lindegaard ratio are used to accurately diagnose cerebral vasospasm using TCD in order to distinguish it from hyperperfusion [13, 14]. The American Heart Association stated that TCD is

rational as a monitoring to detect cerebral vasospasm after aneurysmal subarachnoid hemorrhage [15]. In a systematic review surveying the association between cerebral vasospasm after aneurysmal subarachnoid hemorrhage detected by TCD and delayed cerebral ischemia, the sensitivity (90%) and negative predictive value (92%) of TCD monitoring were high, but only the cutoff value of the mean middle cerebral arterial flow velocity (120 cm/s in most studies) was used to diagnose delayed cerebral ischemia [13].

4.3.4 Stroke Risk Assessment in Patients with Carotid Artery Stenosis

A systematic review reported in 2016 clarified that MES signal detection by TCD monitoring is useful for assessment of the risks for stroke and transient ischemic attack (TIA) in pre-, peri-, and postoperative patients with either asymptomatic or symptomatic carotid atherosclerotic lesions [16], and MES signal detection in patients with symptomatic carotid artery stenosis is a strong predictor of stroke occurring in the near future [17].

4.4 Near-Infrared Spectroscopy

Regional cerebral saturation (rSO_2) using near-infrared spectroscopy (NIRS) has been widely used because it is a promising tool that can serve as an easy-to-install, noninvasive, and continuous surrogate marker to predict the oxygen supply-and-demand balance in the brain. rSO_2 is measured utilizing the characteristic of optical spectrometry that near-infrared light easily penetrates the scalp and skull and reaches the intracranial tissue. Cerebral oxygenation status can change during various intraoperative factors, such as ischemia caused by surgical maneuvers, hypotension, hypovolemia, hemorrhage, shock, or body positioning, and clinician should therefore take into account the application of NIRS monitoring in the care of high-risk patients in order to improve clinical outcomes.

4.4.1 Measurement Principle

Regarding penetration of light in biological tissue, light cannot move on in the body because of strong absorption by hemoglobin (Hb) when the wavelength is about 650 nm or shorter and because of strong absorption by water when the wavelength is about 1250 nm or longer. Accordingly, near-infrared light with a wavelength of 700–1000 nm, so-called biological window, has high biological permeability, and it is used to measure Hb oxygenation in the body. The absorption spectrum for near-infrared light is different between oxygenated and reduced Hb, and the iso-absorptive point is present near 805 nm. rSO2 is calculated from the ratio of oxygenated Hb to total hemoglobin at the microvasculature level (arterioles, venules, and capillary blood vessels). Since direct measurement of oxygen saturation in brain tissue is difficult, the venous blood/arterial blood ratio is fixed to 70:30 or 60:40 and incorporated in the algorithm of rSO2 calculation. Regarding the principle of rSO2 measurement using NIRS, the Beer-Lambert method is the basis. Originally, the absence of light scattering is a precondition of the Beer-Lambert method, but light scattering is strong, and the actual optical path length is long in biological tissue, for which the Beer-Lambert method is not applicable without modification. To solve this problem, the modified Beer-Lambert (MBL) method is used. There is another rSO2 calculation method using space-resolved spectroscopy (SRS). The principle of SRS is also based on the same light-scattering theory as the MBL method. The rate of change relative to the distance is calculated by measuring emitted continuous lights using two light receivers adjacent to each other to remove the influence of optical path length. The balance between quantitativity and practicability is favorable.

rSO2 measurement by NIRS is influenced by anemia [18], skull thickness, cerebrospinal fluid layer [19], extracranial blood flow [20], and posture [21]. Accurate rSO2 measurement is tried by changing the wavelength of the near-infrared light, analytical method, and distance between the light-emitting part and light receiver corresponding

to the model of measurement device. At present, it is necessary to interpret measured values based on the characteristics of NIRS and each measurement device.

4.4.2 Clinical Use of Near-Infrared Spectroscopy

rSO2 measurement by intraoperative NIRS monitoring is used for patients at high risk of perioperative cerebral ischemia, such as those with carotid endarterectomy [22], stent placement in the carotid artery, and traumatic brain injury [23, 24], and to detect cerebral vasospasm after subarachnoid hemorrhage [25]. It is desirable to initiate rSO2 measurement before initiation of anesthesia (initiation of oxygen administration) and set the baseline at the measured value. Normally, the normal value of rSO2 before oxygen administration is 60–75%, but intra- and interindividual variabilities are large. At present, reports with high evidence level are lacking, and no clear evidence for whether perioperative NIRS monitoring reduces incidences of postoperative cognitive dysfunction, stroke, delirium, and death has been shown [26], and no clear cutoff value of rSO2 has been determined. However, NIRS monitoring is clinically used widely because of its advantages: low invasiveness and ease of use [27]. Generally, 20% or more decrease from the baseline rSO2 or a 50% or lower measured value is regarded as an alarm point for hypoperfusion and hypoxia of the brain.

rSO2 measurement is frequently used for multimodal monitoring in combination with electroencephalography and TCD monitoring to evaluate cerebral hypoperfusion during carotid endarterectomy. In carotid endarterectomy, countermeasures, such as shunt insertion, are considered when rSO2 reaches the warning criteria [22]. It is also used to detect cerebral vasospasm after subarachnoid hemorrhage and delayed cerebral ischemia, and rSO2 <50% without systemic hypoxemia is a predictor of symptomatic cerebral vasospasm [13]. A decrease in rSO2 associated with low blood pressure under general anesthesia in a beach chair position has been shown to have no association with postoperative cognitive impairment or biomarker of brain injury [21]. However, it is necessary to prevent careless induction of cerebral hypoperfusion under general anesthesia in a beach chair position in consideration of the gravitational effect of head elevation on cerebral perfusion. Specifically, it is recommended to set blood pressure by subtracting 1.35 mmHg from the blood pressure measured in the arm or leg every 1-cm distance between the measured site and head. It is also employed to predict return of spontaneous circulation (ROSC) during resuscitation after cardiac arrest. The systematic review clarified that the success rate of ROSC after cardiac arrest increases as the initial and average rSO2 increase [28].

4.5 Electroencephalography

Electroencephalography (EEG) provides important information of cerebral oxygenation and metabolic rate and has been used to predict the postoperative outcome of the neurological function. EEG is very sensitive to ischemia in the cerebral cortex, and EEG activity disappears 20–30 s after loss of blood flow. Although EEG has not widely spread as an intraoperative monitoring of the brain due to its complexity of recording and evaluation, EEG is one of the most powerful tools for neurophysiologic intraoperative monitoring, particularly during carotid endarterectomy.

EEG represents summated postsynaptic potential generated in pyramidal cells in the cerebral cortex. For the recording electrode, disc or needle electrodes are used and placed on the scalp following the International 10–20 system. Each channel represents the information right under the electrode, and the EEG signals are classified into delta (δ) (1–4 Hz), theta (θ) (4–8 Hz), alfa (α) (8–13 Hz), and beta (β) (13–35 Hz) waves on the basis of frequency.

Alarm is given when changes in EEG are clearly detected, such as persistent changes in the frequency and amplitude and laterality. In cerebral ischemia,

slowing of EEG signal and reduction in EEG amplitude occur. However, these should be carefully evaluated because EEG can be affected by the depth of anesthesia, type of anesthetics, and physiological changes in hemodynamics during surgery.

4.5.1 Electroencephalography Monitoring During Carotid Endarterectomy

EEG is most frequently used for brain monitoring to detect cerebral hypoperfusion during carotid endarterectomy [29, 30]. Countermeasures against cerebral ischemia, such as shunt placement, are considered on the basis of ischemic changes on EEG (Fig. 4.1). In a meta-analysis investigating reliability of intraoperative EEG monitoring to predict neurological complication after carotid endarterectomy, the specificity was 84%, the sensitivity was 52%, and the diagnostic odds ratio was 5.9, clarifying that neurological complication after carotid endarterectomy can be predicted at a high specificity by intraoperative EEG monitoring [30].

4.5.2 Monitoring of Depth of Anesthesia by Electroencephalography Analysis

In shallow sedation induced by anesthetics, low-amplitude faster frequency waves (β waves) are main EEG signals. High-amplitude slow frequency waves (α waves) become dominant with increasing anesthetic depth. When sedation becomes deeper, low-frequency δ waves and θ waves become dominant, i.e., EEG becomes high-amplitude slow waves as the anesthetic concentration increases.

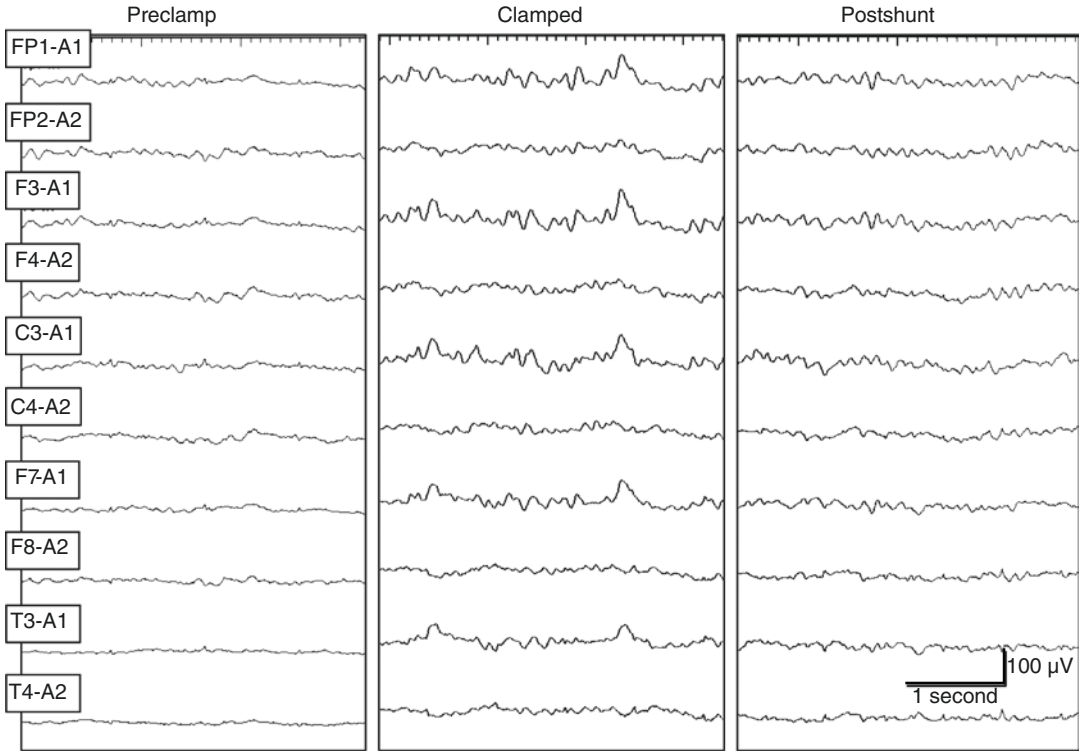

Fig. 4.1 Electroencephalography during a left carotid endarterectomy surgery. This is an electroencephalography (EEG) tracing 1 min after the left carotid artery clamp was applied. The ipsilateral attenuation of EEG activities was observed over the left hemisphere on clamping. Restoration of EEG back to the baseline was observed on shunting.

At a deeper sedation level, flat brain waves and high-amplitude slow waves alternately appear, showing a burst and suppression pattern. The flat region increases as sedation deepens, and EEG finally becomes completely flat.

The bispectral index (BIS) (Medtronic, Minneapolis, MN, USA) which analyzes EEG and converts the sedation level into numerals has spread. Recently, the patient state index (PSI) calculated from four-channel EEG data of SedLine (Masimo, Irvine, CA, USA) has been used. In monitoring of the depth of anesthesia, such as BIS and PSI, anesthetic concentration-dependent changes in EEG are measured by an exclusive sensor attached to the forehead, and the depth is converted to numerals using the correlation determined by analysis of EEG database. It is recommended to maintain the BIS value at 40–60 and PSI value at 25–50 during general anesthesia, but it is necessary to adjust anesthetics not only based on the values of BIS or PSI but also confirming waveforms of actual EEG.

4.5.3 Electroencephalography Monitoring in Intensive Care Unit

Intermittent EEG monitoring is sufficient to diagnose seizures, but continuous EEG monitoring is necessary to detect and manage nonconvulsive seizures and nonconvulsive status epilepticus [31]. Specifically, continuous EEG is recommended to rule out nonconvulsive seizures in brain-injured patients and comatose critically ill patients without primary brain injury with unexplained or persistent altered consciousness. In addition, EEG is also usable to detect cerebral ischemia in unconscious patients after subarachnoid hemorrhage and predict improvement of the comatose state after cardiac arrest.

4.6 Evoked Potential

Evoked potentials (EPs) are the electrophysiologic responses of the nervous system to sensory or motor stimulation. Stimulus is applied to the nervous system while recording the EPs from various points along the stimulated pathway. Intraoperative monitoring of EP has been widely used to assess the functional integrity of neural pathways in anesthetized patients during surgery that has a risk of neural damage. However, EPs are sensitive to suppression by pharmacological influences, but only ABR is resistant to anesthetic agents and neuromuscular blockades. Therefore, it is imperative that anesthesiologists understand the effects of certain medications on EP and select an anesthetic regimen that facilitates reliable intraoperative EP monitoring. Table 4.4 shows the effects of anesthetic agents and neuromuscular blockade on various EPs. Additionally, the recommended anesthetic regimens during various EP monitorings are shown in Table 4.5.

Table 4.4 Influence of anesthetics on evoked potential

Inhibitory action	Myogenic motor evoked potential	Somatosensory evoked potential	Visual evoked potential	Auditory brain stem response
Large	Thiopental Inhalation gas anesthetics Nitrous oxide Muscle relaxant	Thiopental Inhalation gas anesthetics Nitrous oxide	Thiopental Inhalation gas anesthetics Nitrous oxide Ketamine	
Small	Propofol Narcotics	Narcotics	Propofol Narcotics	
None	Ketamine	Propofol Ketamine Muscle relaxant	Muscle relaxant	Propofol Thiopental Inhalation gas anesthetics Narcotics Muscle relaxant

Inhalation gas anesthetics include isoflurane, sevoflurane, and desflurane

Table 4.5 Recommended anesthetic regimen for monitoring of various types of evoked potential

	Myogenic motor evoked potential	Somatosensory evoked potential	Visual evoked potential	Auditory brain stem response
Recommended anesthetic regimen	Propofol Narcotics	Propofol Narcotics Muscle relaxant	Propofol Narcotics Muscle relaxant	No limitation

Based on available evidence, different warning criteria may be needed for different EP monitorings. The goal of intraoperative EP monitoring includes helping to prevent neurological deficits without unnecessarily compromising surgical treatment. False positives could interfere with surgical treatment and undermine the confidence of surgeons in EP alerts. Therefore, when a significant change in EP is observed during surgery, it should be reported to the surgeon after a false positive has been excluded. False positives can be tested for by first verifying the mechanical setup of the equipment as a potential cause (e.g., dislodgement of the stimulatory or recording electrodes, a lack of electrical stimulation, broken wires, etc.). If there are no such problems, the anesthetic and physical parameters should be checked. Following which, the anesthesiologist should be asked if any anesthetic agents that might attenuate EP have been administered as a bolus or if the continuous dose of such an agent has been increased. Changes in body temperature and blood pressure, which have significant effects on EP, should also be checked. Once all of the above have been confirmed, a warning should be issued to the surgeon.

In this chapter, we describe brief methodologies for intraoperative EP monitoring in the operation room, focusing on somatosensory evoked potential, myogenic motor evoked potential, auditory brainstem response, and visual evoked potential.

4.7 Somatosensory Evoked Potential

Somatosensory evoked potential (SSEP) is induced in the somatosensory area in the cerebral cortex by stimulating the upper or lower limb sensory nerve. SSEP monitoring is used to evaluate the integrity of the deep sensory pathway from the peripheral nerves to the spinal cord, brain stem, and cerebral cortex. SSEP has an advantage that continuous monitoring not interfering with progression of surgery is possible because stimulation does not cause body movement.

SSEP is classified into far-field potential (FFP) and near-field potential (NFP) based on the type of recorded evoked potential and short latency (<30 ms), intermediate latency (30–100 ms), and long latency (>100 ms) based on the derived latency. Short-latency SSEP is frequently used to make a neurological diagnosis because the waveforms are stable compared with those of intermediate- and long-latency SSEP.

4.7.1 Far-Field Somatosensory Evoked Potential and Near-Field Somatosensory Evoked Potential

FFP is evoked potential activity that is located far from the active electrode, and as per volume conductivity law, they are detected by and recorded by the active electrode. Since FFP does not reach the recording electrode through the nerve conduction pathway but it is generated in the sensory pathway and simultaneously recorded by the recording electrode through capacity conduction, the latency is the period from initiation of stimulation to generation of the potential, which is short. In addition, it is necessary to use a non-head reference electrode because the potential is equal to that in the potential-generated region in any region on the scalp. Generally, the earlobes are used as a reference electrode.

NFP represents the potential recorded at an electrode near the potential-generated region,

and in SSEP, changes in potential in the sensory area in the cerebral cortex are recorded. NFP markedly changes when the electrode moves. Since the recording electrode is near to the source of potential generation, the amplitude of recorded potential is large. NFP is mainly recorded through nerve conduction.

4.7.2 Stimulation and Recording Methods of Somatosensory Evoked Potential

For the nerve to be stimulated, electric stimulation is applied to the median or ulnar nerve at the wrist in the upper limb and to the tibial nerve on the medial side of the ankle in the lower limb. The recording electrodes are placed following the International 10–20 system. C3' and C4' at 2 cm posterior to the sensory area of the hand, C3 and C4, are used in the upper limb, and Cz' at 2 cm posterior to Cz is used in the lower limb. SSEP is recorded through the sensory area on the opposite side of the stimulated side. Since SSEP is small, it is recorded by averaging, and many additions are necessary for FFP because it is smaller than NFP.

4.7.3 Assessment of Somatosensory Evoked Potential

SSEP waveforms are described with the latency and amplitude (e.g., negative waves with a latency of 20 ms are presented as N20). Representative recorded SSEP induced by upper limb stimulation is shown in Fig. 4.2. The origin of each waveform component and its evaluation are summarized in Table 4.6. In our institution, P13 or P14 is used for spinal cord tract monitoring and N20 for monitoring of the cerebral cortex. P13 and P14 are FFP, and N20 is NFP. When the lower limb is stimulated, the latency of induced waveforms is different depending on the

Table 4.6 Origin and evaluation of SSEP peaks (upper limb)

Peak	Origin	Evaluation
N9	Brachial plexus	Peripheral nerve
N11	Posterior funiculus	Lower cervical spine
P13	Nucleus cuneatus	Upper cervical spinal cord function
P14	Medial lemniscus	Function of the lower medulla oblongata
N18	Thalamus	Thalamic function
N20	Cerebral cortical sensory area	Cerebral cortical function

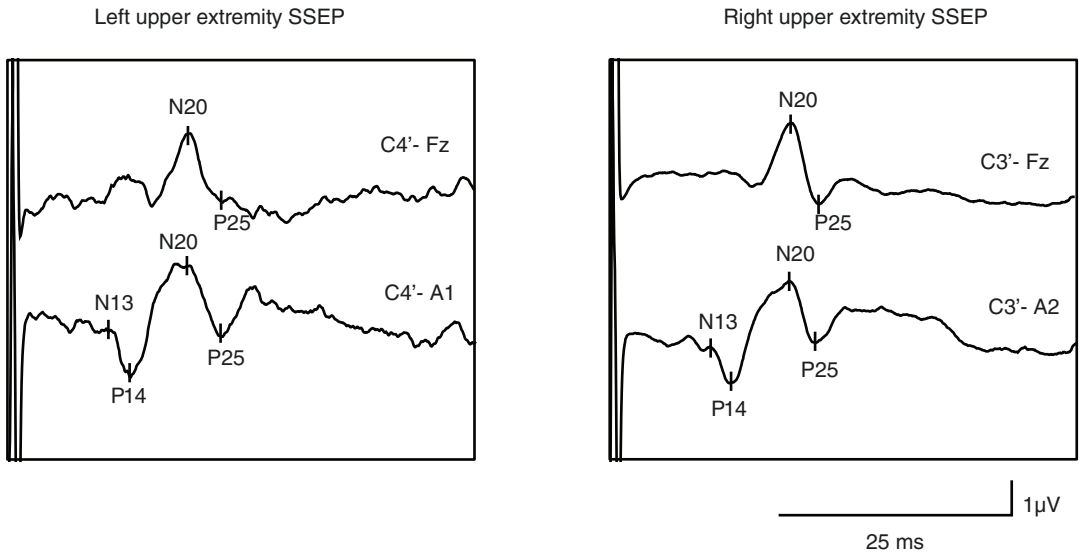

Fig. 4.2 Somatosensory evoked potential. This figure shows somatosensory evoked potentials obtained by median nerve stimulation

position of the reference electrode. P31, which is FFP, is measured by placing the reference electrodes to the earlobes (A1, A2) to monitor the spinal cord tract, and P38 or N46, which are NFP, is measured to monitor the cerebral cortex. The intraoperative warning criteria are either a 10% increase in latency or a 50% reduction in amplitude compared with the control waveform.

4.7.4 Anesthetic Considerations

Since anesthetics inhibit synaptic conduction and influence evoked potentials, if no synapse is present in the region between the stimulation and recording sites, the potential is not influenced by anesthetics. Therefore, P13 and P14 of FFP, which is upper limb SSEP, and P31 of lower limb SSEP described above are not influenced by anesthetics. On the other hand, cortical SSEP, which is NFP, may be influenced by anesthetics because it is mediated by synapses (Table 4.4). Muscle relaxants do not influence SSEP. For the anesthetics for surgery with SSEP monitoring, basically, total intravenous anesthesia with propofol, remifentanil, and fentanyl is performed (Table 4.5).

4.8 Myogenic Motor Evoked Potential

Myogenic motor evoked potential (MEP) monitoring has been introduced as a theoretical technique to directly assess the motor system not reflected by SEPs during surgery [32–34]. MEP is a strong candidate for the intraoperative monitoring of the corticospinal tract at the corona radiata, the internal capsule, the brainstem, or the spinal cord, because it provides a method for monitoring the functional integrity of descending motor pathways. Myogenic MEP is recorded from the upper and lower extremities on the contralateral side of an electrical short train of multiple pulse stimuli applied to the motor cortex (Figs. 4.3 and 4.4). Currently, the intraoperative recording of myogenic MEP for monitoring the brain has become clinically feasible and reliable after the development of stimulation techniques such as a short train of multiple pulses and direct cortical stimulation.

4.8.1 Stimulation and Recording Methods of Myogenic Motor Evoked Potential

4.8.1.1 Stimulation Technique

A short train of multiple pulses should be used for efficient depolarization at the motor neuron [33]. A train of three to six pulses with an interstimulus interval of 2–5 ms is the recommended setup for electrical stimulation to the motor cortex under general anesthesia. The techniques of stimulation for myogenic MEP monitoring during cerebrovascular surgery include two different methods as transcranial electrical stimulation or direct cortical stimulation. Direct cortical stimulation allows a more focal and superficial excitation of the motor cortex. Recently, myogenic MEP using direct cortical stimulation has been recommended for supratentorial surgery, because transcranial stimulation may result in missing the occurrence of ischemia in the cortical area due to stimulating the motor tracts deep to the motor cortex [34].

Transcranial Stimulation

Transcranial stimulation is commonly used in a situation where craniotomy does not expose the motor cortex [35–37]. A pair of corkscrew electrodes or subdermal needle electrodes is typically placed on the scalp 1–2 cm anterior to C3/C4 or C1/C2 (International 10–20 System). If the incision precludes the placement area of stimulation electrodes, stimulation electrodes can be moved further from the motor cortex. However, this may require a higher current to elicit myogenic MEP and often causes stronger movement of surgical field and may promote deeper current penetration. The anode is always over the targeted hemisphere since anodal stimulation activates corticospinal axons at lower stimulation thresholds as compared with cathodal stimulation [38]. Transcranial stimulation can be performed with constant-voltage or constant-current stimulation. Stimulation intensity is decreased gradually until myogenic MEP amplitudes cannot be obtained

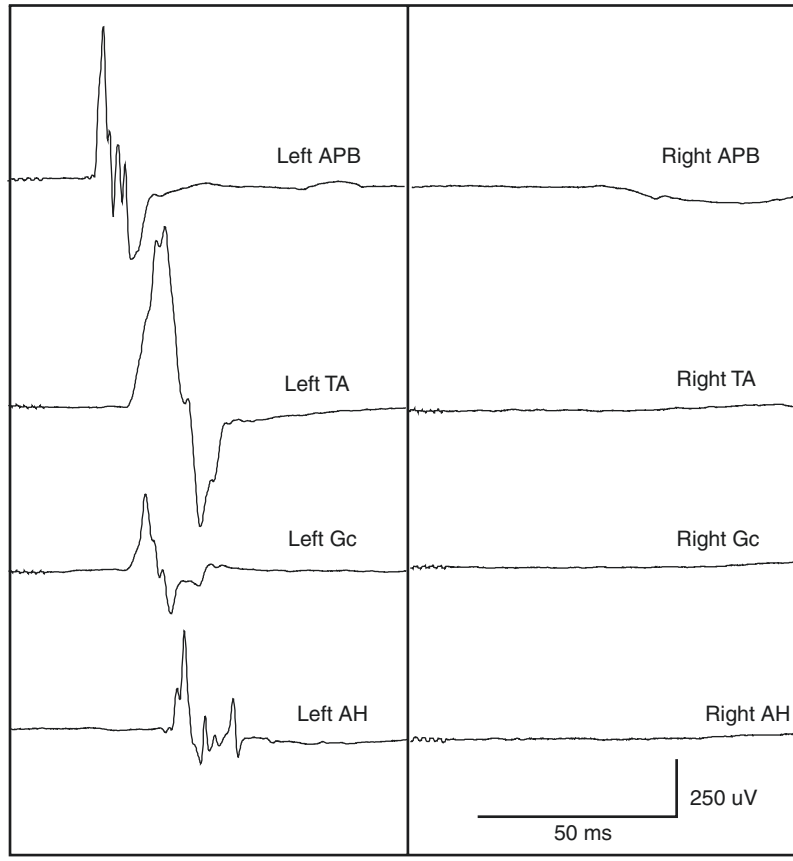

Fig. 4.3 Myogenic motor evoked potential obtained after transcranial stimulation. This figure shows myogenic motor evoked potential recorded from the upper and lower extremities on the contralateral side of electrical short train of multiple pulse stimuli applied to the motor cortex. The right motor cortex was stimulated electrically with stimulation intensity of 110 mA (*APB* abductor pollicis brevis, *TA* tibialis anterior, *Gc* gastrocnemius, *AH* abductor halluces)

from the ipsilateral extremities to determine the threshold. Stimulation intensities are typically not exceeding 400 V or 200 mA. Since the charge delivered is a function of duration and current intensity, pulse duration is an important parameter that needs to be optimized and typically is set from 0.2 to 0.5 ms for constant-current stimulation or to 0.05 ms (50 μs) for constant-voltage stimulation.

Direct Cortical Stimulation

A multi-contact strip electrode is inserted into the subdural space and placed parallel to and over the precentral gyrus, with the laterally located contacts over the arm and hand motor areas, and the medially located contacts over the leg motor area. An electrode placed at Fpz serves as the cathode [37, 39, 40]. For stimulation, a constant current is used up to 15–25 mA. The stimulus intensity is initially set at 8 mA and is increased in 1-mA steps. With optimal electrode placement, a stimulus intensity of 5 mA is often sufficient. Intensity immediately above threshold is chosen for recording from contralateral extremities.

4.8.1.2 Recording Technique

Myogenic MEP is recorded through needle electrodes inserted in the contralateral muscles, mostly from the upper and lower extremities. The muscles used from recording are commonly abductor pollicis brevis in upper extremities and tibialis anterior muscles or abductor halluces muscles bilaterally. However, myogenic MEP should be recorded from the contralateral muscles.

4.8.2 Assessment of Myogenic Motor Evoked Potential

Myogenic MEPs exhibit trial-to-trial amplitude and morphology variability. Therefore, several trials will be needed to select representative or average baseline and confirm consistent

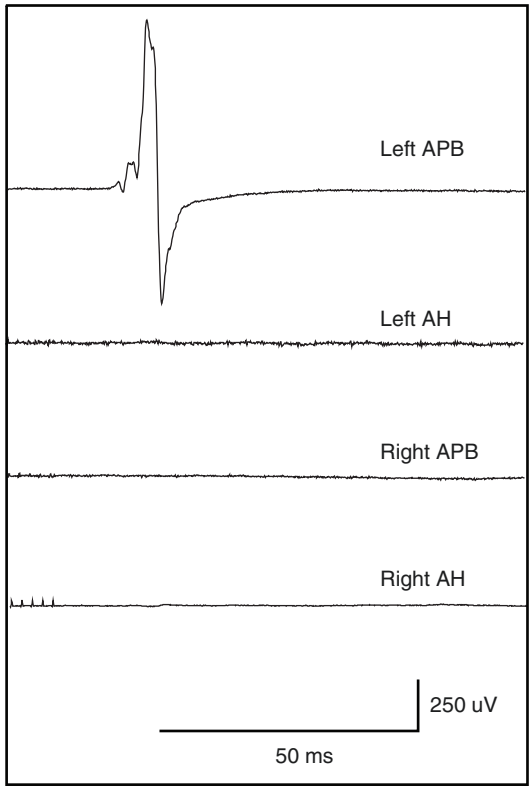

Fig. 4.4 Myogenic motor evoked potential obtained after direct cortical stimulation. This figure shows myogenic motor evoked potential recorded from abductor pollicis brevis in upper extremities and abductor halluces in lower extremities bilaterally after the direct cortical stimulation with intensity of 17 mA was applied to the right motor cortex. When direct cortical stimulation is used, myogenic MEP may be recorded from only the contralateral abductor pollicis brevis to reduce patient movement

reduction in amplitude. Myogenic MEPs are examined based on peak-to-peak amplitude. Generally, a decrease in amplitude is considered significant (i.e., an "alert") for brain and brain stem monitoring when it consists of irreversible disappearance or a consistent reduction in amplitude of more than 50% compared with the baseline [41]. Irreversible disappearance is a strong predictor of new motor dysfunction.

4.8.3 Anesthetic Considerations

Currently, total intravenous anesthesia (TIVA) with a continuous propofol infusion and an opioid is widely considered to be the optimal anesthetic regime for intraoperative monitoring of myogenic MEP [33] (Table 4.5). All volatile anesthetic agents, as well as nitrous oxide, produce a dose-dependent reduction in MEP amplitude (Table 4.4). During monitoring of myogenic MEP, administration of inhalational anesthetics should be avoided. However, a combination of lower dose of propofol with low dose (<0.5 MAC) of inhalational anesthetics may be acceptable [35–37, 42, 43]. Neuromuscular blockade is best omitted for myogenic MEP after intubation. Otherwise, neuromuscular blockade must be partial and controlled. However, the use of a partial neuromuscular blockade might mean that a higher intensity stimulus is required to elicit muscle activity, which can result in false negatives due to the stimulation of subcortical areas of the brain that are located inferiorly to the cortical region [34].

4.9 Auditory Brain Stem Response

Auditory brain stem response (ABR), earlier known as brain stem auditory evoked potential (BAEP) or brain stem auditory response (BAER), is elicited by transient acoustic click stimulation. Since the middle-latency and long-latency auditory evoked potentials are markedly attenuated by anesthetic agents, the short-latency auditory evoked potential that occurs during the first 10 ms after a strong click sound is used for intraoperative monitoring because of its stability under general anesthesia. ABRs can be used to monitor the integrity of cochlea, auditory nerve, and brain stem auditory pathways. Most commonly, ABR monitoring is used during microvascular decompression surgery and tumorectomy surgery for cranial eighth nerve tumor (such as vestibular schwannomas) and cerebellopontine angle tumors with the goal of preserving auditory nerve function. ABR monitoring can help to avoid excessive stretch of cranial eighth nerve from cerebellar retraction, causing postoperative hearing loss.

4.9.1 Stimulation and Recording Methods of Auditory Brain Stem Response

ABR is recorded from the vertex after acoustic click stimulation delivered thorough the earphones that are connected to the transducers via lengths of flexible plastic tubing. Stimulation intensity should be set high enough to produce robust ABR but not high enough to cause ear damage. The click stimulation would be applied with an intensity of 90–120 dB peSPL and a frequency of 11–20 Hz to the involved ear. If preexisting hearing loss is present, a higher intensity may be needed. Simultaneously, white noise for masking is applied with 60–70 dB peSPL to the contralateral ear. Clicks can be of two polarities including compression clicks, consisting of a propagating wave of increased air pressure, and rarefaction clicks, consisting of a propagating wave of decreased air pressure. Alternative click polarities are preferred to reduce the electrical stimulus artifact in the operation room where electrical artifacts are often problematic. Care must be taken that the tubing connecting the earphone is not compressed or kinked during the patient positioning. The earphone should be held in place and covered with adhesive waterproof dressing in order to prevent fluids from entering the ear canal. The recording electrode is placed at Cz (International 10–20 System). Reference electrodes are placed at A1 and A2 (International 10–20 System) or the mastoid processes. Generally, 500–1000 trials are averaged to obtain an interpretable and reproducible ABR.

4.9.2 Assessment of Auditory Brain Stem Response

ABR consists of negative seven peaks (in Roman numerals I–VII) representing electric activity of the auditory nerve, nuclei, and fiber tracts of the ascending auditory pathways (Fig. 4.5). Wave I refers to the initial depolarization in the most distal part (cochlear end) of the auditory nerve. Wave II represents the central portion of the auditory nerve. Wave III represents the caudal pons, around the region of the superior olivary complex. The generators of IV are close to those of

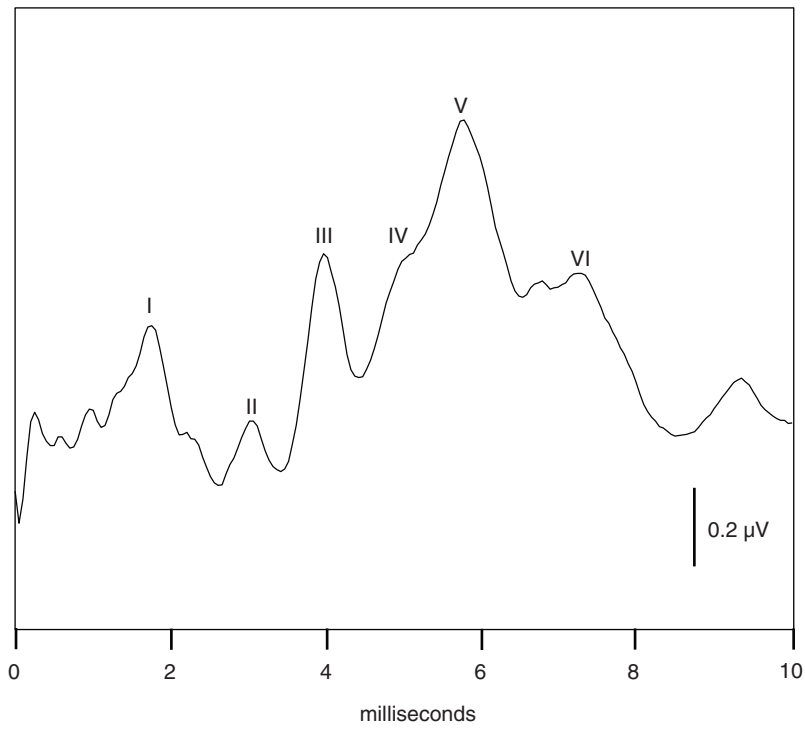

Fig. 4.5 Auditory brain stem response. The first seven peaks of the auditory brain stem response (ABR) are produced near the structures in the brain stem. Typically, evaluation of ABR focuses on waves I, III, and V during monitoring

wave V that represents the termination of the lateral lemniscus in the inferior colliculus. Waves VI and VII are supposed to arise at the level of the medical geniculate nucleus and auditory radiations, respectively. However, they are not recordable in all normal subjects and not used in clinical practice. Both the latencies and amplitudes of waves I, III, and V, which are the most consistent components, are used intraoperatively to evaluate. Sometimes measurement of amplitude of wave III may be unreliable due to unclear trough after wave III, but usually waves I and V can be obtained consistently. As with most of other sensory evoked potentials, the warning criterion for amplitude of BAEP is more than a 50% decrease from baseline. In terms of warning criterion for latency, different warning criteria may be appropriate for different clinical situations [44]. Prolongation of latency of more than 10%, or roughly 0.5 ms, is used as a warning criterion in surgery for cerebellopontine angle tumor at a high risk of hearing loss. In contrast, the warning criterion for latency is more than 1-ms prolongation when ABR monitoring is used during microvascular decompression that is less likely to suffer hearing loss.

4.9.3 Anesthetic Considerations

Anesthetic agents have only a minor effect on ABRs [45], and neuromuscular blockade does not affect them (Table 4.4). Since anesthetic regimen is not restricted by the use of ABR monitoring (Table 4.5), stable and robust ABRs are recorded readily under general anesthesia. However, ABRs are affected by body temperature. The body temperature decrease produces an increase in component latencies of about 7% for each 1 °C [46].

4.10 Visual Evoked Potential

Some surgical procedures can pose a risk of visual impairment in the intraoperative period, including neurosurgical procedures, particularly tumorectomies involving the optic chiasm for pituitary adenomas, craniopharyngiomas, tuberculum sellae meningiomas, or other tumors; the removal of brain tumors from the optic pathway or the structures in its vicinity, such as the optic nerve, optic radiation, or occipital lobe; and internal carotid artery aneurysm clipping, which poses a risk of impeding the blood flow to the ophthalmic artery. Intraoperative visual evoked potential (VEP) monitoring can be used to assess the functionality of the optic pathway from the retina to the visual cortex and allows visual impairment to be avoided or minimized. VEP responses are recorded from occipital scalp electrodes (O_1, O_2, Oz; International 10–20 System) after the application of a flash stimulus to the retina in patients under general anesthesia [47].

4.10.1 Stimulation and Recording Methods of Visual Evoked Potential

The recent use of high-intensity LED flash stimulation devices has enabled the stable and reproducible recording of VEP waveforms under general anesthesia [48, 49]. In this method, a flash stimulation device is placed over both eyelids while the patient's eyes are closed. Flash stimulation can be performed at a frequency of <4 Hz but is generally performed at a frequency of around 1 Hz. The flash stimulus is set to an intensity that is slightly higher than the intensity level at which the maximum VEP amplitude is evoked. When flash-stimulating the retina, it is necessary to confirm that the flash stimulus has reached the retina by taking electroretinogram (ERG) recordings at the same time as the VEP recordings [48, 50, 51]. Recording electrodes are placed 4 cm above the external occipital protuberance (Oz; International 10–20 System) and 4 cm to the left and right of Oz (O1 and O2, respectively; International 10–20 System) in most adults. Needle electrodes are capable of obtaining more stable recordings than surface electrodes. A reference electrode with unipolar induction is best and should be placed at a relatively inert

position, such as the earlobe (A1 and A2; International 10–20 System), mastoid process, or forehead (Fz; International 10–20 System) [52]. VEP is processed by averaging because they are extremely small.

4.10.2 Stimulation and Recording Methods of Electroretinogram

An ERG must be obtained during VEP monitoring [48, 51]. Flash stimulation-induced ERG can easily be recorded using electrodes placed around the eyes. ERG are processed by averaging. ERG monitoring is particularly important during frontal craniotomy. In cases in which the flash stimulation device is displaced as a result of the skin flap on the forehead being turned during craniotomy, a flash stimulus of sufficient intensity cannot be delivered to the retina. Under such conditions, it can be mistakenly believed that the resultant attenuation of VEP responses was caused by surgical manipulation (a false positive) if the intensity of the flash stimulus delivered to the retina is not checked using ERG, and the dislodgment of the flash stimulation device is not noticed.

4.10.3 Assessment of Visual Evoked Potential

VEP waveforms must be recorded at least two or more times to confirm that they are reproducible. In patients with blindness or severe visual field defects prior to surgery, it is difficult to obtain a stable VEP waveform because the optic nerve cannot be sufficiently stimulated by flash stimulation. VEP is evaluated by examining the peak-to-peak amplitude between negative waves near 75 ms (N75) and positive waves near 100 ms (P100) (Fig. 4.6). A reduction in VEP amplitude is considered to be significant (i.e., an "alert") when it consists of a persistent reduction in amplitude of more than 50% compared with the baseline. The continuous disappearance of VEP waveforms can be interpreted as indicative of the onset of severe postoperative visual impairment. Although hemianopia or larger visual field defects can be detected based on a significant decrease in VEP amplitude, it might be difficult to detect the occurrence of smaller visual field defects such as scotoma and quadrantanopia.

4.10.4 Anesthetic Considerations

Anesthetic agents that do not affect VEP waveforms must be chosen to allow highly reliable VEP monitoring. Since the optic pathway is mediated by three synapses, including the lateral geniculate body, from the retina to the visual cortex, responses from the optic pathways are easily suppressed by anesthetic agents. The effects of anesthetic agents on VEP are summarized in Table 4.4. All inhaled anesthetic agents suppress VEP by extending their latency and reducing their amplitude in a concentration-dependent manner, even at low concentrations [53]. Nitrous oxide causes a marked attenuation of VEP amplitude [54] and the disappearance of VEP waveforms when combined with inhaled anesthetic agents [55]. Among intravenous anesthetic agents, only propofol has a small suppressive effect on VEP, while other intravenous anesthetic agents are not suitable for use during intraoperative VEP monitoring because they markedly suppress VEP, even at low doses [56, 57]. Opioids of normal clinical use and neuromuscular blockade can be used because they have no effects on VEP. Therefore, an anesthetic regimen suitable for VEP monitoring is total intravenous anesthesia with propofol, opioid, and neuromuscular blockade (Table 4.5). However, even propofol suppresses VEP when administered in large doses, which is why the depth of anesthesia should be regulated using a bispectral index monitor or another device during VEP monitoring.

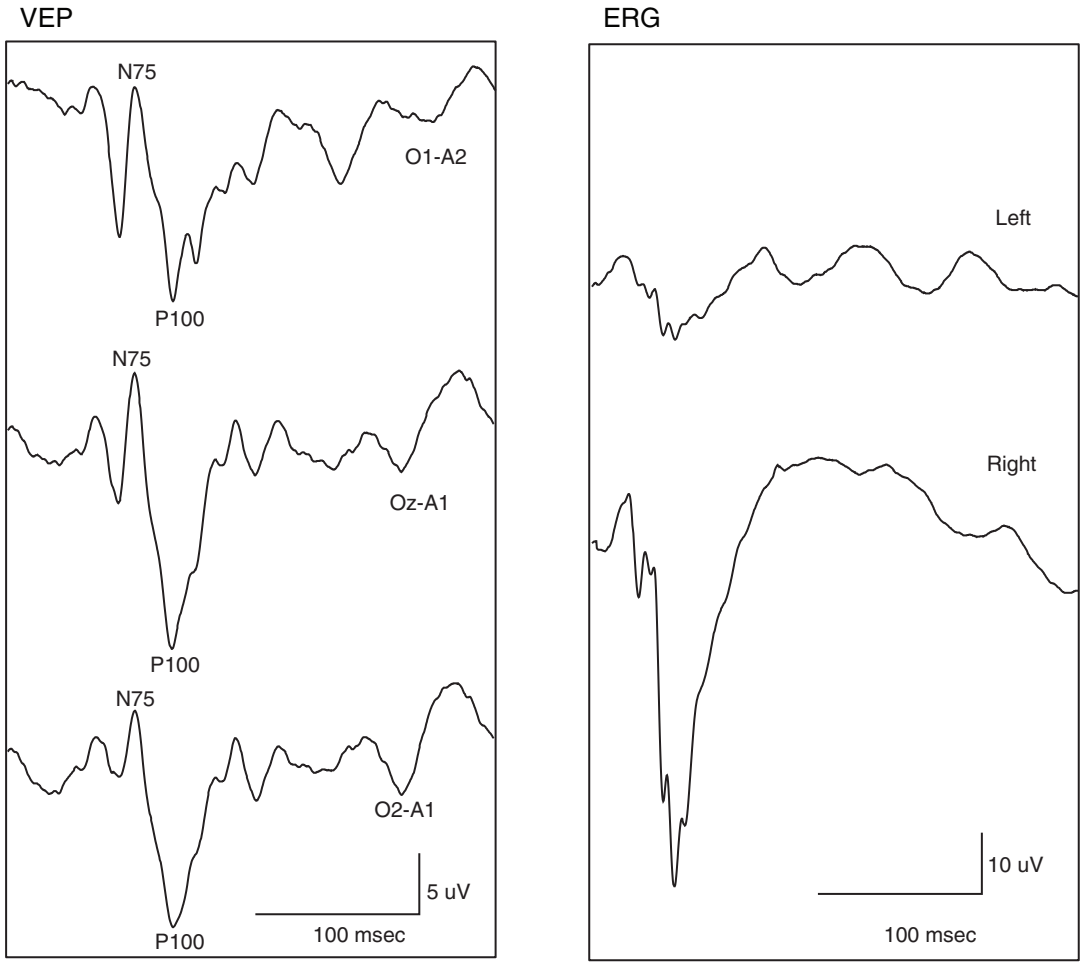

Fig. 4.6 Visual evoked potential and electroretinogram. This figure shows flash stimulation-induced visual evoked potential (VEP) on the left side and electroretinogram (ERG) on the right side. Flash stimulation was applied to the right eye

Key Points

- Intraoperative monitoring of the brain is now considered the standard care to improve patient safety and optimize patient outcomes.
- Currently, multimodal approaches are available for intraoperative monitoring of brain including ICP, TCD, NIRS, and EPs (SSEP, MEP, ABR, and VEP).
- Selecting an anesthetic regimen that facilitates reliable intraoperative EP monitoring (SSEP, MEP, VEP) is critical because anesthetic agents and neuromuscular blockade can interfere with SSEP, MEP, and VEP monitoring.
- The use of ABR monitoring does not impose any limitations on the anesthetic regimen.

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Intraoperative Neuromonitoring for the Spine

5

Dhritiman Chakrabarti and Deepti Srinivas

5.1 Introduction

Spine surgeries are fraught with risks of inadvertent damage to neuronal structures critical for motor and sensory functions. This is especially true with regard to complex surgeries involving tumors within the spinal cord, spine deformity corrections, and multiple level fusions. The advent of intraoperative neuromonitoring (IONM) as a safeguard against such a mishap started in the late 1970s and the early 1980s for orthopedic surgeries. Earliest papers in this regard were published by Dr. Richard Brown, a neurophysiologist, in the 1970s, and there has been a gradual growth in the acceptance and utilization of these techniques, as they became more feasible in the operating room due to technological advancement [1].

This chapter will discuss the commonly used modalities in IONM for spine surgeries including somatosensory evoked potentials (SSEP), motor evoked potentials (MEP), spontaneous electromyography (EMG), and triggered EMG. In essence all these modalities rely on stimulation of a specific neural tract at one end and capturing the response of the same at the other, with appropriate impulse and response management to get a good signal to noise ratio.

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5.2 Somatosensory Evoked Potentials

SSEPs are used for monitoring the integrity of the somatosensory pathway, specifically the dorsal column. The potentials are evoked by providing a train of electrical impulses on peripheral mixed nerves—commonly median and ulnar nerves in the upper limb and posterior tibial and common peroneal nerves in the lower limb. The impulse generates two responses—one orthodromic, visible as a muscle twitch in the respective hand or foot, and one antidromic, which is carried by the neural tract to the somatosensory cortex. This antidromic response in turn can be measured anywhere along the tract—usually the lumbar, thoracic or cervical spinal cord, Erb's point for brachial plexus, and scalp for cortical responses [2].

5.2.1 Relevant Anatomy

The pathway starts at the sensory receptors of the body, travels through peripheral nerves to enter the dorsal horn of the spinal cord, and ascends up the ipsilateral dorsal column to synapse at the dorsal column nuclei at the junction of spinal cord and the medulla. The fibers from the thoracic and cervical segments (upper body) terminate at the cuneate nucleus and those from the lower body at the gracile nucleus. The fibers from

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these nuclei ascend up in the medial lemniscus after crossing over contralaterally to relay in the ventral-posterior-lateral nucleus of the thalamus. Third-order neurons then travel through the posterior limb of the internal capsule to the postcentral gyrus where they are distributed in a somatotopic fashion (legs in midline with the trunk and upper limb laterally) [3].

5.2.2 Stimulus Characteristics

Stimulus is provided by either subdermal electrodes or surface electrodes, in vicinity of the nerves to be stimulated. The distance between the positive and negative electrodes should be 1–2 cm, with the negative electrode being proximal. A constant current stimulator is used, with stimulus intensity kept at a level to produce noticeable twitch in the hand/foot (if not paralyzed) or if paralyzed, increased progressively from 20 to 100 mA until a good SSEP waveform is elicited. Increase in amplitude basically increases the number of nerve fibers depolarized. The stimulus is a monophasic rectangular pulse of 100–300 μs duration. Stimulus rates govern the time in which a good waveform is produced, but high stimulus rates have been known to reduce SSEP amplitude. Optimal rate for the upper limb is approximately 10 pulses per second (pps) and for lower limb 5 pps. Stimulus rates in multiples of the electrical line frequency (50/60 Hz) should be avoided. In patients of neuropathy, lower stimulus rates produce better waveform. Also, during bilateral monitoring alternate stimulation should be used (with a delay of 100 ms), rather than simultaneous. Filter setting should be kept at 1–5 Hz for high pass and 500 or 1000 Hz for low pass [2].

5.2.3 Response Capture

Intraoperative SSEPs are usually recorded by placing needle/corkscrew electrodes on the scalp, dorsal neck (at level of C7), or Erb's point for the upper limb and scalp or lumbar/thoracic spine for the lower limb. Referencing and appropriate active electrode placement is an important aspect of SSEP monitoring. Since the final waveform is simply a subtraction of reference from the active and given the time-locked nature of SSEP waveform, proper placement of reference electrode can delineate certain peaks of SSEP waves (Table 5.1) [2].

Table 5.1 Shows electrode placements for recording SSEP waveforms

	Active	Reference
Upper limb		
Scalp	C3′/C4′ (3 cm posterior to C3/4)	Contralateral scalp electrode; dorsal neck; Fz
Dorsal neck	Seventh cervical vertebra level	Contralateral parietal scalp
Erb's point	Above mid clavicle	Contralateral parietal scalp
Lower limb		
Scalp	Cz′ (3 cm posterior to Cz)	Fz; Fpz; Ipsilateral mastoid; dorsal neck
Spine	Lumbar or thoracic spine (rostral to surgical site)	Upper neck; scalp
Popliteal Fossa	Popliteal fossa	Upper neck

Scalp electrode nomenclature is according to the 10–20 electrode system

5.2.4 Response Delineation

The problem with SSEP response is its extremely small magnitude—of the order of 2–4 μV—compared to the background noise of electromyographic or EEG signals. To delineate the SSEP waveform, multiple impulses are fired (usually 500–2000) and responses captured as a time-locked electrical "snapshots" and then averaged. The background activity, due to its random nature, slowly gets canceled out to baseline, while the time-locked SSEP response adds up to a prominent waveform.

This time-locked nature of response creates a temporal dispersion of impulses when the nerves carrying the responses have differing conduction velocities (due to variation in fiber diameter)—

more commonly seen in lower limb SSEPs in old age, neuropathies, and poliomyelitic patients. This results in multiple peaks of different latencies and amplitudes, apart from those commonly described. Another implication is that due to longer fiber length, latencies of waves of the lower limb are longer than those of the upper limb and in patients with longer limbs than others [2].

5.2.5 SSEP Waveforms

The waveforms of SSEP can be defined by three characteristics—latency, amplitude, and orientation. The latency of the waveforms is defined by the time lag since impulse and is dependent on nerve length, diameter, myelination, and other factors determining conduction velocities. Amplitude is determined by the number of functional nerve fibers, their spatial orientation, temporal synchronicity of conduction, signal to noise ratio, and many other physiological factors. A 10% increase in latency or a 50% reduction in amplitude is a cause for alerting the surgeon intraoperatively. Orientation, i.e., positive or negative waves, is classically defined for SSEPs and does not vary if the test is conducted appropriately. Traditionally, positive or upright waves are named N, while negative or trough waves are named P, with the latency in milliseconds written in subscript. For example, N_{20} wave means a positive wave at 20 ms after impulse. Table 5.2 lists the waveforms recorded from upper and lower limb SSEPs and their respective neural generators. Although many waveforms have been listed, the most common waveforms observed for intraoperative monitoring are a N_{20} for median nerve and a P_{40} for the posterior tibial, especially when only scalp electrodes are used (Figs. 5.1 and 5.2) [2].

Due to the high variability of latency and amplitudes in the population, population norms for the same are disregarded in favor of using the patient's own baseline as reference for intraoperative comparisons. Thus, the baseline should be acquired at physiologic and anesthetic conditions, which would be maintained constant throughout the surgery.

Table 5.2 Common SSEP waveforms and their genesis

	Waveforms	Neural generators
Upper limb (median nerve)	P9	Impulse volley from brachial plexus to spinal cord
	P14–16	Cuneate nucleus
	N18	Brainstem (superior colliculus)
	N20	Primary somatosensory cortex
	P22, N30 and P45	Unknown
Lower limb (posterior tibial nerve)	N17	At hip joint
	P24	At T12 vertebra
	P31	At foramen magnum
	N34	Brainstem (medial lemniscus)
	P40	Cortex

5.2.6 Anesthetic Considerations

SSEP monitoring requires stringent rules for the anesthesiologist:

1. Bolus dosing of hypnotics is not allowed; infusions are preferred for intravenous and constant dial setting for inhalational agents.
2. Propofol-based anesthesia is better than inhalational anesthesia; dexmedetomidine may be added as adjunct. Opioids may be used liberally.
3. N_2O is contraindicated.
4. Body temperature should be maintained constant near euthermia.
5. Hypotension, hypoxia, anemia, and dyselectrolytemia all influence SSEPs detrimentally and should be avoided.
6. Neuromuscular blocking agents are allowed and preferred as paralysis removes the EMG noise component.

Anything known to suppress cortical synaptic activity will have a detrimental effect on amplitude of SSEPs. In the event of intraoperative reduction in amplitude or increase in latency of the waveform compared to baseline, a thorough check for such factors should be carried out before reporting to the surgeon.

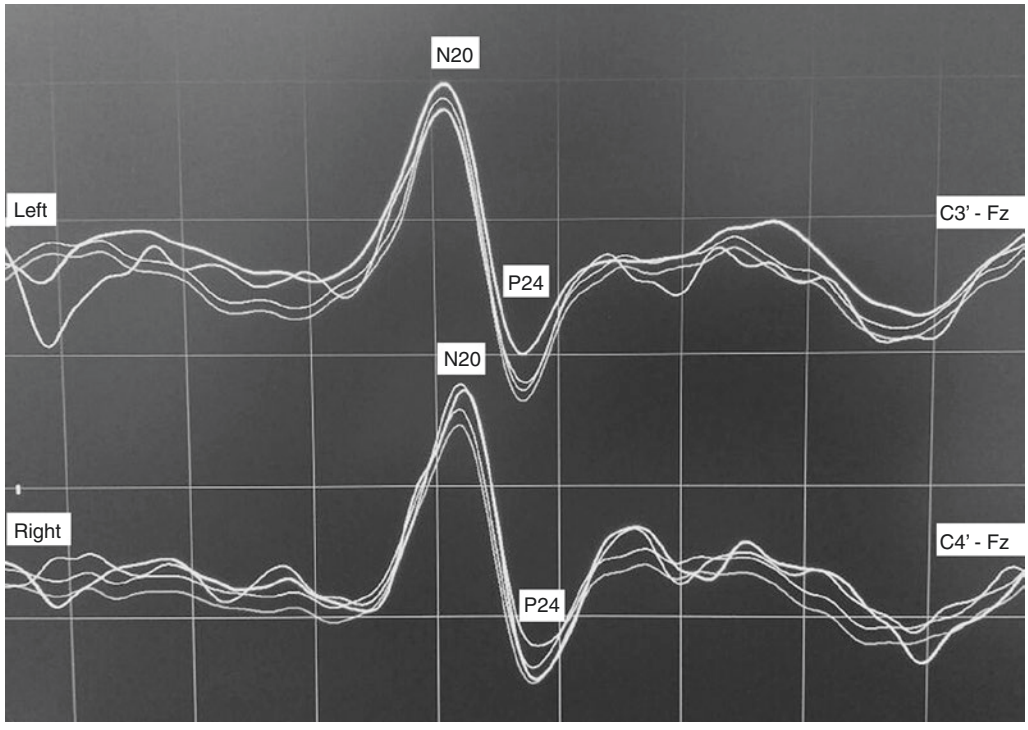

Fig. 5.1 Representative image of median nerve SSEP

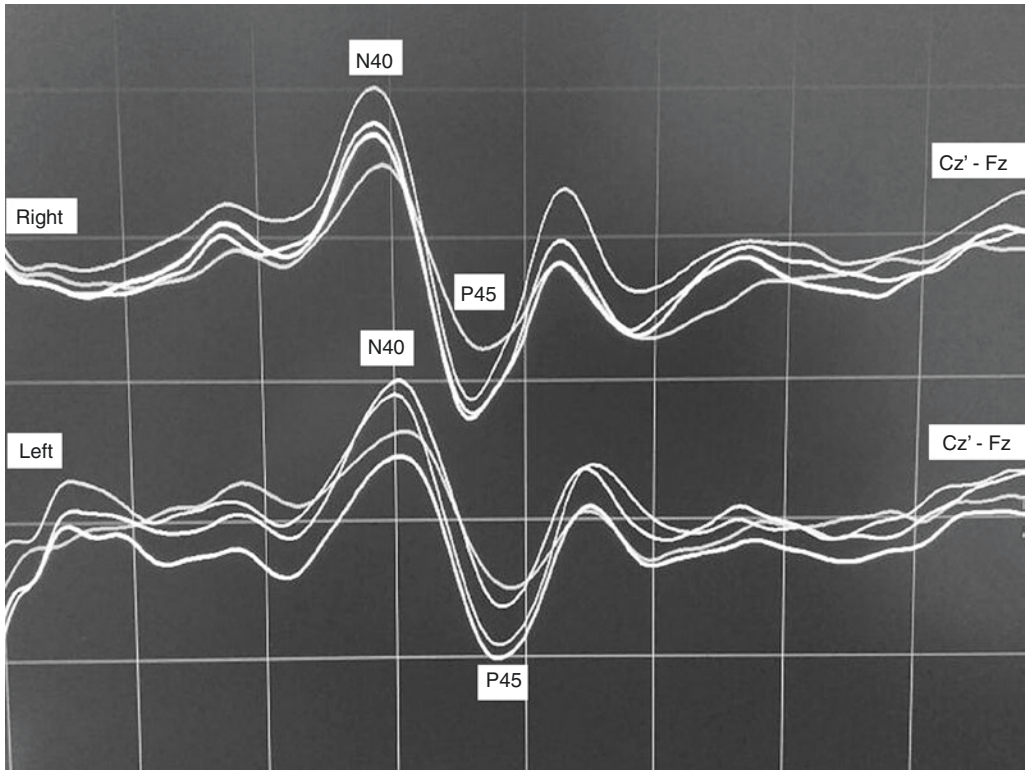

Fig. 5.2 Representative image of posterior tibial nerve SSEP

5.2.7 Uses of SSEP

1. Spinal cord monitoring for intraoperative injuries: SSEP is used for spinal cord monitoring in cases of spinal tumors, scoliosis, spinal canal stenosis, trauma surgery, as well as abdominal aortic aneurysm surgeries. Upper limb SSEP is used for cervical spinal cord monitoring, while surgeries around the thoracolumbar spine require lower limb SSEP. Standard criteria of 50% reduction in amplitude and 10% increase in latency are used for warning surgeon, after ruling out physiological, anesthetic, and technical causes.

   One important limitation of SSEP is that it provides monitoring for the dorsal column of spinal cord which is supplied by posterior spinal artery as opposed to the motor tracts being supplied by anterior spinal artery. Thus, a normal intraoperative SSEP may rarely conclude with the patient having a motor deficit postoperatively [4].

   Another important consideration for SSEP in this regard is the time delay in acquiring waveforms. In comparison with MEPs, SSEPs lag behind by a mean of 16 min in detection of changes [5]. Since reversibility of injury in neuronal structures is time dependent, MEP supersedes SSEP as the modality of choice in this regard. The guidelines for intraoperative neurophysiological monitoring attest to the same as a level I recommendation [6]. To circumvent this problem, SSEP is set up for continuous stimulation (and thus updating the waveform as a moving average) throughout the surgery.
2. Dorsal column mapping: During an intramedullary spinal tumor resection, the surgeon utilizes anatomical landmarks such as dorsal median sulcus and the median dorsal sulcal vein to identify the anatomical cord midline. The "functional" or "physiological" midline can be identified using SSEP monitoring, in case of anatomical distortion due to the tumor. A multielectrode grid is placed over the dorsal column for response capture and the posterior tibial nerve stimulated. Due to somatotopic distribution of nerve fibers in the dorsal column, the highest amplitude of SSEP is recorded nearest to the midline. After bilateral confirmation of the same, the cord midline is identified [7].
3. Cortical surgeries near the somatosensory cortex.
4. Cortical ischemia monitoring during temporary vessel occlusion in intracranial aneurysm surgeries: Upper limb SSEP for middle cerebral artery and lower limb SSEP for anterior cerebral artery territory.
5. Central sulcus mapping: Utilizes change in phase of SSEP waveform across a strip of six electrodes lain directly over the brain surface to locate the central sulcus.

5.3 Motor Evoked Potentials

Initial history of MEP was plagued by its sensitivity to anesthetic agents belying its practical intraoperative utility. With the advent of high-frequency multi-pulse stimulation by Taniguchi in 1993, this shortcoming was addressed, and its role in intraoperative corticospinal tract monitoring has been on the rise [8]. As opposed to SSEPs, MEPs are conducted in an anterograde fashion, with stimulation being provided at the cortex and signal being captured at level of spinal cord and muscles. It monitors the corticospinal tract, and thus intraoperative deficits in this modality correlate directly with postoperative motor deficits. This modality has come into vogue recently, mainly as a supplement to SSEPs for functional monitoring of the spinal cord. Higher sensitivity of MEPs to anesthetic agents hampered its initial popularity, although it is fairly commonly used nowadays in neurosurgery.

MEPs are generated by transcranial electrical or magnetic stimulation of the cortex, which produces signals captured at the spinal cord level—"D" and "I" waves, and at the muscle level—compound muscle action potentials (CMAP).

5.3.1 Relevant Anatomy

The motor system of the humans can be divided into two parts—upper (comprising cerebral cortex, basal ganglia, and cerebellum) and lower (spinal cord pathways). The motor pathway starts

at the primary motor cortex (precentral gyrus) in the posterior part of the frontal lobe, which is somatotopically organized similar to the sensory cortex. This area receives afferent connections from the premotor cortex, supplementary motor area, brainstem, cerebellum, and basal ganglia, which provide inputs and feedback and modify the output of the motor cortex. The lower part of the motor system is the continuation of the upper part (corticospinal tract) or helps modifying the motor output by providing inputs to interneurons in the spinal cord, which in turn synapse with the corticospinal tract neurons. It is divided into the lateral system (corticospinal and rubrospinal tracts) and medial system (tectospinal, vestibulospinal, and reticulospinal tracts). Of importance in the monitoring context are the corticospinal tract, which carries the action potential of the impulse to the alpha motor neurons, and the reticulospinal tract, repeated stimulation of which helps facilitate the impulse conduction from corticospinal tract to alpha motor neurons under anesthesia. The final common pathway of the motor system starts at the alpha motor neurons, the axons of which travel through peripheral nerves to supply skeletal muscles [9].

5.3.2 Stimulus Characteristics

Stimulus is usually provided transcranially via corkscrew electrodes with electrical field supplied using a constant voltage or constant current stimulator. Constant voltage stimulators have been found to have higher success rates [10]. Voltage requirement should be titrated to achieve a good baseline MEP and should be maintained the same throughout surgery. Usual starting voltage is 150–250 V and can be increased up to 500–600 V. For upper limb monitoring, C3–C4 electrode placement (10–20 system) is used, while for lower limbs, Cz-Fz/Fpz is preferred. The side being stimulated should be the anode, while the other is cathode (only for upper limb MEP)—anodal stimulation has higher success rates of producing D-waves and CMAPs. A train of 3–6 pulses with pulse width of 50–75 μs and pulse interval of 2–4 ms is used [11–13].

Transcranial magnetic stimulation has advantage over electrical with regard to exemption of stimulation of pain fibers in the scalp and dura and thus is a practical technique in awake patients [14]. However, anesthetic-induced suppression makes it impractical for intraoperative use.

5.3.3 Signal Capture

D-waves are captured at the spinal level using epidural or subdural electrodes implanted on a catheter at 2–3 cm distances, which is placed either percutaneously using a Tuohy needle or intraoperatively at the site by the surgeon [11, 12].

CMAPs are recorded using pairs of needle electrodes inserted into the appropriate muscle belly. Distal muscles used for fine movement are more sensitive to damage to corticospinal tract (lateral motor system) per se, while proximal and trunk muscles are supplied by the medial motor system (reticulospinal, tectospinal, and vestibulospinal tracts) and thus not so sensitive. For upper limb monitoring, thenar and abductor digiti minimi are preferred, and for lower limb tibialis, anterior and abductor hallucis are preferred. For gross spinal cord monitoring though, proximal muscles can also be used, and theoretically any limb muscle can be used [11, 12].

5.3.4 MEP Waveforms and Their Genesis

MEPs are generated by electrical stimulation of axons of the motor tract neurons rather than the cell bodies. The initial stimulation produces an action potential which is captured as a negative deflection at the spinal cord level (D-wave), and its importance in monitoring is only up to the alpha motor neuron. This wave is unaffected by anesthesia due to purely axonal conduction without any synaptic activity. If used, a criterion of 50% reduction of its amplitude is used for prediction of neurological deficit.

After the initial stimulus, the signal is propagated to neighboring motor cortical neurons via

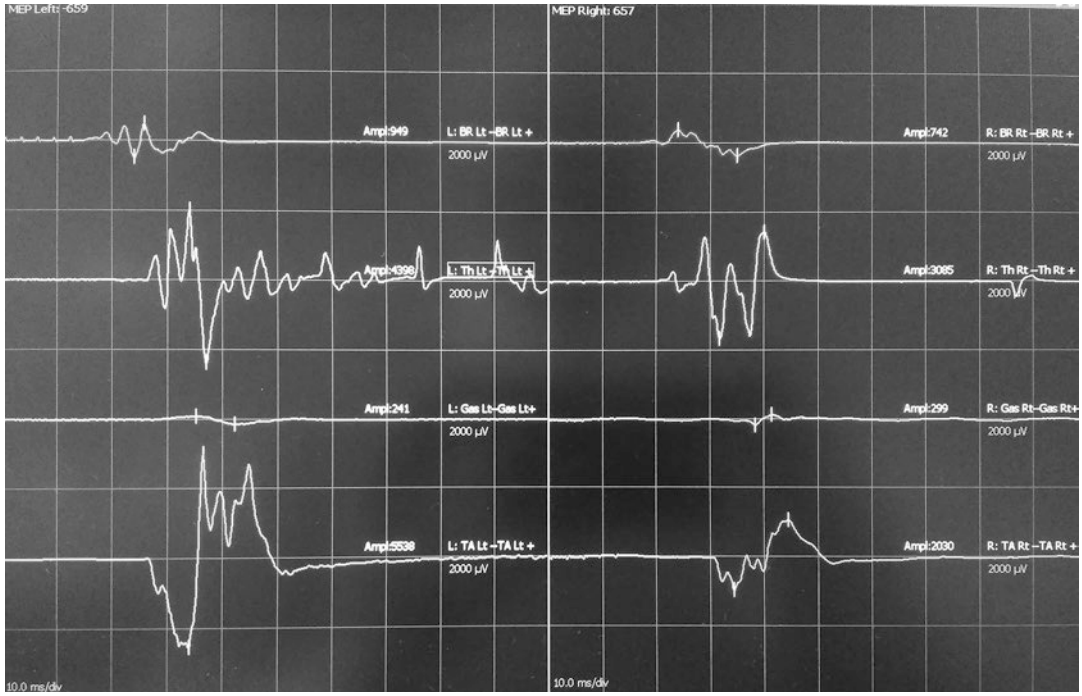

Fig. 5.3 Representative image of MEP monitoring of brachioradialis, thenar muscles (superior 2 waveforms) and gastrocnemius, tibialis anterior muscles (inferior 2 waveforms). Left and right panels are two sides being monitored, respectively

synaptic connections, and these produce multiple small waves (I waves), also captured at the spinal cord level. The "I" waves follow the "D" waves with a latency of 1.5 ms. These waves are affected by anesthetic agents due to predominant reliance on synaptic activity for their genesis. The signal then propagates to individual muscles, and EMG of the muscle twitch is captured as polyphasic CMAPs (Fig. 5.3). The CMAPs demonstrate a run-to-run variability even in individual patients, and thus the waveform acquired after the end of a train of impulses is displayed, rather than averaging approach as in SSEP. Due to reliance on muscle end plate for their genesis, CMAPs are severely affected by neuromuscular blocking agents and to a lesser extent by inhalational anesthetic agents (which in turn affect excitability of alpha motor neurons).

One important consideration is that, laterality of D and I waves cannot be determined. Since it is impossible to determine how much of contralateral corticospinal tract has been stimulated, reduction of amplitude of D-waves does not help in determining the laterality and extent of damage. Hence, CMAPs are used much more commonly than D-waves during MEP monitoring [11].

5.3.5 Neurogenic MEPs (NMEP)

A version of MEP stimulation involves direct stimulation of the spinal cord using epidural electrodes, with signal capture on the spinal cord distally. However, it has been revealed through collision studies that this stimulation produces a mix of sensory and motor pathway action potentials and thus lacks specificity. The contribution of the sensory pathways provides the main component of the NMEP wave, and thus it truly cannot be called an MEP. This approach has thus been aborted in favor of traditional MEPs [11, 15].

5.3.6 Anesthetic Considerations

Since cortical synaptic activity is required for acquiring MEPs, anesthetics have a detrimental effect on this modality. The basic rules stay similar to SSEP, except that MEPs are more sensitive to anesthetic agents than SSEPs and the requirement of exclusion of neuromuscular blocking agents from the anesthesia protocol. Although certain researchers have proven that partial neuromuscular blockade may allow MEP monitoring, this practice is not widely followed, and muscle relaxant usage is eschewed [16, 17].

Due to the lack of muscle relaxation and nonspecific activation of the motor cortex, MEP stimulation cannot be continued throughout the surgery akin to SSEP. It has to be done in an on-demand fashion, with the surgeon forewarned, due to physical movement of the patient's whole body during the stimulation. Also a bite block needs to be placed imperatively to prevent tongue bites and lip lacerations.

5.3.7 Uses of MEP

Uses of MEP for monitoring of the spine are similar to those of SSEP, though it is rarely used as a standalone monitor (due to technical difficulty of obtaining it intraoperatively). Usually it is used as a supplement to SSEP for monitoring corticospinal tract, which gets excluded with SSEP. Due to the extreme variability in MEP waveforms in the same patient, criteria for warning are not consistent (30–100% amplitude reduction in literature) [18]. It would be safe to say that clinical judgment should be used after taking into account SSEP waveforms, with 50% reduction as a threshold for suspicion. The threshold criteria for brain surgery should be less than that of spinal cord surgeries [19].

5.4 Spontaneous Electromyography

Spontaneous EMG, as opposed to SSEP and MEP, does not rely on specific stimulation of a neural tract to observe changes. In essence it may be compared with electroencephalography, such that spontaneous background activity of muscles gets monitored and any changes point to mechanical, thermal, or metabolic irritation of the neural tract in real time. Better temporal resolution of this technique compared to evoked potentials makes it an invaluable adjunct to neurosurgical tract monitoring techniques.

5.4.1 Stimulus Characteristics and Response Capture

Stimulus for this technique is physiological or iatrogenic perturbation of neural tracts at the operative site. Without stimulation, no activity will be recorded from the muscle, but during surgical manipulation such as stretching or compression of nerves, spontaneous discharges are observed. However, false-positive discharges occur frequently during cauterization and cold saline irrigation since electrical discharges and temperature changes can stimulate neuronal activity [20].

The response capture is done using bipolar needle electrodes (≥5 mm apart) inserted into specific muscles following the motor distribution of specific parts of the spinal cord (Table 5.3). The same electrodes used for MEP monitoring may be repurposed for this when MEP is not being conducted.

The recordings are done with a gain of 50–500 μV and filters of low pass at 10 KHz and

Table 5.3 List of muscle targets for electrode insertion for spontaneous EMG monitoring of spinal cord levels [20]

Spinal cord level	Target muscle
C4	Supraspinatus
C5	Deltoid/biceps
C6	Biceps/wrist extensors
C7	Triceps/wrist flexors
C8/T1	Intrinsic muscles of hand
T6–T12	Rectus abdominis
L1	Iliopsoas
L2	Adductor longus
L3	Vastus medialis
L4	Vastus lateralis
L5	Tibialis anterior/extensor hallucis longus
S1	Medial gastrocnemius
S2–5	Perianal muscles

high pass at 20–30 Hz. For cautery artifact removal, a switch may be provided directly connected to the amplifier, albeit with the knowledge of inability of obtaining recordings during cauterization.

5.4.2 Waveform Characteristics

The discharges may be visualized on screen and more often be linked to an audio output, which provides a real-time feedback to the neurosurgeon. The semiology of waveform is extremely variable; thus, the presence of the wave or duration and frequency of discharges is more important clinically. A single burst of discharge maybe ascribed to a specific maneuver on part of the neurosurgeon or nearness to a nerve root, but trains of neurotonic discharges imply constant irritation and maybe indicative of nerve root damage [20].

5.4.3 Anesthetic Considerations

Physiological variables (temperature and blood pressure) and choice of hypnotic agents have no effect on spontaneous EMG recordings. However, neuromuscular blocking agents need to be excluded from the protocol. As with MEPs, the discharges may be recorded at partial neuromuscular blockade (up to 75%); however due to uncertainty over interindividual variability, it is preferred they be excluded [21].

5.4.4 Limitations and Pitfalls

1. False negatives: Although this modality tests the integrity of the nerve, it is possible for the nerve to be stimulated, even after transaction, if the stimulation occurs on the distal part of the transected nerve, thus providing a false impression of continuity [20].
2. False positives: Trains of neurotonic discharges can be elicited by irritation of the nerve root with sudden temperature changes (warm or cold saline) or with mechanical irritation due to irrigation, which in themselves are benign. Overall this modality has a high sensitivity for nerve root damage but low specificity [21].

5.4.5 Uses

Any surgery with a risk of damage to a known motor nerve can be monitored using this technique. Cranial nerve monitoring also comes under the ambit of this monitoring modality, but will not be discussed in this chapter. In the spinal surgery context, any of the spinal nerve roots from cranial to sacral may be monitored for a variety of surgeries such as decompression, deformity correction, fusion, pedicle screw placement, or tumor resection [20].

5.5 Triggered EMG

Triggered EMG will be discussed here in the context of pedicle screw monitoring. The monitoring is based on the electrical insulating ability of the pedicle bone, which requires a higher current for stimulation of the underlying nerve root compared to when it is breached. This technique was initially demonstrated by Calancie in porcine model for accuracy of screw placement [22].

5.5.1 Stimulation Characteristics

The stimulation is conducted using a handheld probe by the surgeon, with stimulator being anodal and cathode being placed in the nearby surgical tissue. The stimulation may be either a constant current type or constant voltage type. Although theoretically a constant voltage has advantage over constant current, due to the latter one being susceptible to current shunting in variable intraoperative conditions, usually a constant current stimulation is done, with thresholds for medial pedicle breach being set in mA. The stimulation current of 5–30 mA is used, with threshold for suspicion of pedicle breach ranging from 5 to 10 mA. The variability in this threshold is due to interindividual variability in bone thickness, due to variability in bone thickness in lumbar and thoracic vertebrae, and due to the inherent weakness of constant current stimulators of current shunting, which leads to high false-positive and false-negative rates and unnecessary surgical delays. The stimulator may be used on the pedicle screw head itself or as exploratory probing of the pedicle screw tract [11, 20, 21].

5.5.2 Response Capture

The response is captured at the muscle level using similar electrode configuration for free-running EMGs. Bipolar electrodes may be placed directly in the muscle belly (higher specificity but smaller waveform amplitude), or monopolar electrode with subdermal reference (higher amplitude, lower specificity) may be used. The waveform acquired is a CMAP, and criterion for suspicion is the current threshold at which it is acquired. Usually <6 mA gives high probability of medial breach, and >8 mA provides a low likelihood of breach [23–25].

5.5.3 Anesthetic Considerations

The same protocol as free-running EMGs is followed and neuromuscular block is prohibited.

Key Points

- The neural tracts in danger of damage during surgical procedures of the spine can be monitored using a variety of modalities specific for various tracts and can be either spontaneous or evoked.
- Somatosensory-evoked potentials (dorsal column), motor-evoked potentials (corticospinal tract), spontaneous electromyography (EMG), and triggered EMG (nerve root monitoring) are the various modalities commonly in use for this purpose.
- SSEP is based on retrograde conduction of impulses from peripheral nerve stimulation, which are recorded at somatosensory cortex on the scalp. MEP is based on orthodromic conduction of impulses from stimulation of the motor cortex and recording the same from the spinal cord (D and I waves) and muscles (compound muscle action potentials).
- Spontaneous EMG is usually used as an adjunctive monitoring and helps recognize nonspecific neural tract irritation with excellent temporal resolution.

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Part III

Anesthesia for Neurosurgery

6 Anesthesia for Supratentorial Brain Tumor (SBT)

Fenghua Li and Reza Gorji

6.1 Introduction

Supratentorial craniotomy is performed for a variety of indications. The supratentorial region of the brain is the area overlying the tentorium cerebelli. It contains two cerebral hemispheres separated by the falx cerebri. Each hemisphere in turn is subdivided into four lobes which are the frontal, parietal, temporal, and occipital. Other supratentorial contents include the basal ganglia, thalamic nuclei, lateral ventricles, hypothalamus, and corpus callosum. Lesions in the supratentorial lesion are broad based. This chapter will focus on the treatment of tumors in the supratentorial region in adults. Other causes for a craniotomy are discussed in subsequent chapters throughout the book. These include endocrine tumors, treatment of epidural and subdural hematomas, traumatic brain injury, and intracranial vascular lesions including aneurysms and other vascular malformations. In this chapter, we discuss the unique challenges of a supratentorial craniotomy for supratentorial brain tumor (SBT) for the anesthesiologist. While there are common themes with infratentorial craniotomies, a unique set of principle apply to this procedure and location which must be understood in order to provide safe and state-of-the-art care to the neurosurgical patient.

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6.2 SBT Types

There are over 120 types of brain tumors. Common ones are listed in Table 6.1. The majority of brain tumors in adults (>80%) are SBTs. The World Health Organization classifies brain tumors by grade (I–IV) that correlates with clinical symptoms and presentation [1]. The higher-grade tumors are associated with more neurological side effects because of tissue destruction, necrosis, and associated edema. Knowing the tumor type and grade is very important because they have different effects on surgical approach and potential complications thus

Table 6.1 Common brain tumors

Astrocytoma
Choroid plexus
Craniopharyngioma
Ependymoma
Germ cell tumor
Glioblastoma
Glioma
Hemangioma
Juvenile pilocytic astrocytoma
Lymphoma
Medulloblastoma
Meningioma
Neurofibroma
Oligodendroglioma
Pineal tumor
Pituitary tumor
Schwannoma

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anesthesia management. Gliomas and meningiomas are the most common brain tumors. Gliomas account for about 30% of adult brain tumors. Meningiomas account for 35–40% of tumors. Pituitary tumors account for the remaining 15–20% of brain tumors. The remaining tumor is a primary central nervous system lymphoma (2–3%) and craniopharyngiomas (1%) [2, 3].

These gliomas can originate from astrocytes, oligodendrocytes, and ependymal cells. Gliomas peak incidence around age 70. The gliomas have divided histologically with glioblastomas accounting for over 50% of the gliomas. Astrocytomas (histologic classification) are about 25% of the remaining tumors followed by ependymomas and medulloblastomas accounting for smaller single-digit percentages [4]. The most common tumors of the ventricular system are choroid plexus papillomas and ependymomas [5].

6.3 Incidence and Epidemiology

The incidence of primary brain tumors in the United States is 29 per 10,000 persons [3]. As noted above, meningiomas and glial tumors account for two-thirds of such tumors. Adolescents and young adults typically present primary brain tumors, while adults in their 30s and 40s present with metastatic disease (tumors) with increasing frequency. In the latter case, if there is a primary brain tumor, it is likely a low-grade glioma.

There does not seem to be any identifiable risk factor in most primary brain tumors. Radiation exposure is the only established risk factor for primary brain tumors. About 5% of primary brain tumors are caused by genetic factors and are inherited. Genetic predisposition to tumor development may be present in neurofibromatosis types 1 and 2, Li-Fraumeni syndrome [6, 7], nevoid basal cell carcinoma, tuberous sclerosis, Von Hippel-Lindau disease, Turcot's syndrome, and familial polyposis [8]. In neurofibromatosis type 2 there is a genetic link to chromosome 22 specifically in the area of the neurofibromatosis type 2 gene.

Radiation could be a causative agent for development of brain tumors. For example, small dose of radiation in children (10 Gy) in the treatment of tinea capitis is shown to lead to tumor development 20 years from exposure date [9, 10]. Head injury is frequently cited as a causative agent for brain tumor development. This is not supported in the literature. In a study of 3000 patients with head injury, there was no increase incidence [11].

6.4 Preoperative Evaluation

6.4.1 History and Physical Exam

Whenever possible, the pre-anesthetic evaluation should be complete and comprehensive. The goal should be to learn about the patient's disease and their risk factors and optimize preexisting medical issues. The primary goal should be to minimize patient morbidity and mortality. When dealing with the American Society of Anesthesiology (ASA) class 3 and 4 patients, every effort should be made to evaluate and optimize patients before surgery [12, 13]. There is good evidence that morbidity and mortality are correlated with the ASA classification [14–16].

The pre-anesthesia history and physical exam is a must before a craniotomy is performed. However, for a craniotomy, additional history must be obtained, and documenting neurologic and cardiac status of the patient is especially important.

6.4.2 Neurologic Examination

In general, the anesthesiologist must perform a neurologic examination in lieu of the one done by the neurosurgeon. This assures:

(a) The location and extent of the disease process.
(b) Nervous system malfunction is documented.
(c) Documentation of patient's physical status and reserve.
(d) Development of a comprehensive anesthetic plan as it applies to the specific patient.

Table 6.2 Pre-anesthetic neurologic examination

Mental status	Appearance, cognitive function, affect, and speech
Motor system	Gait, heel to toe walk Pronator drift, hand grip Flexion and extension of feet Reflex testing biceps, triceps, patella, and Achilles tendons
Sensory system	Test for pain, temperature, and light touch in upper and lower extremities
Cranial nerves	Cranial nerve 2: visual acuity Cranial nerve 3: pupil size and symmetry, adduction, vertical gaze Cranial nerve 4: internal depression Cranial nerve 6: abduction
Cerebellar function	Romberg test

A quick neurologic exam is outlined in Table 6.2.

Therefore, the patient's baseline neurological status must be cataloged and any deficits noted. The clinician should note the signs and symptoms of high intracranial pressure (ICP). Tumor size and location are very relevant and should be documented. These indicate to the anesthesiologist the position the patient will be in as well as other potential difficulties during the procedure which relate to patient position (such as risk for venous air embolism) and tumor location. A seizure history must also be noted. When symptoms are seen in the postoperative period after emergence from general anesthesia, one can easily differentiate between new or recurrent deficits.

6.4.3 Cardiac Examination

Preoperatively understanding the patient's cardiac status is of utmost importance. Cardiac studies including an electrocardiogram and echocardiogram are frequently useful in patients in cardiac disease. These should be guided by patient's condition as well as knowledge of intraoperative events as it relates to neurosurgical intervention. The presence of dysrhythmias, conduction abnormalities, tachycardia, bradycardia, and treated or untreated hypertension will have profound impacts on anesthesia management in the patient undergoing craniotomy. Optimizing these conditions whenever possible is the best course of action.

Hemodynamic instability during a craniotomy can wreak havoc with anesthetic management of patients. In supratentorial craniotomies where the patient is going to be placed in the sitting position, an echocardiogram to rule out a patient foramen ovale (PFO) or other intracardiac shunt is necessary for anesthetic management. A PFO is a relative contraindication to sitting position craniotomy. If a preoperative echo is not possible due to emergent nature of surgery, a transesophageal echocardiogram should be done right after induction of anesthesia. If an intracardiac shunt is identified, then serious consideration must be given to undertaking the craniotomy in a position other than sitting. Sitting position is not the only risk factor for a VAE; tumors (specifically meningiomas) encroaching the superior sagittal sinus are also a risk factor. Other locations where hemodynamic perturbations can occur include the pituitary tumors and craniopharyngiomas. Dissection around the hypothalamus could evoke hypertension from sympathetic stimulator. Diabetes insipidus and cerebral salt-wasting syndrome can also occur with lesions around the hypothalamus.

T-wave abnormalities are common with subarachnoid hemorrhage and tumor bleeding [17]. In fact, electrocardiographic abnormalities may predict adverse clinical outcomes in patients with subarachnoid hemorrhage [18].

6.4.4 Comorbidities Evaluation

Patients with hypertension should have multiple blood pressures documented. All attempts should be undertaken to have blood pressure optimized.

Other comorbid conditions should be optimized as best as time allows. Diabetic patients are susceptible to steroid-induced hyperglycemia. Documenting and appreciating preoperative diabetic control will lead the clinician decision-making much easier. Many patients have chronic pulmonary obstructive pulmonary disease (COPD) as well as obstructive sleep apnea.

Possible ramifications include ventilator management during the anesthetic course and postoperative pulmonary management.

6.4.5 Medications

The patient's medications should be reviewed with specific attention to presence of anti-seizure and glucocorticoid medications. Anticonvulsant medications should continue the morning of surgery. Glucose monitoring is needed as blood glucose will likely to be elevated in patients on these medications. Patients with tumor-related edema should receive perioperative steroids. Dexamethasone is the common steroid used in the perioperative period. Stress dose steroids may be required prior to induction of anesthesia.

Other premedications which could cause CO_2 retention, such as benzodiazepines and narcotics, should be used cautiously in patients with significant increases in intracranial pressure (ICP).

6.4.6 Laboratory Evaluation

Fluid and electrolyte abnormalities are common in patients with brain tumors. Reasons include poor nutrition, preoperative medications, and endocrine abnormalities. Electrolytes, blood glucose, and blood count should be done prior to surgery. Other tests should be done only as indicated. Generally, a blood type and screen should be done prior to induction of anesthesia.

Laboratory data including electrolytes could be obtained and guide the clinician to disturbances caused by the perioperative use of medication including steroids [19] (hyperglycemia) and diuretics (hypokalemia).

6.4.7 Imaging Examination

Reviewing preoperative imaging scans including CT and MRI imaging of tumors with the neurosurgeons is a very useful avenue for gaining insight into the anesthetic management as well as avoiding intraoperative problems. Midline shift and effacement of ventricles suggest an increase in ICP. Hydrocephalus can be detected by imaging study as well.

6.5 Pathophysiology of SBT

6.5.1 Signs and Symptoms of SBT

The supratentorial region of the brain is unique in that it resides in an area surrounded by the skull and dura. Progressive neurological disorder follows a diagnosis of brain tumor. These disorders are caused by local infiltration of tumor and increased intracranial pressure. Local spread of tumor occurs and disrupts the normal-functioning brain cells and supporting neural tissue. Blood supply to the tumor and surrounding normal tissue can cause normal brain necrosis. Depending on tumor type, size, and location, the patient may present varieties of symptoms. Headaches are the most common problem. Seizures can occur due to altered neurotransmitter levels in the brain parenchyma. Other symptoms are loss of motor and sensory function, vision changes, mental status changes, etc.

6.5.2 Recurrent High ICP in SBT

The Monro-Kellie doctrine applies to the supratentorial compartment (Fig. 6.1). The doctrine states that any change in brain contents, namely, blood, brain, and cerebrospinal fluid, will result in reciprocal changes in the other variables to maintain the compartment volume the same since there is appreciably no change in skull compliance [20].

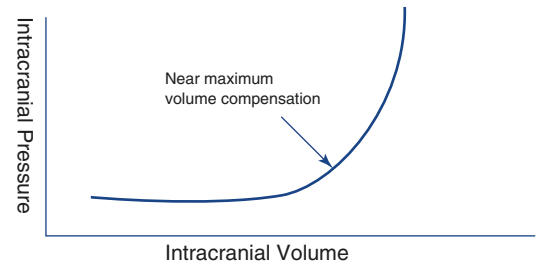

Fig. 6.1 Intracranial pressure-volume relationship

Therefore, an appreciable change in one component such as tumor or hemorrhage will lead to an increase in ICP. As tumor mass increases, ICP will also rise due to tumor mass itself, surrounding peritumor edema and alternations in cerebrospinal fluid circulation once compensatory mechanisms are exhausted. A recurrent issue in neuroanesthesia is prevention of high ICP and reduction of this factor. The objective should be to maintain cerebral perfusion pressure at an adequate level. Cerebral perfusion pressure (CPP) is defined as mean arterial pressure minus intracranial pressure (CPP = MAP-ICP). Uncontrolled increases in ICP have detrimental effects such as brain herniation through the foramen magnum [21]. During the procedure, when the cranium and dura are exposed, the focus shifts to brain relaxation to facilitate surgical access. Common sites for brain herniation are shown in Table 6.3.

The compensatory changes seen with slow-growing masses are reduction in CSF volume followed by reduction in blood volume. Once a critical mass is reached, further increases in volume will lead to increased intracranial pressure (ICP). A midline shift or subfalcine herniation of brain matter can occur as part of the compensation.

To reduce intracranial hypertension, one must consider the four components of the intracranial space:

1. The cellular compartment
2. Cerebrospinal compartment
3. Interstitial compartment
4. Blood compartment

A rise in ICP as seen with a protruding brain during surgery should raise the possibility of an epidural, subdural hematoma especially on the contralateral side.

Table 6.3 Brain herniation sites

1. Sub-falcine
2. Transtentorial
3. Foramen magnum
4. Transcalvarial

A rise in ICP due to high CSF volume can be managed by draining fluid from the lateral ventricle or a lumbar CSF drain. Lumbar CSF drains carry the risk of uncal and foramen magnum herniation, but when such threats do not exist, it can be very useful in improving surgical conditions. A rise in ICP due to increased interstitial compartment can be treated by osmotic and diuretic agents. Steroid use is good for subacute or chronic conditions.

CSF obstruction from the lateral ventricles into the subarachnoid space can lead to hydrocephalus.

Rapid changes in cerebral blood flow are possible by maneuvers performed by the anesthesiologist. The culprit seems to be often overlooked in the venous side of the cerebral circulation. Good head position improves venous drainage. Not allowing high intrathoracic pressures improves venous drainage from the head. Along the same train of thought, endotracheal tube obstructions, any (untreated) pneumothorax, as well as bronchial air trapping should be aggressively treated and avoided at all costs.

Increased ICP if unchecked will lead to brain herniation. Uncal and cerebellar herniation causes ischemia of both tissues which is part of the pathophysiology. Medulla compression will lead to apnea and death if not appreciated and corrected immediately. Widening pulse pressure (hypertension) along with severe bradycardia are other physiologic factors that occur with high ICP.

6.5.3 SBT Effect on CBF

Brain tumors can have a variable effect on cerebral blood flow. Areas around the tumor may be devoid of autoregulation and vascular reactivity to carbon dioxide [22]. Since autoregulation is impaired around the tumor, tissue affected by the tumor may be susceptible to cerebral ischemia if systemic blood pressure is reduced. In addition, hyperventilation to reduce brain size may become limited in scope. This will limit hyperventilation's role in reducing ICP.

The anesthetic drug effects on cerebral circulation must be considered carefully. A negative

effect on cerebral blood flow will result in adverse effect on cerebral blood volume. Careful selection of anesthetic drugs based on concurrent pathophysiology presents challenges to anesthesiologists. Volatile agents such as isoflurane, sevoflurane, and desflurane should be used with caution in cases where ICP is high and compensatory measures near the limits. In elective cases for maintenance of anesthesia, there does not seem to be any difference between propofol-maintained and volatile-maintained anesthesia [23]. Techniques utilizing intravenous anesthesia (less ketamine) are preferable. Consideration needs to be given to the use of prolonged propofol infusions. Fatalities have been reported in patients receiving prolonged infusions of propofol in the ICU. The syndrome is characterized by severe metabolic acidosis accompanied by rhabdomyolysis [24, 25].

Nitrous oxide when used as a sole anesthetic will have the most cerebrovasodilatory effect. When combined with other anesthetics such as narcotics and propofol, the effect is minimized. When ICP is very high and compensatory mechanisms are near their limit, it's prudent to use intravenous anesthetics along with avoidance of volatile agents [26, 27].

6.5.4 Effect of SBT on Cerebral Autoregulation and Blood-Brain Barrier

Cerebral autoregulation (CA) is the capacity of cerebral circulation to adjust its resistance to keep the constant CBF regardless of changes in systemic blood pressure or CPP. However, CA can become impaired in pathological state after brain injury including head injury, stroke, and tumor. The impairment can be minimal to complete depending on the severity of the brain injury [28]. CA may be altered by a supratentorial mass lesion. This can occur in both hemispheres. Sharma and colleagues found that if there is a midline shift of more than 5 mm in association with a large SBT, there is associated loss of autoregulation during the first 24 h after surgery. Carbon dioxide reactivity was found to be within normal limits both before and after surgery in all their patients ($n = 35$). The effect of lesions is not confined to loss of autoregulation; the blood-brain barrier can also have disrupted. This is a variable problem depending on tumor size, type, and degree of malignancy. This was discovered almost three decades ago by Butler and coworkers [29]. By using preoperative contrast-enhanced CT and radionuclide brain scans of 60 patients with surgically verified supratentorial astrocytomas, it is indicated that mechanisms of contrast enhancement and radionuclide uptake are identical in the detection of supratentorial gliomas. Authors stated that the integrity of the blood-brain barrier can be diagnosed by the imaging study. Fidler and Yano studied vascularization and brain metastases. If the metastases were smaller than 0.25 mm in diameter, the blood-brain barrier remained intact; otherwise it was permeable and thus directly impacts response to chemotherapeutic drugs [30]. This was later confirmed in humans with lung and breast cancer who developed brain metastasis [31, 32]. At least in mice, although BBB integrity is altered within the tumor site at later stages of development, the BBB is still functional and limiting in terms of solute and drug permeability in and around the tumor [33].

6.5.5 Seizures in SBT

Seizure commonly occurs with the presence of brain tumors. In fact, some tumors are discovered during the workup of a seizure episode. Unfortunately, they are poorly understood. Epilepsy can be a manifestation of a tumor (primary or metastatic), an infection, and a chemotherapy or even a surgical complication. It causes a significant loss of quality of life. The pathogenesis of tumor-associated epilepsy is multifactorial. It involves alternations in synaptic activity (release and reuptake), the excitotoxicity effects of glutamate, as well as probably genetic factors. Elevated extracellular glutamate stimulates NMDA and AMPA receptors or even

the formation of D-2HG in some gliomas [34]. No doubt, tumor size and location influence the occurrence of epilepsy [35, 36]. Seizure treatment after a neurosurgical procedure is less defined despite being a common occurrence. The use of anti-epileptic drugs post-surgery is common practice but not supported by literature in general. When the risk of seizures is high in the post-op period or likelihood of chronic epilepsy is considerable, treatment should be initiated [37]. The use of anti-epileptic drugs in glioblastoma patients suffering from seizures is almost routine because in this deadly cancer, seizures are a frequent presentation. Anti-epilepsy drugs are therefore routinely used in the pre- and postoperative period in patients undergoing surgical removal of glioblastomas [38, 39]. Levetiracetam followed by lacosamide or valproic acid are the agents of choice. The most frequent problems with the use of anti-epileptic drugs in neurosurgical oncology are cognitive dysfunction, bone marrow toxicity, and skin hypersensitivity.

6.6 Intraoperative Anesthesia Management of SBT

Intraoperative management of patients undergoing SBT requires careful planning and excellent communication with neurosurgeon. The size and location of brain tumor, presence of increased intracranial pressure (ICP), surgical positioning, brain relaxing techniques, use of intraoperative magnetic resonance imaging (iMRI), and patient's comorbidities should be considered in intraoperative anesthesia planning. Attention should be paid to positioning, attenuation of stress response to surgical exposure at different times, optimization of cerebral physiology to avoid secondary insults to brain and to facilitate surgical resection, obtaining good vascular access, avoidance of potential complications such as hemorrhage and seizure, need for intraoperative neuromonitoring during the surgery, and requirement of rapid emergence for neurological evaluation.

6.6.1 Preoperative Sedation

Preoperative sedation should be cautiously used in patients with brain tumor since increase in $PaCO_2$ due to respiratory depression may further increase ICP. Patients with decreased level of consciousness should not receive any sedation. However, patients with small size of tumor and without increased ICP but who are very anxious may benefit from sedation. Anxiolytics such as midazolam 1–2 mg can be given intravenously immediately before or after the patient is brought into the operating room. Opioids such as fentanyl can be used for sedation, but should be used cautiously to prevent respiratory suppression. Sedation with midazolam can exacerbate or unmask focal neurologic dysfunction more than with fentanyl in neurosurgical patients with SBT [40].

6.6.2 Seizure Prophylaxis

Patients who are taking anti-seizure medications preoperatively should be given their regular dose throughout the perioperative period to prevent seizure. Intraoperative seizure occurs rarely during SBT resection under general anesthesia [41], but it happens more often in craniotomy with intraoperative mapping [42] and in awake craniotomy for SBT [43, 44]. Seizure prophylaxis should be initiated prior to incision in patients with higher risk for intraoperative seizure. Common anti-epileptic drugs (AEDs) include levetiracetam, phenytoin, and fosphenytoin. We use levetiracetam for seizure more often because it is not associated with hypotension and tissue injury with extravasation.

6.6.3 Intraoperative Monitors

Standard monitoring for SBT surgery includes EKG, oxygen saturation (S_PO_2), end-tidal CO_2 ($EtCO_2$), temperature, and noninvasive and invasive blood pressure. Invasive arterial line placement is required to continuously monitor blood pressure, pulse pressure variability, and blood sampling. Invasive blood pressure monitoring allows

strict control of blood pressure as both hypertension and hypotension adversely affect ICP and CBF. Radial artery is most commonly used for this purpose. Depending on the need for monitoring CPP and patient's comorbidities, arterial line can be placed before induction or after induction of general anesthesia. Central venous pressure (CVP) monitoring is not routinely monitored during neurosurgery for SBT but may be considered to guide fluid replacement in patients with preoperative cardiovascular dysfunction. As noted in the preoperative section of this chapter, patients who are at high risk for venous air embolism (VAE) should have central venous access for air aspiration. Central venous access is obtained through antecubital fossa (such as PICC line) or femoral and internal jugular routes. Foley catheter is indicated for longer procedure or if mannitol is to be used.

Intraoperative neurophysiological monitoring (IONM) including Electroencephalography (EEG), somatosensory evoked potentials (SSEPs), and motor evoked potentials (MEPs) is sometimes used in SBT resection. Surgical resection close to or at eloquent areas might require brain mapping (electrocorticography) for more precise location and dissection. The modality used for monitoring has anesthesia implications. TIVA is usually required if MEPs are monitored.

Transcranial Doppler (TCD) can be used to estimate cerebral autoregulation and CO_2 responsiveness and then to determine adequacy of cerebral perfusion [45]. It is rarely used in OR because of difficulty of placement. Central jugular venous bulb oxygen saturation ($SjvO_2$) can be measured to determine the adequacy of brain perfusion; however, it is not routinely used. Cerebral oximetry may be an alternative because of noninvasiveness to monitor cerebral oxygenation [46].

6.6.4 Induction of General Anesthesia

6.6.4.1 Goals of Induction

Goals of induction are to avoid hypoxia and hypercarbia, to maintain hemodynamic stability, to reduce intubation-induced hypertension, and to prevent an increase in intracranial pressure.

6.6.4.2 Induction Agents

All intravenous anesthetics except ketamine decrease cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), and ICP. Most intravenous anesthetics can be used to induce patients with SBT to unconsciousness. Both propofol (1.25–2.5 mg/kg) and thiopental (3–6 mg/kg) are preferred induction drugs due to its cerebral vascular constriction and maximum reduction in $CMRO_2$. Etomidate (0.3 mg/kg) is a good alternative induction drug if patients has significant cardiac disease such as coronary heart disease and reduced ejection fraction. However, etomidate can cause myoclonus and adrenal suppression. Ketamine is usually not used for induction because of its increase in CBF, $CMRO_2$, and ICP. Benzodiazepine such as midazolam should be avoided since it has longer half-life, thus causing delay in emergence.

6.6.4.3 Neuromuscular Blockers (NMBs)

Currently used non-depolarized NMBs (rocuronium, vecuronium, atracurium, cisatracurium) have minimal effects on intracerebral hemodynamics. Atracurium causes histamine release that results in a drop in blood pressure from vasodilation; its use in patients with increased ICP should be very cautious. Succinylcholine can cause transient increase in CBF, $CMRO_2$, and ICP, although such increase can be controlled by hyperventilation or deepening anesthesia. Defasciculating dose of non-depolarizing NMBs also attenuates succinylcholine-induced increase in ICP [47]. If patient is at high risk for aspiration and rapid sequence induction is warranted, both succinylcholine and high dose (0.9–1.2 mg/kg) of rocuronium can be used to shorten the time of intubation and to decrease the chance of aspiration.

6.6.4.4 Adjuncts for Anesthesia Induction

An opioid is usually administered prior to induction agent to reduce required dose of induction agent, to suppress airway reflexes, and to mitigate hemodynamic response to laryngoscopy and

intubation. Opioids such as fentanyl, sufentanil, alfentanil, and remifentanil cause minimal effect on cerebral dynamics. Lidocaine is a local anesthetic and may be used to suppress the cough reflex during laryngoscopy and to blunt the hemodynamic response to intubation [48].

6.6.4.5 Induction of Anesthesia and Intubation

General anesthesia is usually induced with propofol or thiopental with supplemental short-acting opioids. NMBs are commonly administered to facilitate tracheal intubation and to avoid coughing and straining. Ventilatory control with mask ventilation is crucial in providing adequate oxygenation and mild hyperventilation. It is important to position the head not to obstruct cerebral venous return to the heart. Mild head-up position may facilitate venous drainage, thus possibly decreasing ICP. Once adequate depth of anesthesia is achieved and muscle relaxation is confirmed with a peripheral nerve stimulator, tracheal intubation with direct laryngoscopes can proceed. Hypertensive response to laryngoscope can be attenuated by either remifentanil or additional bolus of small dose of induction agents or beta-blockers such as esmolol and/or lidocaine (1.5 mg/kg). In emergency cases or patients with high risk of aspiration, rapid sequence intubation is indicated. Video-assisted laryngoscopes offer a better view of the larynx and are becoming popular in intubation.

Patients with difficulty in airway may require awake intubation. Meticulous attention should be paid to maintain hemodynamics stability and to avoid hypoxia and coughing with excellent anesthesia to airway.

6.6.4.6 Patient Position

Positioning patients with SBT for surgery requires meticulous attention to details to prevent positioning-related injuries. The anesthesiologist needs to understand different positionings that have effects on cardiovascular and pulmonary function. The craniotomy for SBT can be done in a variety of positions depending on location of tumor and surgical approaches. These positions include supine, lateral and semi-lateral, prone, concorde, three-quarters, and rarely sitting position for pineal regional tumor. Head/neck flexion, extension, and rotation are always required during positioning. Complications associated with different positions include brachial plexus and peripheral nerve damage, cervical spine injury, ocular injury, skin pressure injury, airway compromise, and VAEs. Hyperflexion of cervical spine impedes venous drainage, causes airway edema, and kinking of endotracheal tube. Ensuring a two-fingerbreadth distance between the chin and chest may prevent these complications.

Placing headpins is a painful stimulation and can result in significant sympathetic response that leads to an increase in ICP. This response can be preemptively prevented by deepening anesthesia and administering short-acting beta-blockers or fast-onset opioids immediately before the pin placement.

6.6.5 Maintenance of General Anesthesia During Craniotomy

Primary goals during surgery are (1) to maintain CBF by optimizing cerebral physiology to avoid brain ischemia and (2) to relax the brain to allow optimal surgical dissection and manipulation to avoid excessive brain tissue retraction and brain edema. The first goal depends on maintaining optimal CPP and reducing $CMRO_2$ as well as preventing intracranial hypertension before dural opening. The second goal depends on control of brain volume and CBF via prevention of hypertension, cerebral vasodilation, and osmolar therapy.

Anesthesia can be maintained by either halogenated volatile agents such sevoflurane or total intravenous anesthesia (TIVA). Studies have failed to show differences in outcomes between volatile anesthesia and TIVA in patients with SBT [49–51]. However, propofol-maintained anesthesia lowers ICP more and has higher CPP compared to volatile-maintained anesthesia, although brain relaxation score is similar after dural opening [23, 52].

The advantages of current volatile agent (desflurane, sevoflurane, and isoflurane) use are their controllability, predictability, and early awakening. However, volatile anesthetics have the ability to increase ICP, CBF, and brain bulk that are unwanted during neurosurgery. Sevoflurane is the least cerebral vasodilation agent among all volatile anesthetics with nearly no impact on cerebral blood volume and ICP in concentrations below 1.0 MAC [53]. Thus, sevoflurane is a better volatile anesthetic for neuroanesthesia. Nitrous oxide (N_2O) can cause increases in CBF, CM, and ICP but preserves autoregulation in response to CO_2. When concurrently administered with volatile anesthetic, N_2O can result in substantial increase in CBF [54]. Thus, N_2O is avoided if volatile anesthetic is administered for anesthesia maintenance.

Intravenous anesthetics offer better control of ICP, CBF, and brain swelling, but prolonged or unpredictable awakening remains a concern. It may result in difficulty in differential diagnosis of delayed wake-up and need for emergency CT scan to rule out surgical complications. Monitoring anesthesia depth during TIVA with processed electroencephalography (EEG) such as bispectral index (BIS) or SedLine helps to reduce drug overdosing, thus decreasing incidence of prolonged awakening. TIVA is usually composed of propofol and remifentanil since both propofol and remifentanil have good pharmacokinetic profile of short context-sensitive half-life. Caution should be exerted when propofol is infused in patients with frontal brain tumor due to higher clearance in these patients [55]. In patients with increased ICP and evidence of midline shift on preoperative CT scan, TIVA with propofol is advantageous to sevoflurane anesthesia due to lowering ICP more.

6.6.5.1 Paralysis During Surgery

Patients are typically paralyzed during craniotomy for SBT resection under general anesthesia unless neuromonitoring precludes the use of NMRs. Paralysis reduces the chance of patient movement and coughing during light anesthesia. Commonly used NMRs are rocuronium, vecuronium, and atracurium. Train-of-four (TOF) peripheral nerve stimulator is used to guide the dose of NMBs and depth of neuromuscular blockade. Deep neuromuscular block of TOF less than two twitches is required until head frame is removed from the head since coughing and movement while the skull is fixed in place can result in cervical spine injury.

6.6.5.2 Narcotics

Opioids have minimal cerebral physiologic effect when ventilation is controlled. Opioids such as fentanyl are used as analgesia as part of maintenance of anesthesia. Short-acting opioids are preferred due to the need for fast emergence from anesthesia for neurological evaluation. Remifentanil is generally administered as infusion at dose of 0.05–0.5 mcg/kg/min. Morphine can cause histamine release in some patients, which could increase CBF.

6.6.5.3 Dexmedetomidine

Dexmedetomidine is a highly selective $alpha_2$ agonist with sedative, sympatholytic, and analgesic properties that may be used as an adjunct during general anesthesia or sedation for awake craniotomy. Dexmedetomidine is a cerebral vasoconstrictor that causes a dose-dependent reduction in CBF in human [56, 57] that could lead to brain ischemia. However, one study showed its decrease in CBF parallels with a reduction in CMR [58]. Intraoperative infusion of dexmedetomidine has also shown a reduction in post-craniotomy pain [59, 60].

6.6.5.4 Blood Pressure Management

Intraoperative blood pressure should be controlled to maintain optimal CPP (CPP = MAP–ICP, or MAP–CVP if CVP > ICP) to perfuse the brain while avoiding hypotension or severe hypertension that may result in brain ischemia or intracranial hemorrhage. Cerebral autoregulation of CBF occurs between MAP of 60 mmHg and 150 mmHg [61]. Outside of this range, the brain is unable to compensate for the changes in CPP; thus, CBF changes passively with corresponding changes in blood pressure. This change in CBF

can result in risk of ischemia in lower blood pressure and brain edema or bleeding at high blood pressure. The goal of BP should be individualized based on patient's comorbidities, intracranial pathology, and anesthetic factors. Cerebral autoregulation mechanism is preserved in brain tumor patients with good clinical status; but patients with large SBT and middle-line shift more than 5 mm have impaired cerebral autoregulation. CPP between 65 and 80 mmHg is accepted for SBT resection. Normal ICP ranges from 5 to 10 mmHg, so MAP 75–90 mmHg is a reasonable range for those uncomplicated patients whose cerebral autoregulation is intact. Individualizing MAP and CPP goal by cerebral autoregulation monitoring to calibrate optimal level is feasible and improves patient outcome [62]. Maintenance of optimal BP is usually achieved by optimizing intravascular blood volume, titrating anesthesia level to surgical stimuli, and administering vasopressors or vasodilators if needed.

6.6.5.5 Intraoperative Fluid Management

Fluid therapy for SBT craniotomy is to achieve euvolemia to maintain adequate cerebral perfusion and to prevent brain edema. We maintain euvolemia using goal-direct fluid therapy strategy by monitoring pulse pressure variability.

Crystalloid: Hypotonic fluid increases brain interstitial fluid and should not be used. Isotonic crystalloid such as plasmalyte does not increase brain interstitial fluid contents with intact blood-brain barrier (BBB). Normal saline (NS) (0.9% sodium chloride) is slightly hypertonic (308 osmol/L) which is preferred to Ringer's lactate that is slightly hypotonic. Large quantities of NS use can cause hyperchloremic acidosis. Alternative use with Ringer's lactate may prevent this problem. Hypertonic fluids such as hypertonic saline (HTS) can decrease the interstitial fluid by pulling water across the cerebral capillary endothelium along its osmotic gradient. HTS can increase brain volume in the brain with impaired BBB [63]. Glucose-containing fluids should be avoided to prevent hyperglycemia that can worsen neurologic injury especially during periods of ischemia.

Colloid: 5% or 25% albumin can be used to quickly restore intravascular volume in hypotension situation. However, comparing to NS, albumin use in severe TBI patients was associated with worse outcome [64]. Excessive starch solutions could result in bleeding because they interfere with factor VII clotting complex and platelet function [65] and should not be administered to patients in SBT surgery.

6.6.5.6 Intraoperative Ventilation Control

CO_2 responsiveness is intact in patients with SBT. Elevation in $PaCO_2$ results in increased CBF and may increase ICP. Goal of ventilation is to maintain normocarbia of $PaCO_2$ between 35 mmHg and 40 mmHg. Hypercarbia should be avoided during craniotomy. Transient therapeutic hyperventilation may be required to treat acute cerebral edema and should be guided with $PaCO_2$ rather than end-tidal CO_2 ($EtCO_2$) that is affected by age, lung disease, and positioning. Cerebral vasoconstriction from hyperventilation may result in ischemia of at-risk brain tissue. Hyperventilation to a $PaCO_2$ of 25–30 mmHg can improve surgical condition during SBT craniotomy [66] but may cause brain ischemia in injured brain [67].

6.6.5.7 Glycemic Control

Hypoglycemia causes and exacerbates neuronal injury and should be avoided during craniotomy [68]. Hyperglycemia worsens neurological function in acute brain damage and increases infection risk and complications [69]. We aim a blood glucose level between 80 and 180 g/dL since tight control of blood glucose increases incidence of hypoglycemia [70]. Hyperglycemia >180 g/dL should be treated with insulin with close monitoring.

6.6.5.8 Brain Relaxation During Surgery

Brain relaxation or brain shrinkage may be required to improve surgical exposure and to avoid brain tissue ischemia resulting from

retractor pressure. It can be part of surgical plan or may be required to unexpected brain swelling and tightness during the procedure [71]. Regimen for achieving brain relaxation include elevation of head to facilitate venous drainage, hyperventilation for cerebral vasoconstriction, osmotherapy with mannitol or HTS, administration of diuretic to reduce blood volume, glucocorticoids to reduce swelling, and cerebrospinal fluid (CSF) drainage if lumbar drain or ventricular catheter is placed preoperatively to reduce brain bulk. Compared to mannitol, equiosmolar HS provides better brain relaxation, while ICU stay or hospital stay is not affected [72].

6.6.5.9 Intraoperative Cerebral Edema Treatment

Once cerebral edema occurs, immediate treatment should be initiated. Chemical brain retractor concept has been most used to treat this condition [73, 74]. This includes mild hyperventilation with goal $EtCO_2$ between 25 and 29 mmHg, mild hyperoxygenation, mild controlled hypertension with goal MAP around 100 mmHg, osmolar therapy with mannitol (0.5–0.75 g/kg) or HS (3–4 ml/kg of 3% HS), normovolemia, and intravenous anesthetic (propofol). Elevation of head, minimal PEEP, maintaining adequate depth of anesthesia and muscle relaxation, drainage of CSF, and avoidance of brain retractors are also implemented. In severe case, high-dose barbiturate therapy (e.g., pentobarbital) which titrates to EEG burst suppression may be used.

6.6.6 Emergence from Anesthesia After SBT Resection

6.6.6.1 Goals of Emergence

Goal of emergence is to maintain hemodynamic stability thus normal CBF and ICP, normothermia, and proper oxygenation and ventilation. Emergence should be smooth without coughing, straining, and hypertension that cause increase in ICP. Patients need to awake enough for an adequate neurologic examination (e.g., responding to commands, moving all extremities to command, adequate vision assessment). Most patients are awoken and extubated in OR after SBT craniotomy.

6.6.6.2 Management of Emergence

NMBs should be fully reversed. Anesthetics for anesthesia maintenance should be titrated down to the level of return of consciousness at the end of procedure that allows neurological evaluation. Tracheal suction, airway overpressure, and patient-ventilator dyssynchrony must be avoided. Opioids such as fentanyl for pain control should be titrated as needed following extubation and neurologic exam. Opioids should not be administered at a dose that is expected to prevent anticipated pain because liberal opioid dosing based on anticipating pain or guided by hemodynamic end points often results in somnolence, a delay in a satisfactory neurologic exam, and occasionally unnecessary head imaging.

6.6.6.3 Control of Emergence Hypertension

Hypertension is common on emergence from anesthesia after craniotomy. Rapid control of systolic BP to less than 140 mmHg is critical in reducing risk of intracranial hemorrhage after craniotomy [75]. Hypertension also worsens cerebral edema in areas where blood-brain barrier is damaged. Vasodilators and beta-blockers are commonly used for treating hypertension, but treatment should be titrated to avoid hypotension that can lead to cerebral hypoperfusion and ischemia. Beta-blockers and nicardipine are commonly used in combination in our institution. Labetalol is a combined alpha-adrenergic and beta-adrenergic blocker with onset within 5 min and duration of 3–6 h and is our first choice if not contraindicated. Nicardipine is a short-acting calcium channel blocker with onset <2 min and duration of 60 min and is used as an infusion at 5 mg–15 mg/h following labetalol boluses. Although esmolol is an ultra-acting beta-1 selective antagonist and is effective in treating emergence hypertension [76], nicardipine is superior to esmolol in treatment of post-craniotomy emergence hypertension [77].

6.6.6.4 Delayed Emergence

When patient is slow to wake up from anesthesia after craniotomy for supratentorial tumor, patient's vital signs should be assessed and abnormalities corrected. Causes of delayed wakening should be identified. Possible causes include residual anesthesia, metabolic abnormalities, neurological abnormalities, and surgical-related complications.

Residual anesthesia: neuromuscular block should be totally reversed, and reversal should be assessed with a TOF nerve stimulator. End-tidal inhalation anesthetic should be checked. A processed EEG such as BIS to check the depth of anesthesia if TIVA is used for the procedure. Naloxone may be used to reverse narcotic overdose.

Metabolic abnormalities: blood glucose level, arterial blood gas, and electrolytes should be measured to rule out hypoglycemia, acid-base abnormalities, and severe electrolyte disturbance. Correction of those abnormalities needs to be done if they exist.

Neurological causes: postictal state needs to be excluded as possible cause of delayed awakening.

Surgical causes: cerebral edema, intracranial hematoma, seizure or postictal status, and ischemia are possible surgical causes for delayed emergence.

If no causes are identified, emergency CT scan needs to be performed to evaluate intracranial hemorrhage, brain edema, pneumocephalus, or other intracranial pathology.

6.6.7 Special Considerations

6.6.7.1 Awake Craniotomy (AC) for SBT

Patients with SBT near or residing in eloquent regions of cerebral cortex requires AC that allows function brain mapping to help identify and protect functional cortex [78, 79]. Recently, AC is regarded as standard of care for those patients [80]. AC has been associated with a greater extent of tumor resection, fewer later neurologic deficits, shorter hospital stays, less postoperative pain, and improved survival [81]. Preoperative evaluation should be done the same as patient going for craniotomy under general anesthesia. However, careful patient selection and preparation are critical to success of AC.

6.6.7.2 Anesthesia Techniques

There is no standardized anesthesia technique for AC. AC in general can be divided into three sequential phases: craniotomy, awake mapping before or through tumor resection, and closure. Different techniques have been used to cover these phases. Monitoring anesthesia care (MAC) with sedation or general anesthesia for initial craniotomy and/or closure (asleep-awake-asleep technique) is usually used for AC. The airway is controlled with endotracheal tube or laryngeal mask airway during general anesthesia time. Each technique has its advantage and disadvantage [82, 83]. The goals should aim for patient comfort and airway safety during awake phase while brain mapping is optimal. MAC with sedation is choice for AC in our institution because of avoidance of airway instrumentation and anesthesia emergence. Midazolam is administered and is titrated to alleviate patient's anxiety. Scalp block and local infiltration at pin sites are performed before head pin placement. Dexmedetomidine in combination with propofol infusion is used for sedation and is titrated to the appropriate level of sedation. Remifentanil is sometimes added as sedation for the craniotomy phase. Failed AC can occur in variety of reasons and is associated with lower incidence of gross total resection and increased morbidities [44]. These include failure in communication with patient, uncontrolled intraoperative seizure, airway problems, or brain swelling.

6.6.7.3 Intraoperative Magnetic Resonance Imaging (iMRI) Use for SBT Resection

iMRI offers near real-time imaging guidance during brain tumor resection. It has been shown to optimize the extent of tumor resection and safety of brain tumor surgery especially for gliomas [84, 85]. iMRI can also detect intraoperative

complications. Thus, iMRI contribute to enhanced clinical outcome and improved patient care. Higher-field MRI scanner is more commonly used intraoperatively due to its increased image quality and spectrum of sequences. The neurosurgical OR suite in our institution is equipped with Brainlab and 3 T iMRI in a two-room solution setup. Anesthesia equipment including anesthesia machines, monitors, stethoscopes, and infusion pumps is MRI compatible and is available in both rooms. MRI safety regulation is strictly enforced. Prior to transporting the patient into the MRI room, a mandatory time-out is done to make sure no ferrous materials are brought into the scanner. ETT must be checked and secured well before the patient is moved onto scanner where it is difficult to access during MRI. Anesthesia is maintained with either volatile anesthetic or TIVA during MIR scanning. ASA standard monitoring is applied in this situation too. However, EKG tracing interference from high magnetic field makes arrhythmias and morphologic changes difficult to detect. Attention should be paid to pulse waveform or arterial wave if available for pulse irregularity. Emergency medications are easily available, and the anesthesiologist monitors the patient closely in the control room.

6.7 Conclusion

Anesthesia for SBT resection is a common procedure. The anesthesiologist must understand and apply principles of neurophysiology and neuroanesthesia to the perioperative care of these patients. Anesthetic management should aim for maintaining normal cerebral physiology. Tumors and anesthetics both affect brain physiology. Careful application of neuroanesthesia principles along with neurologic and hemodynamic monitoring in conjunction with understanding implications of surgical treatment and concurrent medical status of patient will in most cases result in a safe and successful treatment.

Key Points

- Supratentorial brain tumor (SBT) has profound implications for cerebral physiology including alterations in intracranial pressure and cerebral autoregulation.
- Goals of anesthesia management are to optimize cerebral physiology by maintaining cerebral perfusion pressure, to facilitate surgical resection, to prevent brain ischemia, and to allow rapid emergence for neurologic examination.
- Both inhalational and total intravenous anesthesia (TIVA) with propofol for maintenance of anesthesia are acceptable techniques. However, TIVA has many advantages to alternative techniques involving volatile agents.
- Emergence from anesthesia after SBT resection is just as important as induction of anesthesia, and the altered physiology after surgery makes this period of vital importance to avoid complications. The emergence hypertension should be treated quickly.

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7 Anesthesia for Infratentorial Lesions

Barkha Bindu and Charu Mahajan

7.1 Introduction

Posterior fossa surgeries provide a unique set of challenges for both neurosurgeon and neuroanesthesiologist. The closed space of this fossa and the vital neurovascular structures traversing it demand close attention from both surgeon and anesthesiologist. This chapter focusses on various infratentorial lesions encountered in clinical practice and their presenting features, anesthetic considerations in posterior fossa surgery, choice of surgical position, intraoperative monitoring considerations, and techniques for prevention and detection of venous air embolism (VAE).

7.2 Anatomy

The base of the skull is divided into anterior, middle, and posterior cranial fossae. The posterior fossa is the largest and deepest of these and is tightly packed with vital structures. Posterior fossa can be further divided into anterior and posterior compartments, with fourth ventricle as the reference point. Gliomas and cerebellopontine angle tumors are the most common tumors of the anterior compartment, while cerebellar astrocytomas, medulloblastomas, ependymoma, hemangioblastoma, and metastases are the most common posterior compartment tumors.

Floor of the posterior fossa is formed by the sphenoid, occipital and temporal bones, and mastoid angles of parietal bones. Anteriorly, dorsum sellae of sphenoid bone and petrous part of temporal bone separate it from the middle cranial fossa. It is bounded posteriorly and inferiorly by foramen magnum. Tentorium cerebelli, a dural reflection, separates it from the supratentorial compartment. Falx cerebelli, another dural fold, separates the two cerebellar hemispheres.

Important structures in the posterior fossa include the cerebellum, brain stem (midbrain, pons, and upper medulla oblongata), 3rd to 12th cranial nerve nuclei, vertebra basilar vascular system, and ascending and descending tracts. Venous sinuses seen here include the right and left transverse sinuses that join the superior sagittal sinus and the straight sinus to form the confluence of sinuses (torcular Herophili). This confluence drains into left and right sigmoid sinuses which exit the posterior fossa as internal jugular veins.

Openings and their contents in the floor of posterior fossa include the foramen magnum (spinal cord), internal acoustic meatus (7th and 8th cranial nerves), condylar canal (12th cranial nerve, meningeal branch of ascending pharyngeal artery), and jugular foramen (internal jugular vein, 9th, 10th, and 11th cranial nerves).

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7.3 Epidemiology

Around 15–20% of all adult brain tumors and 54–70% of all pediatric brain tumors arise from the infratentorial region. Most common infratentorial tumors in children are cerebellar astrocytomas, medulloblastomas, and brain stem gliomas. Posterior fossa arteriovenous malformations (AVM) account for 5–7% of all intracranial AVM.

Arnold-Chiari malformations (ACMs), the most common craniovertebral junction anomaly, have a reported incidence of 1 in 1000 live births. It occurs due to underdevelopment of posterior fossa or due to overgrowth of supratentorial compartment. It is divided into four types, type I being the commonest. Type I involves herniation of cerebellar tonsils into foramen magnum. It is often a chance finding, with most patients being asymptomatic for most of their life. Type II involves herniation of cerebellar tonsils and the brain stem into the foramen magnum. It is often accompanied by a myelomeningocele. In type III, part of fourth ventricle may also be herniated and rarely forms an occipital encephalocele. Type IV involves cerebellar hypoplasia with parts of skull and spinal cord exposed.

7.4 Clinical Features and Surgical Procedures for Posterior Fossa Lesions

Commonly performed surgical procedures in the posterior fossa region include excision of tumors, surgeries for vascular lesions and decompression of cranial nerves by vascular structures, craniocervical abnormalities correction surgeries, and evacuation of hematomas and decompressive craniectomies.

1. Tumors: Posterior fossa tumors can be intra-axial (arising from within the brain parenchyma or extra-axial (arising from structures other than brain parenchyma, such as meninges, nerves, etc.). In the anterior compartment, most common intra-axial tumors are gliomas, while extra-axial tumors commonly arise from cerebellopontine angle (CPA). The common ones are acoustic schwannoma, meningioma, epidermoid tumors, cysts, glomus tumors, and metastasis. Posterior compartment tumors are predominantly intra-axial and include cerebellar astrocytomas, medulloblastomas, ependymoma, hemangioblastoma, lymphoma, and metastasis.
   They can present with symptoms of cranial nerve impairment, cerebellar symptoms, and raised intracranial pressure (ICP).
2. Vascular lesions: These can be aneurysms or arteriovenous malformations (AVM). Aneurysms are rare but can arise from the vertebrobasilar system or from the posterior inferior cerebellar artery. Unruptured aneurysms can present with symptoms of mass effect or from direct compression of cranial nerves. Ruptured aneurysms of posterior fossa may have a poor prognosis. Commonly involved cranial nerves are 7th and 8th nerves.
   AVM are also rare in posterior fossa and difficult to treat due to their proximity to vital structures. Management options for AVMs include surgical resection, endovascular obliteration, and radiosurgery. AVMs more commonly present with hemorrhage, rather than with headache or seizures.
3. Craniovertebral junction anomalies: These include Chiari anomalies, congenital bone diseases, metabolic diseases, and genetic anomalies. Surgical procedures for these lesions target toward stabilization of the lesion. Surgical approaches used can be transoral, lateral, or posterior. ACMs generally undergo foramen magnum decompression surgery.
   Common presenting features of ACMs include symptoms related to hydrocephalus. Other common symptoms are headache, neck pain, and paresthesia and weakness of hands.
4. Hemorrhage and infarct: Posterior circulation aneurysmal bleed, cerebellar bleed, or development of infarct may cause rapid rise in ICP and compression of the brain stem. These lesions may require external ventricular drain (EVD) insertion or decompressive craniectomy surgery.

These lesions cause obstruction to cerebrospinal fluid (CSF) flow causing symptoms of acute hydrocephalus and features of brain stem dysfunction.

7.5 Preoperative Assessment

Detailed medical history, symptoms and signs of raised ICP, cranial nerve palsies (impaired cough and gag), and cerebellar signs (ataxia, nystagmus, etc.) must be noted. Physical status and cardiovascular and pulmonary status of the patient can influence the choice of surgical position and must be thoroughly assessed [1]. Site, size, and vascularity of tumor and presence of hydrocephalus can be known from imaging studies. History regarding preoperative CSF shunting procedures must be assessed. Airway assessment must be done as in any other surgical patient. Airway might be challenging in patients with craniovertebral junction abnormalities who may have reduced neck movements or an unstable spine. These patients must be counseled preoperatively regarding awake intubation. Some groups perform a flexion-extension radiograph preoperatively in all patients to rule out spinal instability [2]. Any pre-existing volume deficit and electrolyte disturbances must be addressed. Positioning options and monitoring requirements and need for postoperative mechanical ventilation must be discussed with the surgeon and anesthetic plan prepared accordingly.

For patients to be operated upon in sitting position, the practice of preoperative screening for intracardiac shunt is variably followed. Some centers perform a preoperative transthoracic bubble screening to look for patent foramen ovale (PFO) [3]. Both transesophageal echocardiography (TEE) and noninvasive transthoracic echocardiography (TTE) can be used for preoperative screening. However, confirmation of a PFO does not always mandate a change in the planned surgical position. Feigl et al. for the first time conducted a study on patients with known PFO operated in the sitting position. A strict standardized protocol that included scheduled jugular compression to detect any bleeding that could imply venous air entrance was followed. They confirmed the safety of sitting position in patients with PFO [4]. Fathi et al. in a systematic review of PFO and neurosurgery in sitting position recommended screening for PFO considering its percutaneous closure 2–4 weeks before surgery [5]. However, prospective studies are required to formulate evidence-based recommendations. Some centers search for PFO only after induction of anesthesia using TEE [6], but it is not 100% sensitive. However, arterial embolism can occur even in the absence of cardiac shunt by transpulmonary passage of air [7].

7.6 Surgical Positions

Posterior fossa structures can be accessed through various positions. General considerations while positioning include keeping the unmonitored phase as short as possible; this may occur while shifting or positioning the patient on table. Head-up tilt or reverse Trendelenburg position is commonly employed in most neurosurgical procedures. It must be borne in mind that each 2.5 cm elevation of the head above the level of the heart causes a 2-mmHg reduction in cerebral perfusion pressure (CPP).

Various positions for infratentorial tumor surgeries have been extensively studied. In general, sitting position is reportedly associated with lesser blood loss, better cranial nerve preservation, better postoperative course, higher hemodynamic instability, and higher VAE incidence, when compared to other positions [8, 9]. Both sitting and lateral positions are equally safe based on current evidence [10].

7.6.1 Supine Position with Maximal Neck Rotation

This position is useful for accessing lateral structures in posterior fossa. Maximal rotation of the neck to the opposite side may be done depending on the site of lesion. Ipsilateral shoulder may be elevated with a roll, if further rotation is required. This reduces the risk of brachial plexus injury.

This position is easier and quicker to achieve. Patients with any impairment of neck movement should not be subjected to such positioning. Lateral rotation of the neck can impair venous drainage from the brain and theoretically may increase the risk of raised ICP. Also extreme and prolonged rotation of the neck can cause macroglossia.

7.6.2 Lateral Position

Lateral position is suitable for unilateral procedures of the posterior fossa. It facilitates gravitational retraction of cerebellum and drainage of CSF and blood from operating field, thereby improving surgical access. Incidence of VAE is lower, and hemodynamic stability is better than in other positions. Brachial plexus injury and ventilation-perfusion mismatch in a dependent lung are potential hazards with this position [11]. Dependent arm needs to be positioned carefully to avoid peripheral nerve injury.

7.6.3 Park-Bench Position

It is a modification of the lateral position and gives better access to midline structures of posterior fossa. Patient is positioned semi-prone with head rotated and neck flexed such that brow faces the floor. It allows rapid lowering of the head to the left lateral decubitus position in case VAE occurs. Disadvantages include risk of peripheral nerve injuries, macroglossia, and impaired venous drainage from the brain. Also, this position takes much longer time to be established compared to other positions.

7.6.4 Prone Position

This position facilitates access to the craniocervical junction and upper spinal cord in addition to the posterior fossa. Shoulders must be placed at or above the cephalad edge of the operating table. Lower chest and abdomen should be free, and pelvis should be supported by bolsters placed at level of the anterior superior iliac spine. It provides easy surgical access with a low incidence of VAE. Disadvantages include suboptimal positioning in obese patients and those with restricted neck movements, restricted airway access, difficulty in cardiopulmonary resuscitation, pressure point injury to the face, eye compression (with horseshoe frames) causing blindness [12], compression of the inferior vena cava, conjunctival edema, and venous pooling causing hypotension. Apart from being logistically difficult, there is also a risk of dislodgement of airway and invasive monitors. Extreme neck flexion can cause macroglossia, airway obstruction, and cervical spinal cord compression [13].

7.6.5 Sitting Position

Sitting position provides optimal access to posterior fossa (particularly for supracerebellar infratentorial approach to pineal region tumors and CPA tumors) and craniovertebral junction and for high cervical decompression. Due to the associated complications, popularity of sitting position for posterior fossa surgery varies across the world [14, 15]. While it is rarely used in Japan and the United Kingdom now, it continues to be used in India and Germany [3]. Key points to ensure successful use of sitting position are preoperative knowledge of presence or absence of PFO, maintaining the lower head and higher leg position to reduce the incidence of VAE, special monitoring with precordial Doppler, TEE, cerebral oximetry and central venous line, avoiding hyperventilation, and a coordinated teamwork [16].

The sitting position offers several advantages compared to other positions to both neurosurgeon and neuroanesthesiologist (Table 7.1).

Sitting position is generally not used in patients with risk of right to left shunt. Various contraindications for use of sitting position are described in Table 7.2.

The head is generally stabilized with a three-pin head holder. Arterial pressure transducer

Table 7.1 Advantages and disadvantages of sitting position

	Advantages	Disadvantages
Neurosurgeon	Better cerebral venous drainage, better CSF drainage and lower intracranial pressure	Increased incidence of postoperative complications (pneumocephalus, subdural hematoma, quadriplegia, peripheral neuropathy)
	Reduced bleeding and transfusion	
	Reduced need for coagulation due to better tumor-brain interface	
	Better postoperative cranial nerve preservation	
	Gravitational drainage of blood from surgical field with better surgical access	
Neuroanesthesiologist	Better access to airway and thorax	Hemodynamic instability
	Better ventilation due to lower intrathoracic pressure	Increased incidence of VAE
	Lower airway pressures, ease of diaphragmatic excursion	Increased incidence of macroglossia
	Easier to perform cardiopulmonary resuscitation in case of cardiac arrest	
	Better visualization of the face to look for motor response to cranial nerve stimulation	

Table 7.2 Contraindications to sitting position surgeries

Absolute contraindications	Patent ventriculoatrial shunt
Relative contraindications	Atherosclerotic vascular disease
	Severe cervical canal stenosis
	Right to left intracardiac shunt
	Known pulmonary arteriovenous malformations
	Severe hypovolemia
	Severe hydrocephalus

must be zeroed at the level of skull base. Precautions for peripheral nerve injuries must be ensured. All bony prominences must be well padded, elbows supported to avoid brachial plexus stretch, and legs positioned to avoid pressure on common peroneal nerve. Ensure at least 2.5 cm space (2 finger breadth) between chin and sternum; avoid large oral airways and extreme neck flexion and rotation. All steps are taken to prevent excessive cervical spinal cord stretching and obstruction to venous drainage from the head. Excessive flexion of knees on the chest must be ruled out as it can lead to abdominal compression, lower limb ischemia, and sciatic nerve injury.

Physiological effects of sitting position:

- Sitting position has several implications on various organ systems.
- Cardiovascular system: Compensatory responses to physiological hypotension in this position are attenuated in anesthetized patients leading to exaggerated hemodynamic instability. Advancing age and associated comorbidities further accentuate hemodynamic variability. An increase in systemic and pulmonary vascular resistance and decrease in venous return, cardiac output, and CPP occurs.
- Respiratory system: Vital capacity (VC) and functional residual capacity (FRC) increase in sitting position, but the reduction in perfusion of the upper lung causes ventilation-perfusion abnormalities, mitigating any beneficial effects on work of breathing.
- Central nervous system: Head elevation to 90° decreases dural sinus pressure by up to 10 mmHg. This reduces bleeding but increases risk of VAE. Cerebral perfusion reduces in sitting position, increasing the risk of cerebral ischemia. However, cerebral venous drainage improves in sitting position and results in lower intracranial pressure.

7.6.6 Modified Sitting Position

Developed by Jadik et al. in 2009, it aims to achieve positive venous pressure in transverse and sigmoid sinuses, thereby reducing the incidence and severity of VAE and other perioperative complications [17]. A combination of adjustments is made that include elevation of upper body by 30–45°, elevation of legs by hip flexion to 90°, knee flexion to 30°, and anterior head flexion with two finger space distance between sternal notch and chin. Arms are supported to avoid traction of shoulders; legs, arms, and heels are padded. The operating table is then inclined to a lower head and higher leg position, legs as high as the vertex. This position gives better access to lateral structures of posterior fossa.

7.7 Monitoring During Anesthesia

The goals of monitoring are to ensure adequate cerebral perfusion, maintain hemodynamic stability, and detect VAE. Routine monitors including electrocardiography (ECG), pulse oximetry, noninvasive blood pressure, and capnometry are employed prior to induction. Invasive blood pressure (IBP) monitoring is commonly used, especially in sitting position surgeries, with transducer zeroed at the level of foramen of Monroe. After induction, temperature probe, urinary catheter, and central venous catheter are placed.

CVC insertion is commonly done, especially in sitting position surgeries. Commonly used sites are the basilic vein in the antecubital fossa and subclavian and internal jugular veins [1]. The ideal location for tip of multi-orifice CVC is 2 cm distal to the junction of superior vena cava (SVC) and RA. Correct placement can be confirmed by ECG-guided insertion (point where P wave is slightly smaller than QRS complex). It can be also done under echocardiographic visual guidance by confirming the tip of the catheter just inside the atrium. The third method is by withdrawing the catheter while eliciting waveforms on pressure transducer till we obtain a right atrial waveform. An additional concern with central venous catheter insertion pertains to the use of Trendelenburg position. Lowering the head may be particularly detrimental in patients with raised intracranial pressure. Prolonged head rotation for CVC placement must also be avoided. Insertion site must be carefully sealed with dressing to minimize air entrainment, more so in head-up position surgeries. CVC insertion or removal must never be done in head-up position due to the risk of air entrainment. In patients who have a VP shunt in situ, central line should be inserted taking all precautions not to puncture the shunt tubing which usually courses near the IJV in neck.

Neurophysiological monitoring with somatosensory evoked potential (SSEP), motor evoked potential (MEP), and brain stem auditory evoked potential (BAEP) is helpful during positioning and during surgery [17]. Continuous electromyogram (EMG) monitoring of cranial nerves is commonly employed, and neuromuscular blockers (NMB) must be avoided when using EMG.

Intraoperative TEE monitoring is a standard at several centers. TEE uses a 3.5–5 MHz probe that is placed behind the heart. The probe is inserted with patient lying supine. It is positioned such that it lies in the mid-esophagus and provides a four-chamber view or bicaval view of the heart. After final positioning of patient to sitting position, proper position of probe is verified using agitated saline contrast test. For performing agitated saline test, 9 ml physiological saline is mixed with 1 ml of air and agitated ten times using two 10 ml syringes connected via a three-way stopcock. This bolus of saline is injected intravenously, preferably via an antecubital vein. First three heartbeats after the injection are assessed for detecting PFO. Contrast medium can be seen passing through the PFO with microbubbles appearing as opacifications in the left side of the heart in TEE image. Other agents that have been used for bubble contrast study include patients' own blood, mannitol, dextrose, water, etc. Precordial Doppler (PCD), being the most sensitive noninvasive monitor for VAE, is preferred at some places. Transcranial Doppler (TCD) is highly sensitive to detect PFO and can be used as a screening tool. It has a reported

sensitivity of 97% and specificity of 93%. Its sensitivity further increases with use of Valsalva maneuver [18]. Intraoperative TCD monitoring can help in real-time detection of cerebral microemboli. Typical high-intensity transient signals (HITS) can be detected as emboli pass through the vessel insonated [19]. TEE is generally considered as the gold standard for detecting PFO. Several studies have been conducted to compare the usefulness of TCD, TTE, and TEE for detecting PFO. Varying results of these studies regarding the sensitivity and specificity of these techniques have led to significant controversy regarding the best technique for detecting PFO. Stendel et al. reported no significant difference in the sensitivity of TCD and TEE for detecting PFO, while that of TTE was lower than TEE [20]. Alujas et al. compared simultaneous TCD with TTE and TCD with TEE using agitated saline solution to detect intracardiac right to left shunt. Contrary to several earlier reports, this study demonstrated that TTE (100% sensitivity) is superior to TEE (86% sensitivity) for diagnosing PFO. However, TEE may be indicated in patients with poor image quality for TTE or to accurately assess the morphology of PFO when planning its closure [21].

7.8 Anesthetic Management

7.8.1 Challenges in Posterior Fossa Surgery

Specific challenges with infratentorial tumor surgery include those pertaining to the closed, confined space, presence of vital structures (brain stem, cerebellum, cranial nerves), unusual positioning required, longer duration of surgeries, and risk of acute hydrocephalus and VAE.

7.8.2 Goals of Anesthesia

Goals of anesthetic management include facilitating surgical access, reducing ICP, maintaining cerebral perfusion, adequate depth of anesthesia, hemodynamic stability, and oxygenation.

7.8.3 Anesthetic Technique

No anesthetic technique provides clear advantage over another. Intravenous anesthetic agents may be preferred and have been used in several recent studies [4, 22, 23].

Transpulmonary passage of air has been reported in humans even in the absence of intracardiac defects [24]. Intravenous (IV) anesthetics including thiopentone, fentanyl, and ketamine maintain a higher threshold for trapping air bubbles in pulmonary circulation, thereby preventing transpulmonary passage of air, compared to inhalational agents [1]. Induction is commonly performed with propofol or thiopentone, opioids (fentanyl or remifentanil), and a muscle relaxant. Hypertensive response to intubation and pin application can be blunted using additional dose of opioid and hypnotic agent and local anesthetic infiltration at pin sites. Endotracheal tube (ETT) position must be confirmed after final positioning to rule out caudad or cephalad displacement commonly associated with neck flexion and extension, respectively.

Total intravenous anesthesia (TIVA) (using propofol and opioids) is a commonly used technique for maintenance of anesthesia [22, 23]. It minimizes cardiovascular depression. Opioids also have anesthetic sparing effect. Sevoflurane (up to 1 MAC) has been used in some studies [22, 25]. Propofol is supposedly advantageous to inhalational agents since it reduces cerebral blood volume (CBV) and ICP while preserving autoregulation and vascular reactivity.

Osmotic and loop diuretics can predispose to electrolyte abnormalities and hypotension and are therefore routinely avoided in sitting position surgeries [26]. In a shunted patient, it may further reduce the brain bulk and may not be required. Also, incidence of pneumocephalus may be increased postoperatively.

Nitrous oxide (N_2O) is generally not used in posterior fossa surgeries, mainly for two reasons. First, when VAE occurs, N_2O exacerbates the size and hemodynamic effects of entrained emboli [27]. Even after VAE has been treated with 100% oxygen, it is not clear as to when N_2O can be restarted. Some authors suggest that air wash out

from blood takes around 60 min, so, N_2O can be safely started after this time [28]. Other data suggest that N_2O may continue to be problematic up to 2 h after occurrence of VAE [29]. The second reason for avoiding N_2O is its ability to expand air-filled spaces and cause tension pneumocephalus. Accordingly, some authors recommend its discontinuation before dural closure to prevent air accumulation [30], while others suggest that continuing its use until the end of procedure might promote removal of gas after discontinuation of N_2O [31]. However, discontinuation of N_2O has not been shown to prevent pneumocephalus [32]. Hence, at present, there is no clear consensus regarding the use of N_2O in infratentorial tumor surgeries. But, once VAE occurs, it should be immediately stopped.

7.8.4 Hemodynamic Management

Fluid preloading before changing to sitting position has been suggested by some authors [22]. The amount of fluid administered varies from 200 ml to 500 ml of colloid, targeting an increase of >10% in stroke volume variation (SVV) or a central venous pressure (CVP) of 5–12 cm H_2O. Preloading with 6% hydroxyethyl starch (HES) has been found to result in less positive balance and 34% smaller volume of HES requirement compared to Ringer's acetate in craniotomy patients. Also, cardiac index (CI) and stroke volume index (SVI) increased in the HES group [22].

Target mean arterial pressure (MAP) during sitting position surgeries is not clearly defined. Some authors use a target of 60 mmHg intraoperatively. Changing from supine to sitting position causes a decrease in CI, SVI, and MAP and increase in systemic and pulmonary vascular resistances. These hemodynamic changes are further aggravated by pooling of venous blood in lower extremities, cranial nerve manipulation, and occurrence of VAE and therefore can alter cerebral blood flow (CBF) especially in patients with disturbed autoregulation. Head end elevation of 50° causes a difference of 18 mmHg in MAP at the level of tragus compared to that at the level of RA. This means that when a CPP of 60 mmHg is reported, the true CPP measured at the level of tragus may actually vary from 43 to 60 mmHg depending on reference point and degree of elevation. This may be the reason behind cerebral ischemia reported after head-up surgeries [33, 34]. A fall in MAP of more than 30% from baseline in general surgical patients is reportedly associated with postoperative stroke [35]. Hypotension is especially detrimental in patients with altered limits of autoregulation, impaired cerebral perfusion, and abnormal baroreceptor function as seen in patients with hypertension, cardiovascular disease, or prior carotid endarterectomy [1]. Ephedrine and phenylephrine are the most commonly used agents for hypotension. Rarely, inotrope infusions may be required.

Antigravity devices help to prevent venous stasis in lower limbs and should be applied in all patients undergoing surgery in sitting position. Intermittent sequential compression devices reduce the incidence of hypotension and improve cerebral oxygenation [36].

7.8.5 Ventilatory Management

Controlled positive pressure ventilation with muscle paralysis is the preferred technique. Normocapnia ($EtCO_2$ 30–35 mmHg) is maintained. Hypoxemia must be avoided. The use of positive end expiratory pressure (PEEP) is controversial in sitting position. It can increase RAP predisposing to paradoxical air embolism (PAE). However, there is a mixed practice with some anesthesiologist not preferring it while others using moderate levels of PEEP [2]. The use of PEEP is thought to decrease the incidence of VAE, but it can facilitate PAE in case VAE occurs. Biphasic PEEP has been used by some authors in patients with PFO to increase intrathoracic pressure [2].

Spontaneous ventilation during posterior fossa surgery has been reported in some case reports. This technique allows monitoring the

integrity of vital brain stem structures while operating. EEG-guided depth of anesthesia is maintained generally using sevoflurane [37, 38].

7.8.6 Temperature

Normothermia is commonly practiced. Intraoperative hypothermia should be avoided [1].

7.8.7 Glycemic Control

Normoglycemia (blood sugar <200 mg/dL) should be maintained throughout. Both hypo- and hyperglycemia can be harmful [39].

7.8.8 Emergence and Extubation

The decision to awaken the patient at the end of surgery or to sedate and ventilate depends on the preoperative neurological status of the patient and intraoperative course and complications.

Preoperative cranial nerve involvement with impaired gag or cough reflexes, intraoperative excessive brain stem handling, occurrence of severe VAE, and airway edema are some of the common reasons for postoperative sedation and ventilation. Persistent postoperative hypertension must alert the anesthesiologist to the possibility of brain stem compression, ischemia, or hematoma.

If a decision to awaken the patient at the end of surgery is taken, then, emergence must be smooth. Coughing and straining and any abrupt rise in blood pressure must be avoided during extubation. Rapid awakening enables early postoperative neurological examination. Rapid emergence after posterior fossa surgery can be facilitated by using short-acting drugs such as propofol and remifentanil.

Failure to recover from anesthesia must prompt imaging of the brain and a search for anesthetic and metabolic causes, pneumocephalus, operative site or subdural hematoma, brain stem compression, or infarction.

7.9 Intraoperative Complications

7.9.1 Venous Air Embolism

VAE refers to the entrainment of air from an open vein into systemic circulation causing a wide array of symptoms. It can occur in any position where there is an open non-collapsible vein and a pressure gradient between the heart and the operative site. The critical gradient has been reported to be as low as 5 cm [40].

7.9.1.1 Incidence

VAE is a potentially life-threatening complication. Its true incidence is not known, since many cases are subclinical and often go unrecognized. It is reported in wide variety of procedures including pelvic, laparoscopic, orthopedic, and neurosurgical procedures as well as cesarean section [41]. In neurosurgery, VAE is associated most commonly with sitting position but can also occur in any other position. The reported incidence of VAE varies from 10%–17% in prone position [8] and 1.4–12% in horizontal position (supine, prone, lateral, park bench) [8, 42] to 7–76% in the sitting position [43]. Neurosurgical procedures are at higher risk of VAE due to head-up positioning commonly used and presence of numerous large, non-compressible venous channels. The incidence is reportedly lower in children compared to adults due to higher dural sinus pressure in children [44]. Children however suffer greater hemodynamic derangements from VAE compared to adults since the volume of air entrained in children is larger relative to their cardiac volume [45]. However, the incidence of severe VAE producing hypotension ranges from 1% to 6%. This wide variation in the reported incidences is due to the different detection methods and criteria used by various authors as well as retrospective nature of most studies. Most of the detected VAE are not clinically relevant; further, the risk of false positives has increased with greater use of continuous intraoperative TEE.

7.9.1.2 Monitoring

Early detection of VAE is essential to stop further entrainment of air. An ideal monitor for detection of VAE must be sensitive and specific; must detect VAE early; must be noninvasive, quantitative, easy to use, and cheap; should be able to detect air in the left side of the heart; and must tell about clearance of air from circulation. None of the currently available monitors is ideal. Modalities that can be used for intraoperative monitoring of VAE include TEE, precordial Doppler, pulmonary artery catheter, end-tidal CO_2 monitoring, etc. All of them have advantages and disadvantages (Table 7.3). A sudden, sustained fall in $EtCO_2$ is generally indicative of VAE. The degree of fall in $EtCO_2$ used for diagnosing VAE varies from 2 mmHg to 5 mmHg.

Apart from it, direct observation of surgical site should be a routine practice in sitting position surgeries, especially at high-risk stages for VAE. The presence of slow continuous venous bleeding indicates that venous pressure is higher than atmospheric pressure. Absence of such venous ooze indicates a lower venous pressure than atmospheric pressure at that level and must prompt high suspicion for VAE [41].

7.9.1.3 Pathophysiology

Intraoperative VAE can be lethal. The severity of manifestations depends on the volume and rate of air entrainment. The amount of air entrained in turn depends on the size of vascular lumen and the pressure gradient. Effect of air embolism with slow and rapid entrainment in spontaneously

Table 7.3 Advantages and disadvantages of various monitoring modalities for VAE

Monitor	Advantages	Disadvantages	Remarks
Transesophageal echocardiography (TEE)	Most sensitive Can detect up to 0.02 ml/kg of air Can detect microemboli Can identify air in the left heart and PAE Allows early intervention	Invasive, expensive Risk of glottic injury with prolonged use Needs constant surveillance by trained personnel Detects clinically unimportant episodes as well Needs expertise	Too sensitive, detecting any amount of air in circulation, most leading to no adverse sequelae
Precordial Doppler (PCD)	Most sensitive noninvasive monitor Can detect up to 0.05 ml/kg of air Cost-effective Easy to use	Not quantitative Sound artifacts with use of electrocautery Detects clinically unimportant episodes as well Difficult to use in prone and lateral positions and in morbid obesity Needs training Close attention required to appreciate the audible transition	Can be placed over either the right or left sternal border in the second intercostal space; alternately, between the right scapula and spine. Position confirmed by "bubble test" First evidence is change in character and intensity of emitted sound "Washing machine" sound due to turbulence is an early sign of VAE "Drumlike sound" or classic "mill wheel" murmur is a late sign seen after cardiovascular deterioration
Pulmonary artery catheter (PAC)	Degree of increase in PAP correlates with amount of air entrained Early detection possible Offers prognostic information Slightly more sensitive than capnography	Most invasive Small caliber lumen does not help in aspirating air Not specific for air Relatively insensitive (0.25 ml/kg)	Not routinely placed due to availability of more sensitive, less invasive and more effective alternatives Used generally in patients with significant comorbidities and other indications as well Less sensitive than PCD

Table 7.3 (continued)

Monitor	Advantages	Disadvantages	Remarks
Capnography	Most convenient and practical monitor Easily available Can be applied in any position Detection threshold is 0.15 ml/kg of air	Low specificity Sensitivity is lower than TEE, PCD, and PAC Reliability decreases in event of hypotension Unreliable in spontaneously breathing patients	Expired nitrogen monitoring is more sensitive than capnography Sudden, sustained fall of more than 2 mmHg in $EtCO_2$ indicates VAE
Transcranial Doppler (TCD)	Highly sensitive to detect PFO Can be used as a screening tool	Sensitivity of 91% Specificity of 93.8%	Sensitivity increases with use of Valsalva maneuver
End-tidal nitrogen	Most sensitive gas-sensing monitoring modality Can measure 0.04% increase in ETN2	Not available with all anesthesia monitors Not useful if nitrous oxide is used as part of anesthetic regime Utility is limited by hypotension May indicate air clearance from pulmonary circulation prematurely	Changes in ETN2 occur 60–90 s earlier than changes in $EtCO_2$ Comparable or better sensitivity than $EtCO_2$ for large VAE, less sensitive for slow entrained air
Pulse oximetry		Change in oxygen saturation is a late finding of VAE Requires a severe physiological disturbance to occur	
Esophageal stethoscope		Very low sensitivity for detecting mill wheel murmur Can detect about 1.7 ml/kg/min of air	
Electrocardiography		Low sensitivity Changes occur early only with rapid entrainment of air	ST–T changes occur first, followed by supraventricular and ventricular arrhythmias

breathing and in mechanically ventilated animals has been studied and may be applicable to humans as well [46]. The lethal dose of air in humans is not exactly known, but volumes between 200–300 ml and 3–5 ml/kg are reported to be fatal [47]. As much as 100 ml of air per second can flow across a 14 G needle with a 5 cm pressure gradient [48]. The closer the vein of air entrainment is to the right heart, the smaller is the required lethal volume.

The major mechanism of death from massive air embolism is by entrapment of air in the right ventricle outflow tract causing circulatory arrest. Large air emboli can acutely increase RAP, facilitating PAE by passage of air through either a PFO or across pulmonary capillary bed into systemic circulation [7]. Microemboli can either lodge in pulmonary vessels causing obstruction to blood flow or can get resorbed spontaneously depending on the rate and volume of entrainment. Obstruction to pulmonary blood flow can cause ventilation-perfusion mismatch resulting in hypoxemia. Air-blood interactions may also induce production of fibrin clots and thrombus formation causing further obstruction of right ventricle outflow tract (RVOT) or pulmonary blood flow [49]. Microemboli in circulation also precipitate platelet aggregation and release of platelet activator inhibitor. This may lead to systemic inflammatory response syndrome [50]. VAE is known to increase microvascular permeability, causing pulmonary hypertension (PAH) by releasing endothelin 1, pulmonary edema, and free radical damage. Large air emboli of up to

5 ml/kg can cause air-lock scenario leading to right heart failure and cardiovascular collapse. With smaller volumes, right ventricle outflow obstruction can lead to reduced cardiac output, hypotension, and myocardial and cerebral ischemia [51].

7.9.1.4 Clinical Features

VAE can present with pulmonary, cardiovascular, and neurological symptoms. Clinical features depend on the rate and volume of air entrained and whether patient is spontaneously breathing or under positive pressure ventilation. Common cardiovascular features include tachyarrhythmia, ECG changes (right heart strain, ST–T changes), hypotension, and PAH. Pulmonary symptoms include dyspnea, coughing, gasping, and wheezing in awake patients, a fall in $EtCO_2$, hypoxia, and rise in $paCO_2$ with raised airway pressures in anesthetized patients. Neurological manifestations may be secondary to reduced cardiac output (leading to cerebral hypoperfusion causing altered mental status, focal deficits, coma) or due to cerebral air embolism (manifesting as postoperative mental status changes).

Depending on rate of air entrainment, clinical features are as follows:

- Slow entrainment: With slow entrainment, large quantities of air may be tolerated by the heart over a prolonged period. In spontaneously breathing patients, a characteristic "gasp" is seen when entrained air obstructs at least 10% of pulmonary circulation. This "gasp" can actually increase the volume of air entrained by suddenly decreasing the RAP. Accompanying breathlessness, chest pain and a sense of impending death may also occur. A decrease in end-tidal CO_2 and oxygen saturation can occur. ECG changes range from tachyarrhythmia to AV block, RV strain, and ST segment changes. During controlled ventilation, patients do not gasp, preventing further entrainment of air. Much larger volume of air can be tolerated during mechanical ventilation compared to those spontaneously breathing [46]. Peak airway pressure and pulmonary artery pressure (PAP) increase slowly during controlled ventilation.
- Rapid entrainment: Rapid entrainment of air during spontaneous respiration causes rapid, shallow breathing followed by a period of apnea. Irregular breathing may then resume. PAP increases rapidly within 30–60 s followed by gradual return to baseline, in both spontaneously breathing and mechanically ventilated patients. Rapid fall in $EtCO_2$ and oxygen saturation may occur.

Depending on the amount of air entrained, the clinical features vary:

- Acute, small (<0.5 ml/kg): Decrease in EtCO2, desaturation, wheeze, and altered mental status
- Acute, medium (0.5–2.0 ml/kg): Breathlessness, hypotension, pulmonary hypertension, wheeze, ECG changes, myocardial and cerebral ischemia, bronchoconstriction, and jugular venous distension
- Acute, large (>2.0 ml/kg): Chest pain, right heart failure, and cardiovascular collapse

7.9.1.5 Grading of VAE

Several grading scales for VAE have been used (Table 7.4). Most scales grade VAE from 1 to 3 or 5. Criteria used by these scales are variable and include precordial Doppler signals, TEE changes, fall in $EtCO_2$, and hemodynamic changes. Hypoxemia due to VAE is reported in 0.5–18% patients [23]. A decrease in platelet count occurs after VAE [52]. Coagulation and platelet count therefore need to be reassessed after VAE using thromboelastometry and aggregometry.

7.9.1.6 Prevention

Preventive techniques aim to reduce the pressure gradient between the surgical site and RA. The key to prevention of VAE is meticulous surgical hemostasis, and limiting the amount of time, the venous sinuses remain open to atmosphere. Various techniques are employed:

- Surgical positioning: Alternative positions such as prone or park bench may be preferred over sitting position, wherever possible. Elevating the legs increases RA pressure and reduces VAE incidence.

Table 7.4 Grading scales for VAE

Grade of VAE	Girard scale [53]	Tubingen scale [4]	Jadik scale [17]
1	Positive precordial Doppler (PCD) signal without hemodynamic alterations	Air bubbles on TEE	Minor clinical VAE: positive TEE with decrease in $EtCO_2$ of >3 mmHg
2	Positive PCD signal with increase in systolic pulmonary artery pressure (SPAP) of >5 mmHg and/or decrease in $EtCO_2$ of >3 mmHg	Air bubbles on TEE with decrease in $EtCO_2$ of ≤3 mmHg	Moderate clinical VAE: positive TEE with ABP decrease or HR increase
3	Positive PCD signal with increase in systolic pulmonary artery pressure (SPAP) of >5 mmHg and/or decrease in $EtCO_2$ of >3 mmHg	Air bubbles on TEE with decrease in $EtCO_2$ of >3 mmHg	Severe clinical VAE: positive TEE with ABP decrease >40% or HR increase >40%; including situations of CPR
4	At least one positive grade 2 criterion with sudden decrease in ABP or increase in heart rate of at least 40%	Air bubbles on TEE with decrease in $EtCO_2$ of >3 mmHg and decrease of ≥20% in MAP or increase of ≥40% in heart rate (or both)	
5	At least one positive grade 2 criterion with circulatory collapse	Arrhythmia with hemodynamic instability requiring cardiopulmonary resuscitation	

- Central venous catheter insertion: Using Trendelenburg position during insertion and removal of central venous catheter prevents VAE. However, lowering of the head may be detrimental in patients with raised ICP. In such cases, transient Trendelenburg positioning during guide wire or catheter insertion after vein has been identified is suggested. Also, leg raising by placing pillows under the knees increases venous return and RA pressure. Stopping ventilation during CVC insertion reduces the negative intrathoracic pressure during expiration that may promote VAE by suction effect. Application of PEEP and Valsalva maneuver also help increase CVP and reduce the incidence of air entrainment [54].
- Hydration: An increased incidence of VAE is reported in patients with low CVP. Patient must be kept well hydrated to maintain high RAP. Prophylactic fluid loading is variedly practiced; even the target endpoints used vary. It reduces the pressure gradient between RA and surgical site, as well as that between right and left sides of the heart [55]. It also improves hemodynamics in sitting position. A RAP goal of 10–15 cm H_2O is reasonable, depending on the degree of elevation [56]. The highest acceptable RAP should be determined based on patients' cardiac status. A useful practical maneuver suggested is to zero the pressure transducer at the level of RA, then raising it to the level of surgical site to assess if there is a negative pressure gradient. Other parameters of volume status like systolic pressure variation and urine output may also be used to optimize fluid status.
- Military anti-shock trousers (MAST): MAST application reportedly increases RAP in sitting position surgeries [57]. By maintaining a MAST pressure of greater than 50 cm H_2O, RAP is maintained above atmospheric pressure during period of inflation [58]. A decrease in vital capacity [59], hypoperfusion of intraabdominal organs, and compartment syndromes are some of the reported complications with these devices.
- PEEP: The use of PEEP remains controversial. It may prevent VAE but potentially increases the risk of PAE. In humans, moderate PEEP does not increase cerebral venous pressure in sitting position [60]. High levels of PEEP (>5 cm H_2O) are generally required to overcome the pressure gradient between RA and surgical site to effectively prevent VAE. Some reports have suggested no decrease in the incidence of VAE with application of PEEP; rather adverse cardiovascular effects predominate with the use of high PEEP in sitting position surgeries [61]. Further, PEEP can increase the risk of PAE in patients with a

PFO. Hence, prophylactic use of PEEP seems unjustified and may be used to improve oxygenation rather than for VAE prevention.

- Intermittent bilateral jugular venous compression: Gentle manual compression of bilateral jugular veins during those phases of surgery when venous sinuses are known to be open (like skull flap removal, while repairing an injured dural sinus) can prevent further entrainment of air. Also, the impediment to cerebral venous return with resultant increase in cerebral venous pressure by jugular compression provokes bleeding from surgical site helping surgeon to identify open veins. However, routine continuous compression is not recommended. Complications associated with this technique include increase in ICP and decrease in CPP and inadvertent compression of carotid arteries causing dislodgement of arterial plaques, carotid sinus stimulation causing bradycardia, and venous engorgement causing cerebral edema. The use of inflatable venous neck tourniquets has also been proposed for this purpose [62], but not widely practiced.

7.9.1.7 Management

Goals of management for VAE include preventing further air entry, reducing the volume of air already entrained, and hemodynamic support. A series of maneuvers are performed by both neurosurgeon and neuroanesthesiologist.

- Surgeon should immediately be notified to flood the field with saline and use bone wax to prevent further entrainment of air. Simultaneous attempts to identify the site of entry should be made.
- Stop nitrous oxide and administer 100% oxygen. Although 50% N_2O does not increase the incidence of VAE [6], it can rapidly diffuse into air bubbles and increase the size of already entrained emboli. Due to its 34 times higher solubility in blood compared to nitrogen, N_2O must be discontinued once VAE is suspected. Additionally, 100% oxygen helps in eliminating nitrogen and reducing size of emboli. However, the time when N_2O can be reinstituted after VAE occurs remains controversial.
- Bilateral jugular venous compression may be used to increase cerebral venous pressure and prevent further air entry. This technique helps increase the dural sinus pressure resulting in retrograde blood flow.
- Aspiration of air from right atrial catheter is done. These RA catheters can retrieve only about 50% of aspirated air; multi-orifice catheters are more effective [63]. Average amount of air aspirated via CVC is about 15–20 ml, as reported with various devices.
- Surgical site should be lowered below the level of the heart, wherever possible. Durant maneuver (partial left lateral decubitus position) may help in localizing the air lock to the right side of the heart. Further Trendelenburg position may help improve hemodynamics. However, the beneficial effect of such positioning is not entirely clear and is less practical.
- Administration of IV fluids to increase venous pressure and pharmacological support with inotropes can help improve hemodynamics in case of cardiovascular collapse. Agents commonly used include ephedrine [64], norepinephrine, and dobutamine [65].
- Chest compressions may be instituted rapidly to push air out of pulmonary outflow tract into distal vessels and improve forward blood flow [66].

7.9.1.8 Sequelae of VAE

Intraoperative complications of VAE include cardiovascular instability with arrhythmias, hypotension, RV failure and arrest, pulmonary dysfunction manifesting as hypoxemia secondary to increased dead space in lungs, and pulmonary edema. The major adverse consequence of VAE is paradoxical air embolism. Postoperatively, neurological deficits, stroke, RV failure, myocardial ischemia, and lung perfusion defects may be seen.

7.9.2 Paradoxical Air Embolism

PAE can lead to myocardial and neurological consequences including quadriplegia. PAE in humans most likely occurs through a right to left shunt via an intracardiac defect. It generally

occurs when RAP exceeds left atrial pressure (LAP). Up to 50% patients experience reversal of left to right atrial pressure gradient after 1 h in sitting position under anesthesia. However, with a strict management protocol (including the use of modified sitting position, TEE monitoring, intermittent jugular compression, evoked potential monitoring), the incidence of PAE is quite low, even in patients with a PFO [4]. PAE is generally associated with only large VAE, i.e., those associated with a fall in $EtCO_2$ and increase in PAP. The use of PEEP increases the pressure gradient between left and right sides of the heart increasing the risk of PAE. Hypovolemia also predisposes to PAE. Generous administration of intravenous fluids reduces the interatrial pressure gradient and may prevent PAE. Hyperbaric oxygen (HBO) therapy may be considered for treatment. HBO is believed to reduce size of air bubbles by accelerating resorption of nitrogen and increasing oxygen content of blood. However, prospective trials regarding its efficacy are lacking. The optimal time for starting HBO therapy after cerebral embolism is also unclear at this time [51].

7.9.3 Hypotension

Hypotension is common in the sitting position. It can be prevented by fluid preloading, vasopressors, and gradual positioning of patient [67].

7.9.4 Airway Edema

Extreme neck flexion causing obstruction of lymphatic and venous drainage from the head can cause swelling of airway [68]. Edema of the tongue, pharynx, and palate can also occur due to oral airway and TEE probe placement.

7.9.5 Pressure Injuries

Pressure injury to skin, peripheral nerves, and pressure sensitive organs like the eyes is possible.

7.9.6 Spinal Cord Injury

Extreme neck flexion causing stretch of spinal cord or reduced blood supply to the cord can occur with sitting position.

7.9.7 Other Complications

Cardiac arrhythmias including bradycardia, tachycardia, premature ventricular contractions (PVC), asystole, etc. can occur due to surgical handling or damage to cranial nerves and the brain stem. ETT displacement may also occur.

7.10 Postoperative Care

Postoperative care of these patients must include intensive monitoring for any neurological deterioration, adequate ventilation, and analgesia, preventing hypertension and early detection and management of any complications.

7.11 Postoperative Complications

7.11.1 Airway Compromise

Edema of the face and airway and macroglossia or extensive dissection around the floor of the fourth ventricle and cranial nerves might cause postoperative airway compromise.

7.11.2 Pneumocephalus

Overall incidence of 42% is reported after posterior fossa surgery [69]. It can occur in up to 100% patients in sitting position, 72% in park bench, and 57% in prone position [1]. Air can enter into the brain and surrounding spaces after dural incision. Pneumocephalus is usually asymptomatic and resolves spontaneously. Tension pneumocephalus, a life-threatening emergency, can cause neurological deficits and brain herniation. Predisposing factors for tension pneumocephalus

include large volume air accumulation, use of nitrous oxide, postoperative cerebral edema, and re-expansion of the brain after mannitol administration. Incidence is highest in sitting position surgeries followed by park-bench and prone position surgeries [70]. It can be diagnosed on CT scan of the brain. Management is by ventilation with 100% oxygen and drainage of air via a burr hole.

7.11.3 Neuropathy

Nerve injury can occur because of stretching, compression, or ischemic injury to nerves. Peripheral nerve injury to sciatic and common peroneal nerves can occur.

7.11.4 Quadriplegia

Spinal cord injury can manifest postoperatively with quadriplegia or paraplegia. Central cord syndrome can also occur.

7.11.5 Aspiration

Impaired lower cranial nerves and cough reflex may result in aspiration.

7.11.6 Respiratory Compromise

Respiratory compromise in immediate postoperative phase can occur due to injury to the brain stem, pulmonary edema secondary to VAE, and airway edema or due to cranial nerve injury.

7.11.7 Pain

Pain after craniotomy is more severe after occipital and infratentorial approaches owing to extensive muscle dissection.

7.11.8 Anosmia

Few case reports of postoperative anosmia exist, more commonly in trigeminal neuralgia surgery patients [71, 72]. It occurs probably due to tearing of olfactory nerves or striae.

7.11.9 Posterior Fossa Syndrome

It is seen in children operated for medulloblastoma and other midline posterior fossa tumors. There is temporary and complete loss of speech due to involvement of dentatothalamocortical pathway intraoperatively. It is also known as cerebellar mutism. There may also be associated vision loss in these children but with excellent prognosis.

7.11.10 Persistent Postoperative Hypertension

Persistent hypertension and bradycardia must prompt a search for brain stem compression, ischemia, or hematoma.

7.11.11 Postoperative Nausea and Vomiting (PONV)

PONV is common after infratentorial tumor surgery owing to proximity of vomiting center to the surgical site and due to use of opioids for anesthesia. Nausea and vomiting can increase ICP and risk of postoperative bleeding. Agents used for this purpose include dexamethasone, ondansetron, and propofol.

7.12 Conclusion

Infratentorial tumor surgery is a challenge both for anesthesiologist and neurosurgeon. It is associated with some unique complications. Sitting position for infratentorial tumors is less commonly used now. Cautious planning and

monitoring can prevent most of these complications. The incidence of death due to VAE and the incidence of PAE are extremely low.

Key Points

- Infratentorial compartment is an area located below a large dural fold known as tentorium cerebelli. It encloses several vital structures in a confined space, thus posing unique challenges during surgery in this region.
- The sitting and park-bench positions are typically used approach to this region. Associated physiological changes, technique of safe positioning, and associated complications should be thoroughly known to both surgeon and anesthesiologist.
- The anesthetic goals remain the same as other intracranial surgeries in addition to early recognition and prompt management of some typical complications associated with this surgery like venous air embolism.
- The intraoperative neuromonitoring of evoked potentials requires appropriate modification of anesthetic technique.
- The opinion and practice vary, regarding routine use of preoperative echocardiography for detection of patent foramen ovale, preference for inhalational or intravenous anesthetic agents, use of nitrous oxide, and positive end expiratory pressure in patients undergoing surgery in sitting position.
- Decision to extubate or to electively ventilate the patient at the end of surgery has to be carefully made.

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8 Anesthesia for Aneurysmal Subarachnoid Hemorrhage

Nicolas Bruder, Salah Boussen, and Lionel Velly

8.1 Introduction

SAH is a rare disease explaining that the European Medicines Agency has given the status of orphan disease to SAH. Despite its relative rarity, SAH is still a subject of considerable interest explaining an extensive literature on the subject. However, there is a paucity of large, prospective, randomized trials explaining a large variability of clinical practice throughout the world [1, 2]. As expected, a number of retrospective studies have shown decreased mortality and improved neurologic outcome in high-volume centers compared to low-volume ones [3–5]. The definition of high volume is very variable in the literature. In the 2012 American guidelines, high volume is defined above 35 aneurysmal SAH cases per year. However, in a recent study, a relatively stable mortality was obtained above 60 cases/year [4]. There may be multiple reasons to explain these findings as availability of interventional neuroradiologists for coiling; increased experience of neurosurgeons, radiologists, anesthesiologists, and intensivists; better availability of complex procedures as cerebral angioplasty; and dedicated neuro-intensive care units. Except coiling and angioplasty, no magic treatment has appeared in the last 20 years. Nevertheless, there has been a clear trend toward a constant decrease in mortality and improved neurologic outcome in survivors. Despite increasing age of patients admitted for SAH, case-fatality rates have decreased by 17% between 1973 and 2002 [6]. In more recent years, mortality has still declined in the same proportion [7], but 90-day mortality remains around 30%, leaving room for further improvement [8, 9].

The main complication after SAH is cerebral ischemia that may have multiple causes. These causes may be divided between early and late cerebral ischemia (Fig. 8.1). Very early ischemia occurs in the first hours after aneurysm bleeding. It is due to intracranial hypertension, acute cerebral vasoconstriction, microvascular thrombosis, heart failure related to myocardial injury, or neurogenic pulmonary edema. Delayed cerebral ischemia (DCI) develops several days after SAH. DCI and cerebral infarction are the most important prognostic factors for neurologic outcome [10]. DCI has been linked to cerebral vasospasm. However, the absence of causal relationship between angiographic vasospasm and DCI in some studies and the absence of significant improvement in clinical outcome with drugs that have a potent effect against vasospasm have raised other hypotheses to explain DCI [11]. These hypotheses are cerebral vasoconstriction and thrombosis, cortical spreading ischemia, cerebral inflammation, and blood-brain barrier

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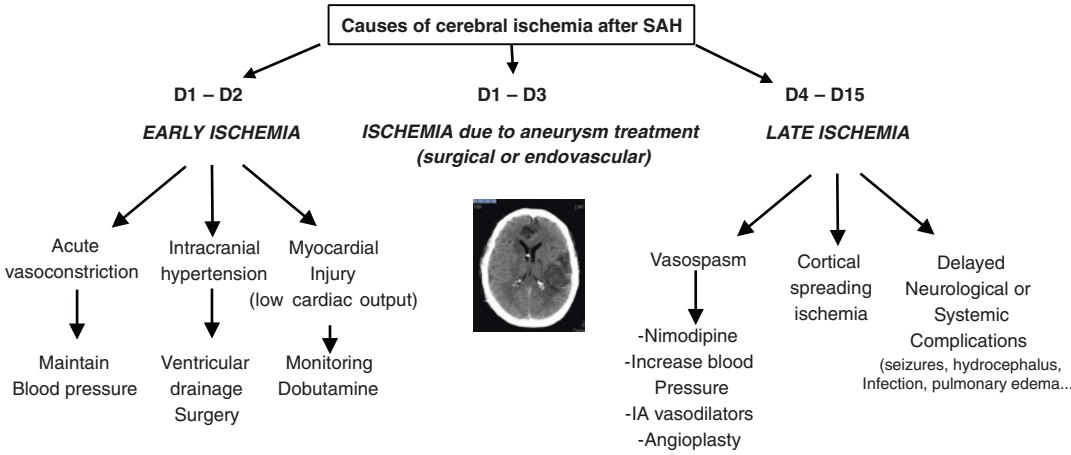

Fig. 8.1 Causes of cerebral ischemia after SAH depending on time after aneurysm rupture

disruption [12]. This chapter will focus on early management of SAH for anesthesia for neurosurgical clipping or endovascular embolization.

8.2 Preoperative Assessment

8.2.1 Central Nervous System (CNS)

The severity of CNS injury is the main predictor of long-term outcome. Several clinical scales have been used. The World Federation of Neurological Surgeons (WFNS) grading scale, based on the Glasgow coma score scale, is widely used (Table 8.1). The amount of blood in the subarachnoid space or in the ventricles has also been associated with the risk of DCI. Several scores have been published, the most popular being the modified Fisher scale (Table 8.2) [13]. Several scores associating clinical, radiological, or biological variables are able to predict mortality or neurologic outcome after SAH. For example, the HAIR score combining Hunt and Hess score, age, intraventricular hemorrhage, and rebleeding was strongly associated with in-hospital mortality [14]. The ABC score, which integrated the Glasgow coma score, troponin I, and protein S100beta at admission, predicted 1-year mortality [15].

Among several causes of impaired consciousness due to SAH, increased intracranial pressure (ICP) is the most relevant one for the anesthetist.

Table 8.1 Grades of the World Federation of Neurological Surgeons (WFNS) and relation to mortality

Grade	Glasgow coma scale score	Motor deficit	Mortality
1	15	Absent	1–5
2	13–14	Absent	5–10
3	13–14	Present	5–10
4	7–12	Present or absent	20–30
5	3–6	Present or absent	30–50

Table 8.2 Modified Fisher scale with an estimation of the associated risks of delayed cerebral ischemia (DCI) and new infarct on CT scan (unrelated to initial bleeding or aneurysm securing procedure)

Grade	Description	DCI %	New infarct on CT %
0	No SAH or IVH	0	0
1	Thin SAH, no IVH in lateral ventricles	12	6
2	Thin SAH, IVH in both lateral ventricles	21	14
3	Thick SAH, no IVH in lateral ventricles	19	12
4	Thick SAH, IVH in both lateral ventricles	40	28

Data from [13]

At the onset of SAH, loss of consciousness occurs in 40% of patients [16]. It is related to the abrupt bleeding into the subarachnoid space, increasing intracranial volume and ICP. In hospitalized

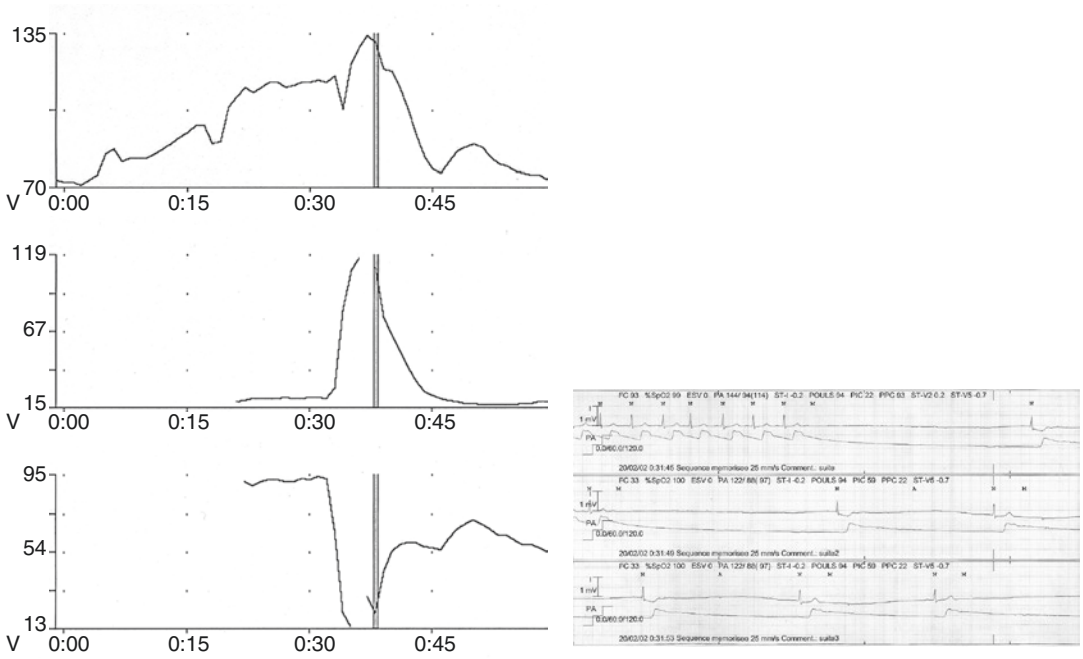

Fig. 8.2 Trends in mean arterial pressure (MAP), intracranial pressure (ICP), and cerebral perfusion pressure (CPP) in a patient in the intensive care unit after subarachnoid hemorrhage. A ventricular drain was placed in order to monitor ICP and treat hydrocephalus. Soon after 0:30 am, the patient suffered a severe headache immediately followed by a rapid decrease in consciousness requiring tracheal intubation. The ICP increased to 120 mm Hg and CPP below 10 mm Hg. Immediate ventricular drainage allowed a return toward normal ICP values in approximately 10 min. The aneurysm was treated by endovascular coiling, and the patient recovered without any neurologic impairment. The EKG trace shows severe bradycardia at the time of rebleeding (Cushing's response)

patients, rebleeding may be associated with a sudden and large increase in ICP, resulting in a severe reduction in cerebral perfusion pressure (CPP) and thus explaining loss of consciousness (Fig. 8.2). As such, assessment of ICP and CPP and control of increased ICP before the aneurysm securing procedure are critical to maintain cerebral homeostasis and prevent cerebral ischemia. Severe intracranial hypertension can be excluded in WFNS 1–2 grades. WFNS 4–5 patients are at highest risk of intracranial hypertension and reduced CPP. Except in the most severe cases with clinical signs of brain herniation (unilateral or bilateral mydriasis), clinical examination cannot help to evaluate the level of ICP or CPP. The amount of blood in the lateral ventricles (more than 50% of each ventricle filled with blood) and the amount of blood in the subarachnoid space are an indication of increased ICP [17, 18]. Transcranial Doppler (TCD) is probably the most convenient and easy to use monitoring device at the bedside to give a qualitative noninvasive access to the cerebral circulation. The decrease in diastolic flow velocity is associated with the decrease in CPP. When ICP increases toward arterial diastolic pressure, diastolic flow velocity progressively disappears. Zero-diastolic velocity is a critical value indicating that any further decrements of CPP are associated with rapid CBF decrease and cerebral ischemia (Fig. 8.3) [19]. In addition, bilateral failure of cerebral autoregulation with TCD has been associated with DCI and unfavorable outcome [20].

8.2.2 Cardiovascular System

Cardiovascular consequences of SAH had first been described long ago [21]. ECG changes may mimic coronary artery ischemia, but studies on

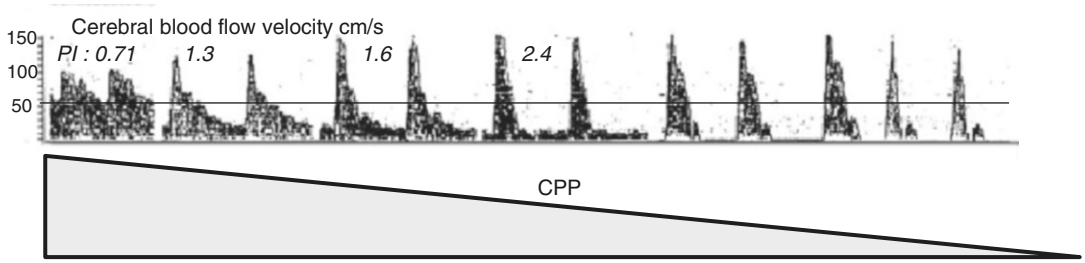

Fig. 8.3 Transcranial Doppler recordings in several patients with decreasing values of cerebral perfusion pressure. The decrease in diastolic blood flow is easily recognized at low CPP values. A diastolic velocity below 20 cm/s is usually associated with impaired CPP (<60 mm Hg)

the coronary circulation ruled out this hypothesis. Arrhythmias are frequent, affecting 35% of patients with life-threatening arrhythmias in 5–8% [22]. Biomarkers of myocardial injury like troponin are frequently elevated and are associated with myocardial dysfunction and outcome.

Echocardiography frequently reveals regional wall motion abnormalities (8–28% of patients), diastolic dysfunction, or global hypokinesia [23]. The most severe clinical presentation of myocardial injury is Takotsubo cardiomyopathy. It is associated with a critical decrease in cardiac output and has to be diagnosed as soon as possible because any attempt to increase blood pressure with vasopressors would further decrease cardiac output and CBF. This acute ventricular dysfunction associated with SAH is generally reversible within 2 or 3 days after admission.

8.2.3 Respiratory System

Pulmonary complications are frequent after SAH and contribute significantly to mortality [22]. As myocardial dysfunction, the incidence of pulmonary complications is related to the clinical grade. Pneumonia occurs in approximately 20% of patients and pulmonary edema in 8–28% of cases. The prevalence of ARDS in retrospective studies is reported to be 4–18% [23]. Neurogenic pulmonary edema (NPE) is less frequent, but the true incidence is difficult to assess because pulmonary edema may be due to heart failure or excessive fluid loading. NPE usually improves within a few days after SAH, but it may be a real problem for anesthetic management. The balance between the risk of surgery in patients with NPE and the risk of rebleeding if surgery is postponed needs a case-by-case discussion.

8.2.4 Other Medical Complications of SAH

Hypernatremia and hyponatremia are common after SAH. Hyponatremia is the most common electrolyte imbalance and usually develops a few days after the hemorrhage with the onset of vasospasm. The mechanisms of hyponatremia are cerebral salt wasting (CSW) and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). CSW is more frequent leading to excessive urine excretion of sodium. Hence, CSW is associated with volume contraction. In this case, patients should be given fluids before induction of anesthesia to avoid hypotension. Conversely, SIADH is associated with free water retention and normal or expanded intravascular volume. Hyponatremia may be treated by the infusion of hypertonic saline solution with frequent monitoring of blood sodium. Some studies have used fludrocortisone or hydrocortisone to treat hyponatremia, but the benefit of these treatments is unclear [24].

Hyperglycemia is common after SAH and has been associated with poor clinical outcome. The increased glucose level is due to the activation of the sympathetic system and the hypothalamic-pituitary-adrenal axis giving rise to an increase in the level of stress hormones (catecholamine,

cortisol, and growth hormone). The release of pro-inflammatory cytokines further increases the stress response and promotes insulin resistance. Patients with hyperglycemia have approximately a three-fold increased risk of poor outcome [25]. Some studies have shown a benefit of glycemic control on neurologic outcome or a decrease in the rate of infection [26, 27]. However, overly strict glycemic control may lead to brain hypoglycemia and metabolic crisis, even when serum glucose decreases to levels within the normal range [28, 29].

8.3 Timing of Aneurysm Treatment and Rebleeding

Preoperative rebleeding is an independent predictor of unfavorable outcome [30]. In recent studies, reported rates of rebleeding were between 6% and 17% [9, 31, 32]. Most rebleeding occur in the first 24 h, mainly in the first 6 h after hospital admission. In one study, the peak time of rebleeding was within 2 h [31]. The risk factors for rebleeding are a high clinical grade, a high modified Fisher grade, high systolic blood pressure, and external ventricular drainage. Modifiable risk factors include a tight control of blood pressure, provided that CPP is maintained, and emergency treatment of the aneurysm. Retrospective studies show that emergency treatment of the aneurysm reduces the risk of in-hospital rebleeding and improves clinical outcome [9, 33]. Poor-grade patients also deserve an early treatment despite a high mortality rate because a favorable clinical outcome may be obtained in approximately one-third of patients [34, 35]. However, the aneurysm securing procedure requires the presence of a highly specialized team that may not be available 24/7. Each center has to weigh the benefit of an early procedure with the emergency team versus waiting a few hours to perform the procedure in a better environment. In all instances, waiting for more than 24 h to secure the aneurysm does not seem reasonable. For the anesthetist, hemodynamic control is a main goal to prevent rebleeding. In the past, induced hypotension has been used. However, even short periods of induced hypotension have been related to an increased risk of neurologic deficits [36, 37]. In WFNS 1–2 patients, a systolic blood pressure < 140 mm Hg may be recommended before securing the aneurysm, although it does not eliminate the risk of early rebleeding. In WFNS 3–5 patients, the management of blood pressure is more difficult because the level of ICP is difficult to predict. After external ventricular drainage, ICP monitoring allows to determine the best arterial pressure range. A CPP > 60 mm Hg is probably reasonable to limit the risk of cerebral ischemia. Without ICP monitoring, transcranial Doppler may help the management of blood pressure. A low diastolic velocity and high pulsatility index are an indication of impaired cerebral blood flow. Treatments to decrease ICP or increase blood pressure have to be considered. In contrast, systolic hypertension with normal TCD recordings indicates that reduction of blood pressure is probably safe.

8.4 Anesthetic Management

Emergency anesthesia is necessary in all cases to secure the aneurysm and prevent rebleeding either by the endovascular approach or for surgical clipping of the ruptured aneurysm. There are general principles that apply to both procedures and specificities to each approach. The main determinant of anesthetic management is preoperative patient status. Patients in good clinical grades (WFNS 1–2) do not have intracranial hypertension and are usually free of significant hemodynamic, respiratory, or metabolic complications. In this case the priority is to prevent aneurysm rerupture through adequate hemodynamic control, especially during painful procedures (laryngoscopy and intubation, craniotomy). For surgery, anesthetic management should follow the general principles of anesthesia for intracranial surgery (maintain cerebral homeostasis, brain relaxation to improve the quality of surgical exposure, early emergence allowing early neurologic examination). Patients in bad clinical grades (WFNS 3–5) are more difficult to manage due to intracranial hypertension and concurrent major medical complications.

8.4.1 General Principles of Anesthesia for Surgery or Interventional Neuroradiology After SAH

8.4.1.1 Monitoring

Hemodynamic Monitoring

Invasive blood pressure monitoring is mandatory in order to obtain hemodynamic stability, preferably before induction of anesthesia and laryngoscopy. Central venous catheterization is useful in most patients undergoing surgery. It allows central venous pressure monitoring in order to detect preexisting hypovolemia or hypovolemia induced by mannitol or hemorrhage during aneurysm rupture. Ultrasound-guided central venous catheter insertion is strongly recommended because carotid artery puncture needing manual compression would be particularly deleterious in patients with impaired CBF. Myocardial dysfunction and hemodynamic instability may need a continuous infusion of catecholamine. A pulmonary artery catheter is seldom used now to monitor cardiac output. Another option is to use transpulmonary thermodilution allowing monitoring of cardiac output and preload. In bad-grade SAH patients, bedside transpulmonary thermodilution monitoring decreases the consequences of delayed cerebral ischemia, reduces the incidence of pulmonary edema, and improves clinical outcome [38, 39].

Monitoring of Brain Function

ICP monitoring is easy to perform in all patients with intraventricular drainage. This is particularly useful in grade IV–V patients who often have intracranial hypertension. In surgical patients, ICP and CPP may be monitored from induction of anesthesia until dura-mater opening. Afterwards, cerebrospinal fluid (CSF) drainage improves brain relaxation. In patients treated by the endovascular approach, ventricular drainage allows monitoring of ICP and CPP throughout the procedure. In case of aneurysm rupture, cerebrospinal fluid drainage is the best method to rapidly decrease ICP and restore CPP (Fig. 8.2).

Monitoring brain oxygenation would certainly be useful. Cerebral venous oxygen saturation ($SjvO_2$) reflects the balance between cerebral metabolic supply and demand. It is obtained by the placement of a catheter in the jugular bulb through retrograde jugular vein catheterization. Matta and colleagues found this monitoring useful for intracranial surgery in general and for aneurysm surgery in more than half of their patients [40]. An acute decrease in $SjvO_2$ may be a sign of aneurysm rupture. However, frequent $SjvO_2$ changes occur without obvious causes, most often leading to an increased $SjvO_2$ [41]. Near-infrared spectroscopy (NIRS) allows continuous monitoring of brain regional oxygen saturation. However, this monitoring is not reliable enough to guide therapeutic management in the operating room during neurosurgery. Extracranial contamination of the signal may lead to spurious changes in NIRS values especially during vasopressor treatment [42].

Other Monitoring

Standard monitoring includes ECG monitoring, pulse oximetry, end-tidal capnography, monitoring of neuromuscular blockade, and temperature monitoring. In addition, a urinary catheter and at least one 14- or 16-gauge peripheral catheter should be inserted. Blood glucose monitoring is useful because hyperglycemia has been associated with cerebral ischemia and poor outcome after SAH [25]. Tight blood glucose control with intensive insulin therapy is potentially dangerous by increasing the risk of hypoglycemia. The optimal blood glucose level is still unknown, and the objective to maintain it below 10 mmol/L (2 g/L) seems reasonable.

8.4.1.2 Management of Increased ICP

With hemodynamic control, reduction of increased ICP is a major goal of anesthetic management. There are several methods to reduce ICP or improve brain relaxation during surgery. CSF drainage is the most effective treatment. However, excessive drainage should be avoided because it has been associated with a risk of aneurysm rupture. Osmotic agents are another option to reduce ICP by reducing brain water content. Typically, 0.5–1 g/kg mannitol (150–400 mL 20% mannitol) infused over 20 min once

or twice before surgery has a rapid onset of action, with a peak effect after 30–45 min, lasting for 2–3 h. Hypertonic saline is an alternative to mannitol. Equiosmolar doses of hypertonic saline and mannitol have similar effects on brain relaxation and brain metabolism [43]. Urinary losses due to mannitol have to be replaced with normal saline to prevent hypovolemia. Hyperventilation and hypocapnia reduce cerebral brain volume and ICP and improve operating conditions during craniotomy [44]. However, this effect is related to cerebral vasoconstriction and may lead to cerebral ischemia depending on the balance between improved CPP and constriction of cerebral blood vessels. It should be used for only short periods of time. It may be particularly useful during surgery to limit brain bulk and provide better operative conditions. Intravenous anesthetics reduce brain metabolism, CBF, cerebral blood volume, and ICP if flow-metabolism coupling is maintained. Inhaled anesthetics are cerebral vasodilators and may increase ICP. Thus, in patients with intracranial hypertension, total intravenous anesthesia is a better option.

8.4.1.3 Induction of Anesthesia

The objectives of the induction period are to avoid both hypotension giving rise to cerebral ischemia and hypertension increasing the risk of aneurysm rerupture. Propofol and thiopental with sufentanil or remifentanil are the mostly used agents. Etomidate (0.2–0.3 mg/kg) may be an interesting alternative in patients with depressed myocardial function because this agent is associated with minimal hemodynamic effects. Remifentanil is very effective to blunt the hemodynamic response to laryngoscopy or pin head-holder application. Bolus infusion is associated with a significant risk of bradycardia and hypotension. Using a target-controlled infusion system, the concentration of remifentanil to blunt the hemodynamic response to noxious stimuli is usually between 4 and 6 μg/L. The concentration has to be decreased rapidly upon cessation of the painful stimulus to avoid hypotension. A continuous infusion of remifentanil is particularly useful when a difficult airway is anticipated because it allows long-lasting laryngoscopy with hemodynamic stability. If low-doses of sufentanil are used during induction of anesthesia, esmolol (1 mg/kg) can be used to blunt the hemodynamic response to laryngoscopy in patients without myocardial injury. Cisatracurium, vecuronium, and rocuronium can be used for muscle relaxation, but atracurium may be hypotensive.

In patients with a full stomach, the priority is to prevent tracheal aspiration and at the same time prevent the hypertensive response to tracheal intubation. Propofol or thiopental with succinylcholine (1.5 mg/kg) or rocuronium (1.2 mg/kg) may be used. In patients with preserved myocardial function, we use either a small bolus of remifentanil (0.25–0.5 μg/kg) or esmolol (1 mg/kg) before intubation.

8.4.1.4 Maintenance of Anesthesia

Depending on the preoperative neurological condition, either total intravenous anesthesia with propofol and remifentanil or sevoflurane with remifentanil or sufentanil can be used. Sevoflurane is a better choice than isoflurane because it is associated with faster recovery, especially after long-lasting procedures. Desflurane may be used but is a more potent cerebral vasodilator than sevoflurane [45, 46]. Nitrous oxide is a cerebral vasodilator and may increase ICP. In one study, nitrous oxide was associated with a greater risk of delayed ischemic neurologic deficits [47]. Thus, a mixture of air/oxygen is most often preferred either during inhalation or intravenous anesthesia. If sufentanil is used during anesthesia, total doses should be less than 2 μg/kg in order to allow rapid awakening and neurologic assessment. After a continuous propofol infusion, the dose or the target concentration has to be reduced toward the end of surgery (wound closure) to avoid accumulation of the drug leading to delayed recovery. Hypertension and tachycardia related to light anesthesia may be controlled by low-dose esmolol (0.5 mg/kg) or labetalol (5–15 mg).

Movement or coughing should not occur during neurosurgery or interventional neuroradiology. Continuous neuromuscular blockade with monitoring is the best option to prevent

movement. High-dose remifentanil may also be used at the expense of systemic hypotension [48].

A lung-protective ventilation strategy with low tidal volume (6–8 mL/kg) and positive end-expiratory pressure (PEEP) has been demonstrated to improve clinical outcome and reduce lung complication after anesthesia [49, 50]. However, neurosurgical patients were systematically excluded from the studies on lung-protective ventilation because recruitment maneuvers or high levels of PEEP may have deleterious effects on the brain. The application of low tidal volume is not a problem during neurosurgery because the respiratory rate can be increased to decrease $PaCO_2$. But low tidal volume without PEEP gives rise to atelectasis, especially when it is sustained for a few hours. High levels of PEEP and recruitment maneuvers have not shown beneficial effects compared to lower PEEP levels and no recruitment maneuvers [51, 52]. In addition, changes in the level of PEEP that result in an increase in driving pressure (plateau pressure—PEEP) are associated with more postoperative complications [53]. In neurosurgical patients, increasing PEEP was not associated with a substantial increase in ICP or decrease in CBF when blood pressure was maintained [54, 55]. In the operating room, low levels of PEEP (5–8 cm H_2O) associated with low tidal volume and no recruitment maneuver seem to be the best option for intraoperative ventilation in neurosurgery. Higher level of PEEP may be needed in patients with neurogenic pulmonary edema needing to find a compromise between oxygenation, deleterious hemodynamic effects of PEEP, and ICP.

8.5 Anesthesia for Neurosurgical Clipping

Specific objectives of anesthesia for ruptured intracranial aneurysms are to obtain an optimal state of brain relaxation to facilitate brain dissection, protect the brain from ischemia, and be prepared to manage aneurysm rupture. The methods to obtain brain relaxation are similar to those used to decrease ICP before skull opening. During surgery, positioning has a major impact on brain tension. A 10° reverse Trendelenburg position lowers ICP with minimal effects on blood pressure [56]. The head is usually turned laterally, and care must be taken to avoid jugular vein compression. Hyperflexion or hyperextension of the head also impairs cerebral venous return. In patients who do not have external ventricular drainage, lumbar CSF drainage is a good option to obtain brain relaxation. Care should be taken to minimize CSF loss during insertion of the drain and to close the drainage system until dura-mater opening because an abrupt decrease in ICP may lead to aneurysm rupture. A volume of 100–150 mL of CSF can usually be removed until the surgeon is able to clip the aneurysm.

Prevention of hemodynamic response to painful stimuli is important both to limit ICP increases and maintain hemodynamic stability. Pin headholder application and surgical incision are two critical times. A small bolus of remifentanil (0.5–1 μg/kg) or an increase in target blood concentration to 6.5 μg/L (EC90 to blunt cardiovascular responses to head fixation) [57] is effective. Other methods are injection of a bolus of esmolol (1 mg/kg) or local anesthetic infiltration of the pin site [58]. Brain dissection is painless, and the depth of anesthesia and analgesia is usually decreased to avoid hypotension. In this case, close monitoring of neuromuscular blockade is mandatory.

8.5.1 Anesthesia Management During Temporary Clipping of the Parent Vessel

Temporary clipping of the aneurysm parent vessel has become standard practice and is used in more than 50% of patients. The safety of this procedure has been demonstrated for short-lasting clipping times and was not associated with an increase incidence of DCI [59]. The duration of safe temporary clipping is very variable. Retrospective studies have shown that an occlusion less than 10 min long was safe [60, 61]. Temporary clipping lasting more than 20 min and multiple clipping episodes were significantly associated with cerebral ischemia [61]. An increase in blood

pressure to improve collateral brain blood flow during temporary clipping is recommended although the evidence to support it is scarce [62]. Thiopental-, etomidate-, or propofol-induced burst suppression in order to provide brain protection has been used. Some retrospective data suggested a decrease in postoperative brain infarction rates, especially for clipping duration above 10 min [60]. Hypothermia for intraoperative neuroprotection has been tested in the IHAST trial, a prospective randomized trial including 1001 patients [63]. Intraoperative hypothermia did not improve the neurologic outcome. A post hoc analysis of this trial did not show any effect of drugs used for neuroprotection on long-term clinical outcome [64].

Optimization of clip placement is essential for good long-term results. Microvascular Doppler ultrasonography has been used to assess the quality of the surgical procedure. One study demonstrated ongoing flow in the aneurysm in 12% of patients and occlusion of an adjacent vessel in 28% of cases [65]. Doppler was found to be more convenient and as effective as intraoperative angiography. Indocyanine green video angiography is a convenient method to confirm aneurysm occlusion and assess the cerebral circulation in the operative field [66]. However, it does not seem to be 100% reliable compared to conventional angiography [67]. Adenosine-induced cardiac arrest has been used as an alternative to limit the necessity of temporary clipping with good results [68].

8.5.2 Management of Intraoperative Rupture

Intraoperative rupture is a relatively frequent event. It occurred in 13% of cases in an international multicenter study published in 1990 [69]. More recently, an intraoperative rupture rate between 10.7 and 18% has been reported during surgery after SAH [70, 71]. Large aneurysms, clinical grade, anatomic location on the posteroinferior cerebellar artery, and the anterior or posterior communicating arteries have been associated with an increased risk of rupture. Intraoperative rupture is associated with a bad clinical outcome [70]. However, the difficulty to manage aneurysm bleeding is related to the timing of rupture during the surgical procedure. When the rupture occurs early during cerebral dissection, the time needed to gain access to the aneurysm and stop bleeding may be long and associated with significant blood losses, hypotension, and brain damage. In contrast, rupture during manipulation of the aneurysm is easily controlled by temporary clipping followed by aneurysm clipping with little consequences.

Aneurysm rupture with significant hemorrhage obscures the operative field under the microscope, making surgery impossible. Thus, the priority is to stop or minimize the hemorrhage. If possible, this is best achieved with temporary clipping [72] because even short periods of hypotension have been associated with poor outcome [36, 37]. Hypotension may be used as a rescue treatment to allow surgery. The adequate blood pressure level is the highest value providing an acceptable view in the operating field. Isotonic crystalloid solutions are the first choice to replace blood losses. Perioperative autologous blood transfusion may be used if prepared from the beginning of the procedure. Homologous transfusion is seldom necessary, but blood and plasma must be available rapidly in the case of major bleeding.

8.6 Anesthesia for Endovascular Treatment

In most centers, intracranial aneurysms are now frequently treated by the endovascular than the surgical approach. A large trial (ISAT trial), comparing endovascular coiling or surgical clipping of the aneurysm, concluded to a better outcome with the endovascular approach [73]. The relative risk reduction in dependency or death with the endovascular treatment was 22.6% in 2143 patients. This study was criticized because it included mostly patients with anterior cerebral artery aneurysms. However, it demonstrated that endovascular treatment may be considered a valid alternative to surgery.

8.6.1 Specific Objectives of Anesthesia for Interventional Neuroradiology (INR)

– Immobility

The placement of superselective intravascular catheters has to be very accurate. This is achieved by using "roadmapping." Even slight movement of the head can markedly degrade the image. In addition, forceful movement of the head (e.g., coughing) when a microcatheter is in situ may cause arterial dissection and thrombosis.

– Prevention of hypothermia

The environment in the INR suite is cold and large volume of contrast media may be used. The risk of hypothermia remains high. There is limited access to the patient to allow efficient warming during the procedure. It is suggested that preoperative surface warming be used to prevent hypothermia.

– Avoid patient injury

It is very imperative to secure the head and arms because the radiology table is often moved which may result in patient injury. The tracheal tube must be secured properly and any conflict with the radiology machine should be prevented.

– Radiation safety

Exposure by the anesthesia team to radiation hazards should be avoided as much as possible. A remote anesthesia monitor in the radiation safe area is useful.

8.6.2 Problems Associated with Anesthesia Outside the Operating Room

The problems associated with remote anesthesia location should not be underestimated. The anesthesia equipment should be checked regularly and before each anesthesia because another one (monitoring, ventilator, gas supply, etc.) may not be available rapidly in case of failure. Some specific features may compromise patients' security. For example, the access to the patient in INR facilities is limited due to bulky equipment. The personnel are often less familiar with anesthesia than the one working in the operating room. In emergency situations, it may be difficult to obtain valuable help. At any time, help must be speedily and effortlessly available. The INR location should be close to other remote anesthesia locations (vascular interventional radiology, endoscopy, interventional cardiology, etc.) in order to improve anesthetic organization and safety.

8.6.3 Morbidity and Mortality of INR

The range of morbidity in INR procedures is between 10% and 20% and mortality between 1% and 4% [74–76]. The two main complications are cerebral hemorrhage and cerebral artery thrombosis.

8.6.4 Cerebral Hemorrhage

In a meta-analysis in 2002, the risk of intraprocedural aneurysm perforation was 4.1% for the endovascular treatment of ruptured aneurysms [77]. The combined risk of permanent neurologic disability and death associated with this complication was 38%, a figure comparable to the 63% rate of periprocedural death or disability in a more recent study [70]. In the CLARITY study in 2010, including 782 patients, the intraprocedural rupture rate was 4.3% [78]. Aneurysm rupture was more frequent in MCA aneurysms and in patients younger than 65 years. There was no death related to rupture, and the morbidity was very low (0.6%), suggesting that management of aneurysm bleeding during endovascular treatment has been much improved in recent years. Rupture of aneurysm usually occurs when the patient is fully anticoagulated, needing to be prepared for managing the complication in order to

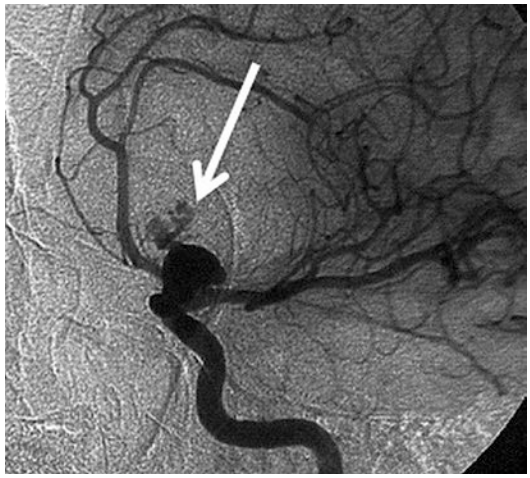

Fig. 8.4 Intraoperative rupture of an aneurysm just before coil embolization. The extravasation of contrast media outside the aneurysm (arrow) allows the diagnosis of aneurysm rupture

Table 8.3 Management of intracranial bleeding due to aneurysm rupture during coil embolization

Stop bleeding	Control intracranial hypertension	Brain protection
Inform the neuroradiologist Call for help Antagonize heparin (protamine) Occlude the aneurysm as fast as possible or inflate a balloon in the artery *Do not infuse antihypertensive agent* Give thiopental (decreases blood pressure and ICP)	*During procedure* Mannitol 1 g/kg Hyperventilation ($PaCO_2$ 26–30 mm Hg) Stop inhaled anesthetic agents (or shift to propofol) Give thiopental Allow mild hypothermia *Post procedure* Ventricular drainage	Ventilate with 100% O_2 Mild hypothermia Thiopental Ventricular drainage

stop bleeding as soon as possible. In an anesthetized patient, the signs of SAH due to aneurysm rupture are those due to intracranial hypertension. The early signs of rupture are severe hypertension and bradycardia (Fig. 8.2). This should not be interpreted as light anesthetic depth. Communication with the neuroradiologist is essential because injection of contrast media is necessary to confirm the diagnosis and take appropriate therapeutic measures (Fig. 8.4). The management of aneurysm bleeding is summarized in Table 8.3. Heparin should be immediately reversed with protamine. Antihypertensive agents compromise cerebral perfusion and should not be given. During severe hypertension, thiopental is the only possible agent to lower blood pressure because it is frequently associated with a parallel decrease in intracranial pressure and may afford cerebral protection. A treatment for raised intracranial pressure is indicated. Increasing the inspired oxygen fraction improves brain oxygen content. It is relatively innocuous and may afford some cerebral protection. After the procedure has been completed, a CT scan is needed to assess the extent of intracranial bleeding and discuss the indication of ventricular drainage. The neurosurgical team should be informed of the complication, and the anesthesia team should be prepared to go to the operating room if needed.

8.6.5 Cerebral Artery Thrombosis

8.6.5.1 Risk of Thrombosis

The most frequent severe complications of INR are the thrombotic complications. The risk of thrombosis is related to vessel wall damage, thrombogenicity of contrast material, guidewires, microcatheters, vascular coils, and stents. In a review on 1547 patients, the immediate and delayed thromboembolic risk after coil embolization of aneurysm was 8.2% [79]. The risk is high in the first 48 h, and then it decreases rapidly. In the CLARITY study, the incidence of thromboembolic events was 12.5% [78]. A higher rate was observed in smokers, in aneurysms larger than 10 mm or with a large neck. Thromboembolic events lead to permanent neurologic deficit or death in 3.8% of patients. The risk of thrombosis is particularly high with stents, needing treatment with an antiplatelet agent before the procedure, which is rarely possible after SAH.

8.6.5.2 Prevention of Cerebral Artery Thrombosis

Considering the risk of thrombosis, intravenous heparin is mandatory during the procedure. After a baseline activated clotting time (ACT) is obtained, 50–70 units/kg is given to obtain an ACT of 2–3 times the baseline value. ACT should

be checked every hour to maintain adequate anticoagulation. The injection of acetylsalicylic acid has been associated with a lower rate of thromboembolic events [80]. Nevertheless, it may increase the risk of bleeding if a neurosurgical procedure is needed (ventricular drainage).

8.6.5.3 Treatment of Cerebral Artery Thrombosis

This complication should be recognized and treated as soon as possible. The first step is to promote oxygen transport to the ischemic brain which can be achieved by increasing the blood pressure in order to recruit collateral arteries and by increasing the inspired oxygen fraction to 100% in order to increase the diffusion of oxygen to the ischemic penumbra. The second step is to recanalize the vessel. The activated coagulation time is checked, and additional heparin is given if the ACT is less than 250 s. Infusion of thrombolytics in situ (rt-PA, maximum dose 0.9 mg/kg) has been used with an approximately 50% recanalization rate [81]. Fragmentation of the clot mechanically improves the efficiency of thrombolysis. Glycoprotein IIb/IIIa receptor antagonists (abciximab, eptifibatide, tirofiban) have been associated with a higher recanalization rate than thrombolytics, a lower perioperative morbidity, and a better long-term outcome [82]. The incidence of bleeding was low in the reported case series. Thus, they can be used as first-line agents in case of vessel thrombosis. Mechanical thrombectomy is a logical option, but the experience is very limited in this indication.

8.7 Emergence and Recovery After Anesthesia

Early clinical assessment is essential after surgery or coil embolization. After an uneventful procedure, grade 1 or 2 patients should be allowed to awaken as soon as possible. Moderate hypertension (systolic blood pressure < 180 mm Hg) is usually not aggressively treated. Higher blood pressure levels may cause cerebral hemorrhage or swelling and should be treated with low-dose labetalol (5–10 mg), nicardipine (0.5–1 mg), or urapidil (10–20 mg) as needed. Any new neurologic deficit in the immediate postoperative period should raise the possibility of clip or coil complication and lead to emergency CT angiography. Grade 3 or 4 patients usually need postoperative ventilation, but neurologic examination is possible after stopping anesthesia to rule out any new focal neurologic deficit. Grade 5 patients are sedated and ventilated in the postoperative period. TCD is a convenient monitoring to assess the patency of arteries of the circle of Willis.

The main risk in the postoperative period is cerebral ischemia related to vasospasm. A systolic blood pressure above 120 mm Hg is a safe objective to maintain adequate brain blood flow.

In the postoperative period, the patients are usually monitored in an intensive care unit, to detect medical or surgical complications. A brain CT scan 24–48 h after the aneurysm securing procedure is important to detect any ischemia related to the procedure.

8.8 Conclusion

Anesthesia for patients with SAH requires a clear understanding of the cerebral consequences of aneurysm rupture. Hemodynamic management needs to balance the risks of cerebral ischemia due to impaired CBF and the risk of rebleeding. Several medical complications, including heart failure and neurogenic pulmonary edema, are challenging to perform emergency anesthesia for a major surgical or endovascular procedure. The objectives of anesthesia are both to make the aneurysm securing procedure as safe as possible and at the same time maintain brain homeostasis in order to prevent cerebral ischemia.

Key Points

- The main complication after aneurysmal subarachnoid haemorrhage (SAH) is cerebral ischemia.
- Cerebral ischemia may occur early after SAH, due to the cerebral bleeding, during the treatment of the aneurysm (surgery or interventional neuroradiology), and after 5 to 15 days after SAH (delayed cerebral ischemia).
- Cardiac and pulmonary complications are frequent after severe SAH, needing appropriate monitoring in the ICU.
- In patients with severe SAH, cardiac output monitoring has been demonstrated to improve outcome.
- The management of intracranial hypertension is a hallmark of anaesthesia for the aneurysm securing procedure.
- Delayed cerebral ischemia may be related to cerebral vasospasm and other pathophysiological processes.
- Close clinical and transcranial Doppler monitoring is needed to detect cerebral vasospasm and initiate emergency treatments to avoid the development of cerebral ischemia.

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9 Anesthesia for Cerebrovascular Lesions

Shiwani Jain and Manish Kumar Marda

9.1 Introduction

Cerebrovascular disease consists of a group of conditions which can lead to a cerebrovascular accident, such as a stroke. These events affect the blood vessels and blood supply to the brain and involve both venous and arterial circulations. If a blockage, malformation, or hemorrhage prevents the brain cells from getting enough oxygen, brain tissue sustains extensive damage, which can be irreversible in a few cases. In the following chapter, we shall be discussing about the pathophysiology, clinical presentation, and management strategies of the carotid artery stenosis, Moyamoya disease, and arteriovenous malformations.

9.2 Carotid Artery Stenosis

Carotid artery stenosis can lead to life-threatening stroke and significant disability. The two routinely performed procedures for carotid artery stenosis are carotid endarterectomy (CEA) and carotid artery stenting (CAS) [1]. Table 9.1 enumerates the various indications for CAE.

Table 9.1 Indications for CAE (American Academy of Neurology: www.aan.com/professionals/practice/index.cfm)

Carotid stenosis (% by angiography)	Recommendation
Symptomatic patients	
70–99%	CEA is established as effective for recently symptomatic (<6 months)
50–69%	CEA may be considered in patients with expected survival >5 years, periprocedure mortality/stroke <6%
<50%	Not indicated
Asymptomatic patients	
60–99%	In patients between 40 and 75 years, if periprocedure mortality/death is <3%, life expectancy >5 years

The risk of perioperative stroke in patients undergoing CEA is 3.4% in asymptomatic patients and 5.2% in symptomatic patients [1–3]

9.3 Preoperative Evaluation

Patients with carotid artery stenosis are usually suffering from multiple comorbid conditions, and preoperative control is desirable. Hypertension is present in 65% of CEA patients, and it should be well controlled prior to surgery, as patients with uncontrolled hypertension are more likely to have postoperative hypertension, transient ischemic neurological deficits, and other complications like intracerebral hemorrhage and hyperperfusion syndrome [3–5].

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The combined death and stroke rates in patients with bilateral carotid disease undergoing CEA was almost twice that of patients with unilateral disease [6].

The prevalence of coronary disease in the patients presenting for CEA is as high as 77% [7, 8], and severe coronary disease has been found to be present in 37% [9] of CEA patients. In fact, after stroke, myocardial infarction (MI) is the commonest cause of death after CEA [1, 2].

Preoperative pulmonary function testing, incentive spirometry, chest physiotherapy, steroids, and bronchodilators should be initiated in patients with respiratory involvement.

Diabetes mellitus may be present in patients with carotid artery disease, and the preoperative blood sugar control with absence of ketoacidosis is essential as both hypoglycemia and hyperglycemia can have adverse neurological effects especially during the cross clamping period when there is a likelihood of cerebral ischemia. Hyperglycemia has been found to be associated with increased risk of stroke, myocardial infarction, and death after CEA, and this was found to be independent of previous cardiac disease, diabetes, or other comorbidities [10].

9.4 Treatment Options for Carotid Artery Disease

The following are the management options for carotid artery stenosis [11–14]:

- Conservative management
- Surgical management—carotid endarterectomy (CEA)
- Endovascular management—carotid artery stenting (CAS)

Surgical procedure (CEA) is done to evacuate the clot from ICA while doing end-to-end anastomosis of the dissected artery. Bleeding from ICA is prevented by cross clamping of the artery leading to potential ischemic complications. There is also risk of thromboembolism if debris of the clot enters cerebral circulation.

To reduce the chances of this problem and prevent cerebral ischemia and, consequently, stroke in the perioperative period, a shunt is placed to bypass the cross clamped carotid artery [13]. However, shunt placement is not totally risk-free, and it can lead to plaque or air embolization and even carotid dissection. Moreover, flow through the shunt may sometimes be inadequate to meet cerebral oxygen requirements and still cause cerebral ischemia. Therefore most surgeons place shunt selectively depending upon the intraoperative evidence of ischemia.

Fluctuations in blood pressure and heart are common during the carotid endarterectomy. It can be treated by increasing the depth of anesthesia along with infiltration of local anesthetic agent around the carotid sheath or placing local anesthetic pledgets near the carotid sinus nerve.

The main aim of anesthetic management in CEA is prevention of any adverse cerebral or coronary events. However there are different schools of thought on whether general or regional anesthesia is better for prevention of poor neurological outcome (Table 9.2) [12, 13].

General anesthesia has cerebral protective effect of anesthetic agents on brain, perioperative control of ventilation, and better patient comfort. The GALA trial [14] (a randomized comparison of GA and LA for patients undergoing CEA) found that myocardial infarction, stroke, or death occurred in 4.8% patients assigned to GA and 4.5% of those assigned to LA. The difference in outcome was not significant.

Table 9.2 Regional vs. general anesthesia

Regional anesthesia	General anesthesia
• Awake patient is best to monitor for neurological changes • Postoperative assessment • Greater cardiovascular stability • Postoperative pain control • Shorter hospital stay • Difficulty in situations of airway obstruction • Difficult to manage in case of intraoperative bleeding, stroke, or neurological event	• Better control during the surgery • Better airway control • Additional monitoring required • Patient comfort, no possibility of movement during the surgery

Therefore, there is no sufficient evidence to judge the effect of neurological outcome based on the anesthesia technique alone sequelae.

A combination of meticulous patient selection, preoperative optimization, and employing various methods for cerebral protection is more important.

9.5 CEA Under Regional Anesthesia

Both superficial and deep cervical plexus blocks can be used for the procedure [14]. Ultrasound guidance can also be used to facilitate accurate drug placement and increase the efficacy of the block. Sedatives are usually required to supplement regional anesthesia for patient comfort as well as to allay anxiety. The commonly used agents are midazolam, fentanyl, remifentanil, propofol, clonidine, or dexmedetomidine [15]. Sedation should be titrated in such a way that during cross clamping, the patient is awake and cooperative for neurological testing. Oversedation should be avoided as it can lead to airway obstruction and retention of CO_2, which can aggravate hypertension and tachycardia and can have deleterious effects on the cerebral circulation.

9.6 CEA Under General Anesthesia

The goal of anesthesia is to provide a relatively light plane of anesthesia as CEA is not a very stimulating surgery, and this combined with local anesthesia infiltration is generally sufficient for performing surgery. Various agents have been used successfully for CEA including isoflurane, sevoflurane, desflurane, nitrous oxide (N_2O), propofol, and opioids [15]. The general concerns of hemodynamic stability and cerebrovascular profile of various anesthetic agents would be the criteria for use in CEA, and there are not many studies to make a recommendation of any agent over the others. In one study comparing propofol with isoflurane, it was reported that with emergence, hypertension and myocardial ischemia were more prevalent with more frequent pharmacological interventions in patients receiving isoflurane [15].

9.7 Monitoring

The main purpose of neuromonitoring in patients of CEA is to detect cerebral ischemia early. These monitors should not only be sensitive and specific but should also provide real-time early warning for cerebral ischemia so that prompt measures can be undertaken to prevent intraoperative stroke. Commonly used monitoring techniques include electroencephalography (EEG) [16–18], evoked potential monitoring, transcranial Doppler (TCD), jugular venous oxygen saturation ($SjvO_2$), carotid stump pressure (CSP) monitoring, near-infrared spectroscopy (NIRS), and brain tissue oxygen ($PtiO_2$) monitoring. However, awake and conscious patients are the best to monitor.

9.7.1 Electroencephalography

The EEG shows the balance between cerebral oxygen supply and oxygen demand, and decades of use of this monitoring modality has shown a strong correlation between cerebral ischemia and EEG changes [16–18]. It has high sensitivity for detection of ischemic changes and can serve as a guide for shunting. EEG which becomes isoelectric before irreversible neurological damage; it alerts the team to take prompt measures for cerebral protection. Schneider et al. also reported that with EEG monitoring and selective shunting, the incidence of intraoperative stroke declined, and postoperative stroke occurred only in 1% of patients even for patients with contralateral ICA occlusion. It can be used as part of a multimodality monitoring technique for better detection of intraoperative cerebral ischemia.

9.7.2 Evoked Potential Monitoring

A recent meta-analysis observed that patients with perioperative neurological deficits were 14 times more likely to have had changes in SSEPs

during the procedure. Moreover, patients who had irreversible changes had a 97% chance of an ischemic perioperative insult. The authors found SSEP useful during the surgery. The false-negative rate with SSEP varies between 0 and 3.5%, and it seems to have low specificity; therefore it looks reasonable to combine it with MEP as MEP has lower false-negative rate of 0.4% when compared with SSEP. Also, EEG and SSEP may complement each other when used together since they evaluate different regions of the brain. Selective shunting based on EEG and SSEP monitoring can reduce intraoperative stroke rate during CEA to a near zero level if trained personnel adopted standardized protocols.

9.7.3 Transcranial Doppler

TCD can measure cerebral blood flow velocity and thus indirectly the CBF and cerebral perfusion. It is also helpful in detecting microemboli which can shower during the manipulation or shunting of the carotid artery. Wolf et al. used TCD to detect microembolic signals during the various stages of the procedure and correlated it with cerebral ischemia as detected by diffusion-weighted imaging (DWI) and cerebral infarction as detected by contrast-enhanced MRI. Therefore, TCD remains an important monitoring device during CEA as it is the only reliable monitor for detecting emboli, which accounts for a majority of cerebral insults.

9.7.4 Near-Infrared Spectroscopy (NIRS)

NIRS monitors regional brain tissue oxygenation and cerebral oxygen saturation (rSO_2). The readings can help guide the decision for shunting the carotid artery; however there is limitation to this modality as it cannot measure the global cerebral oxygenation and there are chances of contamination from extracranial tissues.

9.7.5 Stump Pressure Measurement

Carotid stump pressure (CSP) monitoring is used to determine the adequacy of the collateral circulation via the circle of Willis or the external carotid artery circulation. A stump pressure of 50 mm HG has a high specificity for predicting the requirement of a shunt placement. CSP measurement is not used solitarily; it is usually a part of multimodal neuromonitoring.

9.8 Intraoperative Management

Measures that need to be taken during CEA are maintenance of optimal blood pressure, blood glucose levels, and hemoglobin concentration as well as maintenance of normocarbia. Hemodynamic fluctuations are frequently observed during CEA irrespective of the preoperative arterial pressure. Using beta-blockers perioperatively is not indicated, and it has been seen that high-dose beta-blockers started in preoperative period are associated with high risk of stroke [19]. To maintain sufficient perfusion through the circle of Willis, it is recommended that blood pressure be maintained between normal and 20% above preoperative values.

Statins should be continued in perioperative period. In a retrospective analysis done in asymptomatic carotid stenosis patients, it was observed that there are both clinical and financial advantages of using both statin therapy and angiotensin pathway-blockade therapy in patients with asymptomatic moderate carotid artery stenosis [20].

9.9 Coronary Angioplasty and Stenting

The anesthesia and intraoperative neuromonitoring techniques for patients undergoing CAS are similar to any other neurointerventional procedures being done under local anesthesia. The surgical technique involves the introduction of an intra-arterial catheter through a guidewire and deploying a balloon, with or without a stent, thus expanding the lumen of the carotid artery.

All patients are routinely premedicated with antiplatelet drugs (aspirin 325 mg and clopidogrel 75 mg) 3–5 days before the procedure [21–23]. Before the passage of the guidewire, heparin 70–100 units/kg is administered and ACT done to ensure that the activated clotting times are twice the basal value.

Dilatation of the carotid artery and stimulation of the carotid baroreceptors can cause bradycardia and hypotension, and rescue treatment with glycopyrrolate or atropine may be necessary. During the procedure the patient must be monitored for evidence of thromboembolism, dissection, TIA, and stroke. Heparin is not usually reversed at the end of the procedure. A clinical neurological assessment is done at the end of the procedure.

Post-procedure, the patient must be watched for cerebral hyperperfusion following restoration of normal CBF. After the procedure, combined platelet inhibition with clopidogrel and aspirin is continued for at least 30 days and up to 12 months [23, 24].

It is a minimally invasive technique, the main advantages being that it avoids surgical wounds and can be done under local anesthesia. However there are several concerns such as restenosis of the carotid artery, increased rate of stroke, and death. Therefore, though the expertise to perform the procedure is advancing rapidly, there is still no consensus about the target population.

9.10 Postoperative Complications and Outcomes

Risk factors associated with poor outcome (stroke, MI, or death) in patients undergoing CEA are summarized as follows:

- Prior ipsilateral hemispheric neurological symptoms (stroke or TIA) [21, 22]
- Severe contralateral carotid stenosis or distal ICA/CEA stenosis [23–25]
- Very recent stroke or crescendo TIAs [26]
- Symptomatic patients [1]
- Chronic renal insufficiency [13]
- Diabetes [27]
- Hypertension and hyperlipidemia [28–33]

Common postoperative complications include the dysfunction of the carotid chemoreceptors and the baroreceptor, cerebral hyperperfusion syndrome, stroke, myocardial infarction, and death. The AHA guidelines for CEA recommend that the combined risk for death or stroke should not exceed 3% for asymptomatic patients and 5% for symptomatic patients. This risk may be higher in patients undergoing emergency CEA due to unstable neurological status, in unstable patients undergoing combined CABG and CEA, and those presenting for reoperation. Other troublesome complications include hematoma at the surgical site and cranial nerve palsies secondary to intraoperative manipulation. It is advisable to keep these patients under close monitoring in neuro ICU to identify and treat complications early.

9.11 CAS Versus CEA

There is an ongoing debate on the use of CEA or CAS for patients with carotid artery disease. It was Naylor who showed in a randomized, prospective study comparing outcomes following CAS and CEA in patients with symptomatic carotid artery disease that there was a high incidence of ischemic stroke in patients who underwent CAS, whereas none of the patients who underwent CEA had this complication [34].

Brooks, on the other hand, in a randomized study, found that CAS was equivalent to CEA in terms of death and stroke [35]. These authors recently published a 10-year outcome study in which they showed that the incidence of stroke was not different in either group, but incidence of MI was more in patients who underwent CEA [35, 36].

The Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS) was also a large, prospective, randomized trial that compared CEA with CAS conducted in patients with symptomatic disease. This study found that there was no difference between groups in the risk of stroke or death either related to the procedure or within 30 days of treatment which persisted up to 3 years after randomization. However, it was found that the rate of restenosis was twice as high in the CAS group as compared to the CEA group (18% vs. 9%) [37].

The SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial also concluded that in symptomatic patients with comorbidities, CAS using emboli protection device was not inferior

to CEA [38]. These authors found that the incidence of MI, documented by a rise in troponin levels, was higher in patients who underwent CEA. The primary endpoints in this trial were death, stroke, and MI. The CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) found that the combined risk of death, MI, or stroke was comparable for the two procedures, but during the periprocedural period, the incidence of stroke was comparable for CEA versus CAS (6.8% and 7.2%, respectively), and the risk of MI was higher in CEA versus CAS (2.3% and 1.1%, respectively) [39]. A recently published subanalysis of CREST showed that restenosis and occlusion rates were similar up to 2 years after CEA and CAS [40].

9.12 Moyamoya Disease

Moyamoya disease (MMD) is a rare cerebrovascular disease of unknown origin which is characterized by bilateral progressive steno-occlusion of terminal branches of internal carotid arteries with emergence of coexisting abnormal netlike vessels [41].

It is usually bilateral and involves anterior circulation; however it may also present as unilateral disease with potential to progress bilaterally, and posterior circulation can also be involved in later stages.

Prevalence of MMD is high in East-Asian population, females, and patients with family history of MMD. Several polymorphisms in the RNF213 gene have been identified in association with cases of MMD in East-Asian and Caucasian population. This gene has been suggested to play a role in arterial wall remodeling and angiogenesis [41]. However epigenetic or environmental factors may also be associated with disease progression. There is proliferation of intima of distal ICA and/or MCA with constrictive remodeling and fibrocellular thickening. This on one hand results in vascular stenosis and on the other hand stimulates angiogenesis.

Moyamoya vessels are dilated perforation arteries with fibrin deposits in the wall, fragmented elastic laminae, weakened media, and formation of microaneurysms. Another specific finding of MMD is cortical microvascularization.

The common symptoms of MMD are headache, transient ischemic attacks, stroke both ischemic and hemorrhagic, seizures, and abnormal movements. Children commonly present with ischemic symptoms, seizures, and cognitive impairment, while adults are more prone to develop hemorrhagic complications including ICH and SAH [42].

Diagnosis of MMD is confirmed with the help of MRA and/or DSA. The classification given by Suzuki is not commonly used as its practical value is questionable. Recently berlin Moyamoya grading is more commonly used and has been validated.

Cerebral hemodynamic impairment and repeat ischemic symptoms have to date been the main indications for treatment. The idea of revascularization surgery is to perform microsurgical reconstruction using an extracranial-intracranial bypass and paving the way for future vasculogenesis by performing indirect pial synangiosis [42]. The whole purpose of this procedure is to switch the supply of the brain from the internal carotid system to the external carotid system.

As asymptomatic MMD can progress with annual stroke rate as high as high 13%, there are reconsiderations in management of asymptomatic patients.

The Japan Adult Moyamoya Trial suggests the use of direct revascularization surgery for declining the risk for re-bleeding in adult patients of MMD who present with intracranial hemorrhage.

Indirect methods of revascularization like encephalo-myo-synangiosis (EMS), encephalo-galeo-synangiosis, encephaloduroarteriosynangiosis (EDAS), or omentum transplantation are based on the idea that neovascularization can be induced from the extracranial arteries to the cortical arteries by placing vascular-rich tissues on the pial brain surface. A scalp artery with a strip of galea is transplanted to a linear dural opening made through an osteoplastic craniotomy in commonly performed EDAS. These are relatively simpler procedures, and they depend upon neovascularization capabilities of the brain.

Direct revascularization procedures involve anastomosis between extracranial arteries and intracranial cortical arteries like STA-MCA bypass.

Perioperative course of bypass surgery may include cerebral ischemia, hyperperfusion syndrome, or watershed shift.

As the anastomosis is done at the distal part of MCA, the retrograde flow from anastomotic artery and antegrade flow from ICA may lead to watershed shift, leading to temporary reduction in CBF at these areas. Temporary hyperperfusion can also occur and may lead to focal neurological deficits and delayed ICH or SAH. Other complications include thromboembolic complication and mechanical compression by graft [42, 43].

There is not enough evidence regarding optimal anesthesia technique for surgery for MMD. But general principles may be applied. It is very important to maintain cerebrovascular physiology as normal as possible. Hypotension may lead to hypoperfusion, while hypertension may lead to hemorrhage; therefore tight control of MAP with the help of invasive blood pressure may be indicated. Perioperative hypercapnia or hypocapnia should be avoided, euvolemia should be maintained, and antiplatelets should be used. High MAC may lead to steal phenomenon so that anesthesia technique should be tailored accordingly.

9.13 Cerebral Arteriovenous Malformations

9.13.1 Introduction

Arteriovenous malformations comprises of a mass of thin walled blood vessels called the "nidus." These vessels connect the high-pressure arterial circulation to the low-pressure venous circulation, thus bypassing the normal capillary circulation. The architecture of AVMs resembles a complex mesh of abnormally dilated arteries which drain into the venous system. The incidence of symptomatic AVMs is estimated to be 0.82–1.1 per 100,000 population, but their prevalence, as determined by autopsy, varies between 1.4 and 4.3%.

Both the sexes are affected usually in the third and fourth decade of life [44]. The average risk of spontaneous bleeding in patients with unruptured AVM not availing any treatment is around 2–4% per year for all patients.

AVMs are congenital and have unusual angioarchitecture, angiographic, and pathological features. The vessels involved show medial hypertrophy, endothelial thickening, as well as degeneration of the arterial wall. The surrounding cerebral tissue shows signs of atrophy and gliosis due to chronic ischemia [44, 45].

The middle cerebral artery is the most common feeding artery for majority of arteriovenous malformations. Around 90% of AVMs are found in the supratentorial region. Parietal area is most commonly involved followed by frontal and temporal area. AVM feeder vessels are characterized by high blood flow, low resistance, low perfusion pressure, and decreased CO_2 reactivity. Approximately half of AVMs drain into superior sagittal sinus. Coexisting aneurysms may be seen in the nidus or the feeding artery in approximately 10% of the cerebral AVMs. Digital subtraction angiography (DSA) is the gold standard investigation to delineate the vascularity of AVMs.

9.13.2 Signs and Symptoms

The most common presentations of AVMs are:

- Intracranial hemorrhage
- Intraventricular hemorrhage
- Seizures
- Headache and tinnitus
- Focal neurological deficits

Hemorrhage as a presenting feature is very likely to occur in patients with high intranidal pressure, and it manifests as headache and mass effect [44, 45]. Unlike cerebral aneurysms, which manifest as subarachnoid hemorrhage, AVMs usually present as intraventricular or intraparenchymal bleed. The second most com-

mon presentation is seizure, which may be focal or generalized and may give some clue about the location of the lesion. Less commonly, AVM presents with focal neurological deficits, headaches, and even tinnitus.

Unruptured AVMs do not have a clear natural history. ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) [46] was a multicenter, randomized trial which compared the long-term neurological outcome in patients of unruptured AVMs receiving either medical or surgical treatment. The latter included endovascular procedures, neurosurgery, or radiosurgery alone or in combination. This trial showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured brain arteriovenous malformations followed up for 33 months. The trial is continuing its observational phase to establish whether the disparities will persist over an additional 5 years of follow-up.

9.13.3 Grading of Arteriovenous Malformations

The grading system proposed by Spetzler and Martin (SM) is the most commonly employed system (Table 9.3). This is based on size, pattern of venous drainage, and eloquence of adjacent brain and is not only used to predict surgical outcome but can also guide for the appropriate management options.

Table 9.3 Spetzler and Martin grading system

Characteristic		Point(s) assigned
Size	Small (<3 cm)	1
	Medium (3–6 cm)	2
	Larger (>6 cm)	3
Eloquence[a]	No	0
	Yes	1
Venous drainage	Superficial only	0
	Any deep	1

[a]Sensorimotor, language, or visual cortex, hypothalamus or thalamus, internal capsule, brainstem, cerebellar peduncles, or cerebellar nuclei

9.13.4 Management

The common treatment options for AVMs are either conservative, surgical excision, endovascular management, or radiosurgery.

It is recommended that that SM grade I and II lesions must be surgically excised. Grade III lesions should be resected either surgically or via radiosurgery often along with embolization in grade IV or V lesions. In a few selected individuals with grade IV/V lesions, multimodal approach should be applied if the outcome is expected to be favorable.

Endovascular intervention is done as a first-stage procedure preceding to surgical excision. It reduces the size and vascularity of AVM, thus facilitating smooth surgical resection with less blood loss. Meanwhile the surrounding brain tissue also gets adapted to the circulatory changes. Endovascular therapy as a single modality treatment is beneficial for superficially located small- and medium-sized AVMs.

Gamma knife stereotactic radiotherapy or radiosurgery is restricted to AVMs with a nidus size of <3 cm. The risk of hemorrhage persists till the time complete obliteration is achieved which usually takes around 2 years or more in 50–80% of the cases.

9.13.5 Anesthetic Considerations

AVM resection is usually an emergency; however an intracranial hematoma with mass effect needs to be evacuated urgently.

Goals of anesthetic management:

- Adequate brain relaxation
- Stable hemodynamics
- Prevent brain bulge
- Manage blood loss
- Smooth and rapid emergence

Maintenance of euvolemia, normoglycemia, hematocrit, and electrolyte balance is imperative. Induction must be extremely smooth to prevent the rupture of any coexisting aneurysm.

The choice of monitoring, vascular access, anesthetic agents, vasoactive drugs, and muscle

relaxants also should be decided on patient's preoperative status. In addition to routine monitoring, intra-arterial catheters and central venous catheters are necessary to facilitate administration of vasoactive drugs during surgery, especially in the event of massive hemorrhage.

Endovascular therapy can be performed under general anesthesia or intravenous sedation. There is no evidence of superiority of one technique over another. The goals of anesthesia, if the procedure is being conducted under general anesthesia, are the same as for surgery for AVM resection. Under MAC, it is crucial to prevent patient movement, allay anxiety, and provide adequate pain control. The patient should be sedated and yet easily arousable during the procedure. Propofol, midazolam, fentanyl, remifentanil, and dexmedetomidine have been used for monitored anesthesia care during endovascular therapy with good results. To prevent thromboembolic episodes during and after the procedure, baseline ACT should be estimated, and heparin, 70 IU/kg, is given to increase its values two to three times the baseline value. ACT must be monitored hourly during the procedure, and heparin infusion may also be administered postoperatively to prevent thromboembolic complications. Antiplatelet drugs are also routinely used during the procedure. There can be hemorrhagic or occlusive complications during the procedure. Hemorrhage can occur due to perforation of the artery or intranidal rupture. Hemorrhagic complications should be managed with immediate reversal of heparin using protamine, administrations of mannitol, and judicious lowering of mean arterial pressure. Occlusive complications should be treated by inducing hypertension and intra-arterial administration of tissue plasminogen activator. Hypertension increases collateral circulation through the circle of Willis; however there is always a risk of bleeding.

Another dreaded complication during the endovascular procedure is the passage of glue into a draining vein during embolization, and acute hemorrhage can occur. Also, in smaller patients, pulmonary embolism of glue can also occur. It has been observed that the flow through the fistula has been found to be a pressure-dependent phenomenon; inducing hypotension slows blood flow during injection of glue. This technique is also called "flow arrest," and adenosine in the doses of 10–90 mg is used which causes extreme hypotension for 10–20 s. External pacing pads or transvenous pacing must be placed to treat any persistent arrhythmia following the cardiac pause.

Specialized neuromonitoring techniques like cerebral blood flow estimation, EEG, SSEP, MEP, and jugular venous oxygen saturation have also been employed to detect evidence of cerebral ischemia.

Non-pharmacological cerebral protection measures like maintenance of cerebral perfusion pressure, normovolemia, adequate hematocrit, normoglycemia, brain tissue oxygen tension, normocarbia, brain relaxation, and avoidance of hyperthermia should be applied at all times.

The postoperative phase is critical as complications like intracerebral hemorrhage and cerebral edema can even occur days after the procedure. Drugs like beta-blockers like esmolol and labetalol and alpha$_2$ agonists like clonidine and dexmedetomidine can be used to ensure a smooth reversal.

9.13.6 Normal Perfusion Pressure Breakthrough (NPPB)

The theory of normal perfusion pressure breakthrough (NPPB) proposed by Spetzler in 1978 and was instrumental in explaining the edema and hemorrhage that occasionally occur after the excision of cerebral arteriovenous malformations. The pathophysiology of cerebral edema and hemorrhage after AVM resection remains controversial. Due to the advances in neuroimaging, cerebral blood flow, and cerebral perfusion pressure (CPP) measurement, multiple theories have both favored and contradicted the NPPB theory. One such theory proposes occlusive hyperemia. It is a complication that can occur after either complete surgical resection or total obliteration of an AVM by embolization. Initially it was thought that loss of

autoregulation in the normal brain surrounding the AVM could be the contributing cause. However, another theory stated that chronic hypoperfusion in brain tissue surrounding the AVM results in maximal vasodilatation and an inability of the vessels to vasoconstriction response to the resumption of normal perfusion pressure after AVM resection. This results in hemorrhage and edema.

9.13.7 Special Scenarios

9.13.7.1 Arteriovenous Malformations During Pediatric Age Group

AVMs in children constitute 12–18% of AVMs and account for almost half of the hemorrhagic strokes in pediatric age group. The location of pediatric AVMs is usually in the eloquent areas of the brain like the thalamus and basal ganglia.

Children with AVMs can present with seizures, headache, and neurological deficits or as an incidental finding. Neonates and infants may also present with cardiac failure due to high arteriovenous shunting relative to the cardiac output.

Treatment strategies for pediatric AVMs are to be customized in a multimodal manner. Certain factors like the grade of the AVM and its vascularity and patients' preoperative condition greatly influence the outcome.

9.13.7.2 Arteriovenous Malformations During Pregnancy

The two most common causes of hemorrhagic stroke in pregnancy are rupture of cerebral aneurysms and AVMs. Young primigravida is more likely to bleed, and the clinical presentation can mimic eclampsia as these patients present with headache, meningism, and photophobia. Cerebral DSA, CT scan, or lumbar puncture can be used as the diagnostic tools [47].

Management mainly depends upon the severity of mass effect and patients' gestational age. Patients who are stable post hemorrhage, be allowed to reach term and thereafter an elective intervention done.

Anesthetic technique depends on whether the delivery of the fetus is before the surgical intervention for AVM or whether it is being done in the same sitting. A regional technique can be adopted if delivery is before the neurosurgical procedure. If both are done in the same sitting, general anesthesia is preferred. The chief goal of any anesthetic technique in such cases is to maintain uteroplacental blood flow to prevent fetal compromise [44].

9.13.7.3 Vein of Galen Aneurysmal Malformations

The vein of Galen aneurysmal malformations (VGAM) are rare defects seen in around 1% of all intracranial vascular malformations. Yet it represents 30% of all pediatric vascular malformations. The hallmark characteristic of VGAM is an abnormally dilated midline venous structure which is fed by numerous arteriovenous channels. The name VGAM is actually a misnomer because the dilated vein is actually the embryonic prosencephalic vein of Markowski and not the vein of Galen. Based on the angioarchitecture of the lesion, Raybaud et al. concluded that this abnormality probably occurs between the 6th and 11th weeks of intrauterine life [48].

Children with VGAM present early in life with signs of cerebral edema, hypoxia, hydrocephalus, and congestive cardiac failure. The heart failure is high output because majority of the aortic blood flow is channeled through the VGAM's low resistance shunt. This leads to increased blood flow through the right heart and eventually to pulmonary artery hypertension [48, 49]. Hypoxia, hypercarbia, and acidosis further aggravate pulmonary artery hypertension and make it a vicious cycle. This chain of events leads to right to left shunting of the blood via patent ductus arteriosus or foramen ovale and finally to multi-organ failure.

To screen the neonates and make an initial diagnosis, transfontanellar Doppler sonography can be used as versatile bedside tool. However

cerebral angiography is the gold standard investigation for evaluating patients with VGAM.

Management of neonates and infants with VGAM is very challenging and requires close coordination between the neurosurgeon, neuroradiologist, neonatologist, and anesthesiologist for a successful outcome. Endovascular therapy has greatly improved the clinical outcome of these formerly high-risk cases, especially with advances in imaging technology and modern intensive care facilities.

With the advent of endovascular therapy, surgical management of VGAM has assumed less significance. The problems of major intracranial surgery for these malformations are mainly because they are deep-seated lesions with multiple feeders and occurring in neonates and infants with heart failure and other comorbidities.

The approach to management for VGAM depends on the age of the patient, the severity of clinical symptoms, and the angioarchitecture of the lesion. The advancement of endovascular techniques has improved the outcome of VGAM substantially. The blood flow through the shunt and chronic venous hypertension are significantly reduced after embolization of the feeding arteries and draining veins. Lasjaunias et al. have described a 21-point scale based on cardiac, respiratory, hepatic, and renal function [49]. A score less than 8 indicates a poor prognosis and does not warranty emergency intervention. A score between 8 and 12 is an indication for emergency management, and a score >12 indicates a well-preserved neonate in whom medical management is the initial strategy and the endovascular procedure can be done when the neonate is a little older.

The neonate, who presents with congestive heart failure, needs aggressive medical management to control cardiac symptoms. It is preferable that intervention in this age group be postponed till the child is 5–6 months old. However, if the neonate is refractory to medical therapy, emergency embolization is needed to decrease the shunt. Both transarterial and transvenous routes can be used for embolization. However transvenous embolization can lead to sudden closure of venous drainage which could cause cerebral edema and hemorrhage. However, the preferred technique for the neonate in extreme cardiac distress is transvenous embolization. This procedure may be performed multiple times and may be supplemented by transarterial embolization [49, 50].

The anesthetic management of patients with VGAM is very challenging. The main intraoperative goals are to maintain hemodynamic stability, avoid low diastolic blood flow, and prevent myocardial ischemia and worsening of pulmonary hypertension. It is best to use opioid-based technique [48].

Clipping of the aneurysm can result in an acute rise in ventricular afterload and cardiac failure, and appropriate vasoactive drugs may need to be administered. Nitrous oxide is avoided because of its negative inotropic effect and its effect on pulmonary vascular resistance. Babies are kept sedated and electively ventilated in the postoperative period to prevent cardiorespiratory stability.

9.13.8 Dural Arteriovenous Fistula

The morphological picture of arteriovenous fistula (DAVF) comprises of communication between dural arteries and dural venous sinuses, cortical veins, or meningeal veins. It is usually present in adulthood and constitutes around 15% of all cerebral arteriovenous malformations. The main differentiating feature between DAVF and cerebral AVMs is the absence of parenchymal nidus and presence of a dural arterial supply. The common location for DAVF is the transverse, sigmoid, and cavernous sinus [44].

Patients usually present in the fifth or sixth decade of life with symptoms of the specific area involved, e.g., tinnitus in transverse and sigmoid sinus lesions, ophthalmoplegia, proptosis, retroorbital pain, and decreased visual acuity in cavernous sinus lesions. More serious presenting

features include intracranial hemorrhage and nonhemorrhagic neurological deficits such as seizures, cerebellar signs, parkinsonism, etc. Venous hypertension in the pial veins is a risk factor for intracranial hemorrhage. Low-grade DAVFs can be managed conservatively; however patients with high grade should be treated with endovascular treatment to prevent complications like intracranial hemorrhage and neurological deficits.

Endovascular treatment using the transarterial, transvenous, or a combined approach is the treatment of choice since the last two decades. Target is to achieve complete obliteration of the fistula as incomplete obliteration could lead to recruitment of collateral arteries and persistent risk of hemorrhage [44].

The anesthetic goals and technique for endovascular procedures as well as surgical management of DAVFs are the same as for all cerebral arteriovenous malformations.

9.14 Summary

Management of cerebrovascular lesions of the brain is a challenging task for the anesthesiologist, and close coordination with the neurosurgeon and neuroradiologist is necessary for a favorable outcome of these high-risk patients. The anesthesiologist should have detailed understanding of the underlying cerebral hemodynamics, radiological findings, mode of clinical presentation as well as the potential complications. Sudden and rapid blood loss is another very important concern that could occur during the procedure, which would need emergent treatment. The advent of endovascular surgery and the technological advances in this field have greatly improved the outcome of patients of carotid artery stenosis, AVMs, VGAM, and DAVF, and increasingly complex cases are being done in sick patients. It is therefore imperative to have a clear-cut anesthetic and surgical strategy right from the beginning.

Key Points

- Comorbidities like hypertension, diabetes mellitus, and COPD should be optimized before intervention for carotid artery stenosis.
- Hyperperfusion syndrome, stroke, myocardial infarction, and death can occur to post-carotid artery intervention.
- Carotid artery stenting is being increasingly offered to the patients due to advances in technique and skill of neurointensivists.
- Moyamoya disease commonly presents with ischemic stroke, hemorrhagic stroke, seizures, headache, abnormal movements, and cognitive impairment.
- Cerebral AV malformations are responsible for 30–50% of hemorrhagic strokes in pediatric age group.
- Anesthetic management of high-risk infants with vein of Galen malformation is challenging and includes aggressive cardiac monitoring and avoidance of low diastolic pressure.

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Anesthesia for Pituitary Lesions

10

Tullio Cafiero

10.1 Introduction

The goal of this chapter is to provide the anesthesiologists with detailed information and eventually tips and tricks for the management of anesthesia in patients undergoing surgery for the treatment of the pituitary diseases. Indeed, patients harboring pituitary tumors present peculiar features which anesthesiologist should take care of because of the underlying endocrine disturbances. Peer knowledge of anatomy and physiology of the pituitary gland is paramount to understand the potential complications that can arise during the perioperative period. A strict preoperative evaluation and correction of all predictive factors and a definite intraoperative strategy are essential requirements to accomplish a safe and effective anesthesia. Different anesthetic modalities and drugs can be used adequately in the intraoperative period avoiding complications and thus providing an uneventful and good recovery.

10.2 Pituitary Gland Function

The pituitary gland is a pea-sized structure which lies within a bony structure called the sella turcica, and it is attached to the hypothalamus/infundibulum, at the center of the base of the brain. The pituitary gland has two parts—the anterior lobe and posterior lobe—that have separate functions. The anterior lobe hormones are the following: adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), growth hormone (GH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and prolactin. The posterior lobe hormones include antidiuretic hormone (ADH) and oxytocin. Decreased secretion of anterior and posterior pituitary hormones is known as panhypopituitarism, a serious and sometimes fatal disorder. Patients with panhypopituitarism usually have features of adrenal insufficiency and gonadal failure, along with poor responses to stress [1, 2].

Pituitary tumors represent 10% of all intracranial neoplasms and may be classified according to their size and to their function (see Table 10.1).

10.3 Signs and Symptoms of Pituitary Tumors

Seldom pituitary tumors can stay with any clinical symptom. The first symptoms often depend on whether the tumor is *functioning* (producing excess hormones) or *nonfunctioning* (no hormonal excess).

Nonfunctioning macroadenomas (>1 cm in diameter) may cause mass effect on pituitary gland decreasing the physiological production of

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Table 10.1 Classification of pituitary adenomas

Tumoral type	Incidence (%)	Clinical features	Staining[a]	Hormones	Blood	Immunoreactivity	Macroscopic features[b]	
							Dimensions	Aggressiveness
PRL-secreting pituitary adenomas								
Sparsely granulated	10–30	Amenorrhea/galactorrhoea	C	PRL	+	+	35% micro	52%
Densely granulated	1	Sexual dysfunction	A	PRL	+	+	65% macro	
GH-secreting pituitary adenomas								
Sparsely granulated	5–10	Acromegaly/gigantism	C–A	GH	+	+	15% micro	50%
Densely granulated	5–10		A	GH	+	+	85% macro	
GH-PRL-secreting pituitary adenomas								
Mixed cell (somatotroph/ lactotrope)	5	Acromegaly or gigantism ± hyperprolactinemia	A/C	GH/PRL	+/+	+/+	25% micro	31%
							72% macro	
Mammosotroph cell adenomas	2	Acromegaly ± hyperprolactinemia	A	GH/PRL	+/+	+/+	Mixed cell (somatotroph/ lactotrope) like	
Acidophil stem cell adenomas	2	Nonfunctioning or hyperprolactinemia rarely acromegaly	C	GH/PRL	±/+	+/+	Usually aggressive pituitary adenomas	
ACTH-secreting pituitary adenomas								
Cushing disease	10	Hypercortisolism	B	ACTH ± ß-endorphins ß-LPH, MSH	+	–	85% micro	10%
							15% macro	65%
Crook cells adenomas	0.5	Hypercortisolism/nonfunctioning	B		+	±	80% macro	70%
ACTH silent	2	Obesity or weight gain, hypopituitarism	B–C	Endorphins and endorphin-like molecules	–	+	100% macro	82%
Nelson's disease	2	Skin pigmentationObesity or weight gain	B–C	ACTH ± ß-endorphins ß-LPH, MSH	+	+	30% micro	17%
							70% macro	64%
LH-FSH-secreting pituitary adenomas	10	Hypogonadism Nonfunctioning, mass effect symptoms	C–B	FSH/LH alpha subunit	–	+ (±alpha glycoprotein subunit)	100% macro	21%

TSH-secreting pituitary adenomas	1	Hypo- or hyperthyroidism	C–B	TSH	+	+ (±alpha glycoprotein subunit)	Usually macroadenomas	75%
Plurihormonal cell pituitary adenomas	10	Usually acromegaly ± hyperprolactinemia Rarely hormonal glycoproteins secretion	C–A	FrequentlyGH/PRL/TSH, alpha subunitsRarely other plurihormonal secretions	+/±/−/±	Usually +/+/+	25% micro	31%
							75% macro	59%
Null cell pituitary adenomas	15–20							
Nononcocytic	10	Visual disturbance Hypopituitarism Headache	C	None ± slight increase of PRL blood level post-hypothalamus-pituitary disconnection	–	None or minimal hymmunoreactivity for specific pituitary hormones and/or cell-specific transcription factors	2% micro	42%
Oncocytic	5		A		–		98% macro	
Silent subtype III	3	Mass effect; often clinically mistaken for prolactinomas especially in women	C to slightly A	Variable	–	Minimal hymmunoreactivity for specific pituitary hormones and/or cell-specific transcription factors	Macro (males)	
							Micro (females)	

ACTH adrenocorticotropic hormone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *PRL* prolactin, *TSH* thyrostimulating hormone

[a]*A* acidophilic, *B* basophilic, *C* cromophobe cell types classification

[b]*Micro* microadenomas (≤1 cm in diameter), *macro* macroadenomas (≥1 cm in diameter)

hormones or cause signs related to the compression on vital surrounding structures, i.e., visual disturbances and/or oculomotor palsy or even hydrocephalus and/or increased intracranial pressure, whether they hinder cerebrospinal fluid (CSF), obstructing basal cisterns or the foramina of ventricles. Rarely, hemorrhage into a pituitary tumor occurs and produces a complex symptomatology known as pituitary apoplexy, which usually is characterized by ophthalmoplegia, headache, and meningism, along with failure of pituitary functions.

Functioning pituitary tumors increase the production of hormones causing a variety of signs and symptoms.

10.3.1 Hormonal Hypersecretion Syndromes

Growth hormone-secreting adenomas in children can cause gigantism and in adults acromegaly, a syndrome featuring embossing of the bones of the skull, hands, and feet, diabetes mellitus, arterial hypertension, cardiovascular disease (arterial hypertension, obstructive sleep apnea-related pulmonary hypertension, myocardial ischemia), diastema of the teeth, protruding jaw, and macroglossia leading to obstructive sleep apnea (OSAS) [3, 4].

Corticotropin-secreting adenomas cause weight gain and fat accumulation at the base of the neck, causing the so-called buffalo hump, tissue swelling, redness and roundness of the face (moon face), purple stretch marks on the abdomen, thinning of the arms and legs, high blood pressure, hyperglycemia, acne, bruising, anxiety, irritability or depression, changes in menstrual periods in women, and decrease of libido [5].

Thyroid-stimulating hormone-secreting tumors cause weight loss, tachycardia or arrhythmias, anxiety, irritability, tremors, and excessive sweating [6].

Prolactin-secreting adenomas cause in women irregularities or the absence of menstrual periods and galactorrhea and in men hypogonadism, erectile dysfunction, lowered sperm count, and loss of sex drive [7].

10.3.2 Hormonal Hyposecretion Conditions

On the other side, tumors compressing the pituitary gland can cause deficiency of growth hormone inducing growth retardation, weakening of muscle strength, and irritability. Low TSH production can cause fatigue, low energy, and weight gain. Macroadenomas may also present with compression of sellar contents and though cause secondary hypopituitarism.

10.4 Preoperative Assessment

In those patients complaining of a pituitary adenoma, preoperative endocrinological assessment and tailored management strategies are required to reduce the morbidity related to the surgical pituitary procedure itself, above all, upon anesthetic issues. Therefore, multidisciplinary team case discussion is of utmost importance to rule out the optimal therapeutic option before surgery. Cogent and accurate clinical status depiction and detailed imaging are required to define the features of pituitary adenomas. Blood withdrawal to measure baseline levels of prolactin, adrenocorticotropic hormone (ACTH), growth hormone (GH), follicle-stimulating hormone, luteinizing hormone, testosterone hormone, and thyroid-stimulating hormone (TSH) are mandatory; provocative tests may be helpful to rule out hypersecretion. Pregnancy test is mandatory when secondary amenorrhea is present. Obviously, a preoperative evaluation of blood count and serum biochemistry should be run. Preoperative imaging of the sellar and parasellar region nowadays mostly relies on magnetic resonance imaging (MRI), accounting on post-GAD coronal and sagittal scans (Figs. 10.1, 10.2, and 10.3).

When surgical option is viable, relationships between the lesion and the closest neurovascular structures such as the internal carotid arteries, optic nerves, and cavernous sinus should be defined in order to plan the intraoperative management.

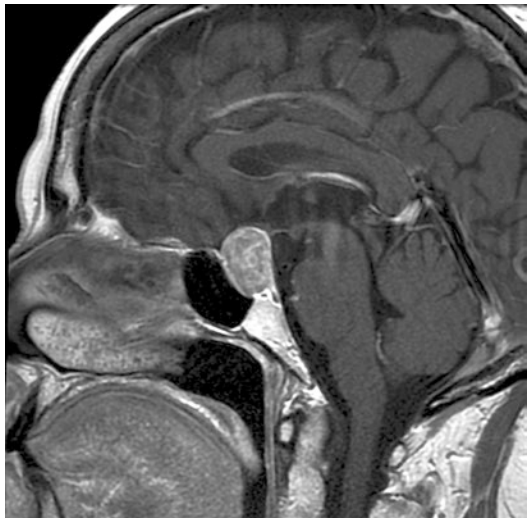

Fig. 10.1 MRI, sagittal view of a case of pituitary macroadenoma

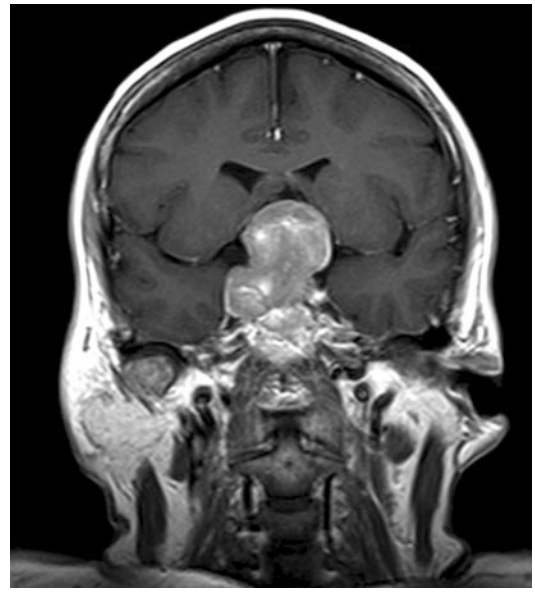

Fig. 10.2 MRI, coronal view of a case of giant pituitary adenoma

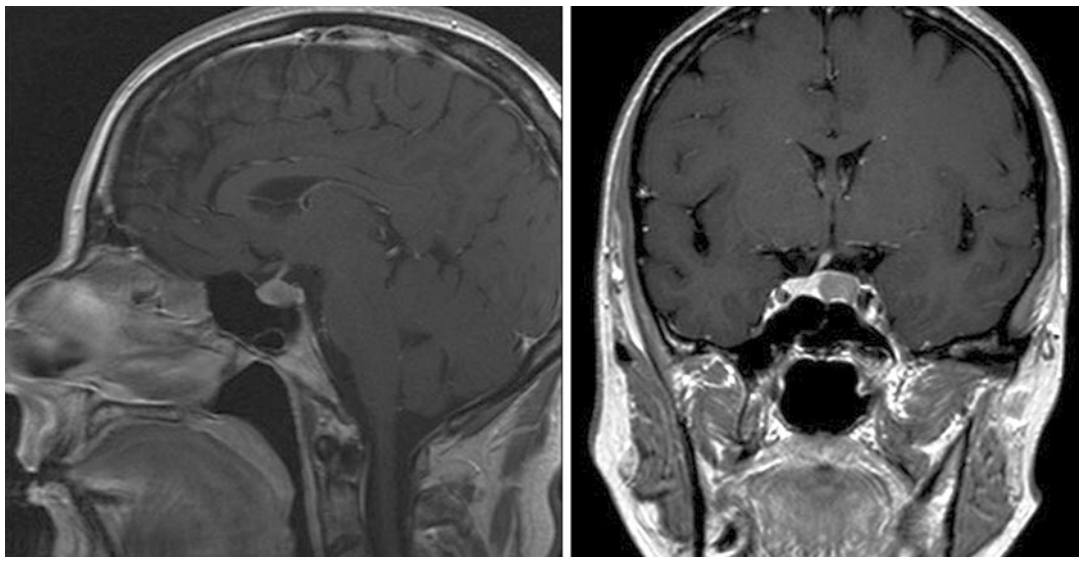

Fig. 10.3 MRI, sagittal con coronal view of a case of pituitary microadenoma

10.5 Treatment

Treatment of pituitary tumors may include surgery (performed in more than 95% of cases), radiotherapy, and medical therapy (dopamine agonists, such as bromocriptine, somatostatin analogs, ketoconazole). Sometimes a combination of these treatments is used [8].

10.6 Surgical Approaches for Pituitary Tumors

Pituitary surgery mostly backs upon three approaches: the transcranial approach, transsphenoidal microscopic approach, and endoscopic endonasal approach. Pituitary surgery has evolved over the last two decades from an open transcranial surgery to the minimally invasive endoscopic endonasal approach [9–12]. The endonasal endoscopic transsphenoidal surgical procedure is a "minimally invasive" approach not requiring a sublabial or a nasal mucosal incision and subsequent dissection through the nasal septum, since it utilizes an endoscope as the sole visualizing tool introduced through a nostril and the paranasal sinuses [13–15]. Patient is placed supine with the head in horseshoe headrest—no three-pin Mayfield-Kees fixation is required [16]—so that risks of embolism are reduced as well as postoperative discomfort.

The endoscopic endonasal surgical procedure gives a better view over the surgical target and, above all, around the hidden angles, thus permitting a greater extent of tumor removal thanks to the better differentiation between the normal and neoplastic tissue (Figs. 10.4 and 10.5). The possibility of avoiding the use of nasal speculum and the nasal packing causes less mucosal trauma, less postoperative discomfort, reduction in the length of hospital stay, and an early return to the daily activities [17].

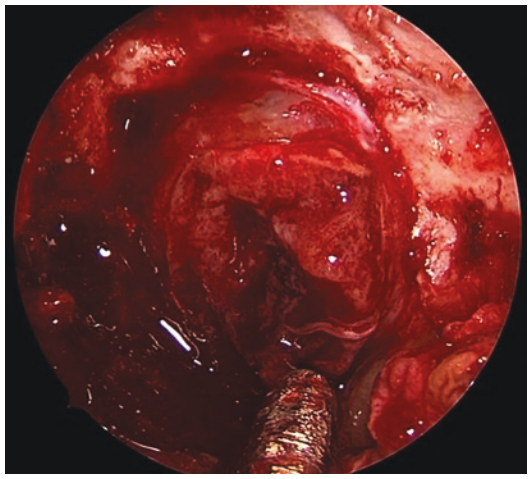

Fig. 10.4 Intraoperative picture of a case of pituitary macroadenoma removal

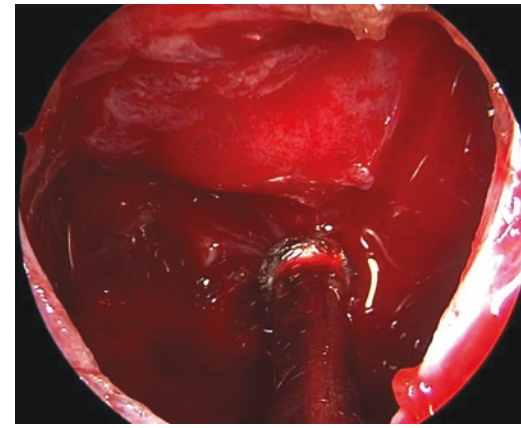

Fig. 10.5 Intraoperative picture of the sellar cavity after the removal of a pituitary macroadenoma

Main disadvantages of this technique include the two-dimensional vision causing a spatial distortion of the periphery of the image and the initial phase of the learning curve [18, 19].

10.7 Anesthetic Management

It is not among the aims of this chapter to address all aspects of neuroanesthesia and hormone replacement therapy; the main goals of the anesthetic treatment include hemodynamic stability, airway management, and quick and smooth awakening at the end of surgical procedure and the prevention of intra- and postoperative complications.

Adequate hemodynamic control is required throughout the procedure, to reduce bleeding of the mucosa and, therefore, have a cleaner and safer endonasal path. Besides, it should be said that the endoscopic endonasal approach ends as soon as the endoscope exits the nostrils. Hence, the anesthesiologist should provide the patient with mild hypotension, in order to have less bleeding, and at the end of the procedure, he/she should be prepared to obtain quick awakening and recovery.

Balanced anesthesia with volatile agents or intravenous drugs fits this purpose; besides, remifentanil, a short-acting opioid, ensures

deep level of analgesia until the end of endoscopic procedure, granting shorter awakening times [20, 21].

Nasal cavities are prepared by local decongestion with cottonoids soaked with solution of a diluted epinephrine: dosage of epinephrine needs to be minded, as arrhythmias and even myocardial infarction can be provoked by mucosal absorption of this agent, with symptoms occurring either at early stage of surgical procedure or later, in the postoperative period [22, 23]. After orotracheal intubation, the tube is moved and fixed at one corner of the mouth, according to the preferred hand of the main surgeon, in order to facilitate the sliding of the instruments inside the nasal cavities during the procedure.

Pituitary surgery via the nose determines blood, secretions, and irrigation liquids accumulating within the pharynx, so that packing is mandatory to these fluids entering the stomach and though prevents postoperative vomiting Adequate analgesia, and mild hypotension are most needed at initial phases of surgery: at our institution, we have had particular success in controlling hemodynamic parameters using intraoperative infusion of remifentanil supplemented by propofol or sevoflurane as the hypnotic component of balanced anesthesia [24]. During the endonasal endoscopic approach, a profound opioid effect is desired, along with the rapid reversal of its effects of the drug. In these terms, remifentanil is extremely valid as its effects rapidly follow the changes in remifentanil infusion rates.

Continuous infusion of remifentanil must be administered by a dedicated IV line: this infusion line should be connected at, or close to, the venous cannula to minimize the potential dead space. The venous cannula and the infusion sets must be secured with adhesive tape in order to avoid obstruction or disconnection of infusion lines. Remifentanil may be given by target-controlled infusion (TCI) with an approved infusion device incorporating the Minto pharmacokinetic model with covariates for age and lean body mass (LBM).

Moreover, rocuronium because of its rapid onset of action and sugammadex which reverses neuromuscular blockade more rapidly than neostigmine can be recommended especially in patients with OSAS [25, 26].

The throat pack is removed prior to extubation, and then the anesthesiologist visualizes the pharynx and removes blood and secretions by gentle and careful suctioning; the extubation is performed when swallowing is present, avoiding straining or coughing because it can provoke CSF leakage and hemorrhage. The patient then rests with the head elevated of 15–20°. Valsalva maneuver—intrathoracic pressures up to 30–40 mmHg—is run to detect eventual CSF leaks and check the effectiveness of the hemostasis.

Monitoring. Standard monitoring is routinely used: ECG (lead II, noninvasive arterial blood pressure, urine output, End Tidal CO_2, and End Tidal volatile agent). Invasive arterial blood pressure monitoring and/or minimally invasive methods for continuous monitoring of cardiac output, stroke volume, and stroke volume variation may be necessary in older patients or in patients belonging to ASA III class.

10.7.1 Anesthetic Management in Patients Suffering from Acromegaly

Acromegaly is a multisystem disease caused by an excess of growth hormone (GH) after puberty. The term acromegaly is the Greek *acron* (extremity) and *megale* (great). This progressive disease has an insidious onset and the mean age at diagnosis is about 40 years. The most frequent cause of acromegaly is a GH-secreting pituitary adenoma and rarely an increased GH release from hypothalamic tumors or from nonendocrine tumors. Headaches and visual field defects (bitemporal hemianopsia) are the most common symptoms which may precede diagnosis. IGF-I is a useful biochemical indicator both for diagnosis and monitoring the efficacy of therapy. Surgical removal of the pituitary gland tumor is generally considered the primary treatment for most patients. The resection of GH-secreting pituitary adenomas in the hands of experienced surgeons results in hormonal remission in 50–70% of patients [27].

When surgery fails to obtain remission, a program of therapy is designed for the patient to include adjunctive medical therapy (somatostatin and dopamine analogs, growth hormone receptor antagonists), radiation therapy, or radiosurgery (Gamma knife, CyberKnife, etc.) [28].

Accurate preoperative evaluation of the patient's airway is necessary when acromegalic patients should undergo surgery [29]. Acromegaly is associated with mandibular enlargement, macroglossia, and subglottic abnormalities and prognathism, so that even mask ventilation can be difficult or impossible, and a challenging orotracheal intubation can be expected. Tumor size was not associated with a difference in the incidence of unanticipated airway management difficulty, and unanticipated difficulty with airway management was more than three times more common in acromegalic patients than in patients with nonfunctioning pituitary tumors [30]. The acromegalic patient has an increased incidence of difficult intubation (62.5%) during induction of anesthesia, and elevated insulin-like growth factor-1 levels are an independent risk factor of difficult intubation [31]. As regards the preoperative airway assessment, it should be emphasized that the sensitivity and accuracy of predictive factors that define difficult intubation are less in acromegalic patients compared with nonacromegalic controls [32]. The intubating laryngeal mask airway (ILMA) can be used as a primary tool for ventilation in acromegalic patients, but the rate of failed blind intubation through the ILMA precludes its use as a first choice for elective airway management [33]. Even though in our experience (>130 pituitary operations per annum at our institution) the airway management and tracheal intubation proceed uneventfully, we prefer to visualize the laryngeal aditus prior to induce curarization by using the video laryngoscope. Video laryngoscopes have been shown to improve exposure of the glottis and to increase first-attempt success rates for tracheal intubation in comparison with the traditional Macintosh, by providing a wider-angle view of the glottis [34, 35]. When a fiber-optic airway intubation may be necessary, we prefer to perform the so-called awake fiber-optic intubation during conscious sedation with propofol and remifentanil, both administered as target-controlled infusion (TCI) regimen [36]. Acromegaly is associated with a two- to threefold increase in mortality, mainly related to vascular disease. Main cardiovascular manifestations of Cushing yndrome are arterial hypertension, myocardial ischemia, pulmonary hypertension, and a dilated cardiomyopathy. In these cases the preoperative evaluation should be supplemented with an ultrasound examination. There is considerable literature that suggests a specific cardiomyopathy in acromegaly, resulting in structural and functional abnormalities. In fact, myocardial hypertrophy and interstitial fibrosis of both ventricles are common in acromegalic patients and may be associated with reduced left ventricular function [37].

These functional abnormalities may be partially reversed by reduction in growth hormone (GH) or insulin-like growth factor type 1 (IGF-1) levels [38]. Furthermore, acromegalic patients are prone to arrhythmias during the intraoperative period, and it is advisable to maintain a stable plane of anesthesia while maximizing pain control. In the postoperative period, the acromegalic patient has a high risk of developing OSAS. OSAS was associated with higher rates of pulmonary and airway complication (tracheostomy, hypoxemia) [39].

10.7.2 Anesthetic Management in Patients Suffering from Cushing Syndrome

Originally described by Harvey Cushing, Cushing disease is the most frequent cause of endogenous hypercortisolism. Cushing syndrome is caused by prolonged exposure to elevated levels of either endogenous glucocorticoids or exogenous glucocorticoids. Exogenous Cushing syndrome is most commonly caused by administration of glucocorticoids. Endogenous Cushing syndrome is subdivided into two types: adrenocorticotropic hormone (ACTH) dependent and ACTH independent. Elevated ACTH levels are usually due to an anterior pituitary tumor—most commonly an adenoma and rarely a carci-

noma. Pituitary ACTH-secreting adenomas are derived from corticotroph cells in the anterior pituitary. Adrenocorticotropic hormone (ACTH)-secreting tumors account for 2%–6% of adenomas and are associated with obesity, arterial hypertension, diabetes, and other morbidities [40]. The diagnosis of Cushing disease—properly named to define the pituitary origin of ACTH hypersecretion—is challenging as patients often present with an insidious history [41]. Nevertheless, efficient diagnostic and screening strategies lead to the diagnosis of a significantly higher number of cases of Cushing disease. Differential diagnosis of Cushing syndrome can be made using a salivary cortisol test or performing a low-dose dexamethasone suppression test. MRI is the mainstay of imaging for pituitary microadenomas, and dynamic contrast-enhanced imaging with gadolinium has significantly improved diagnostic accuracy [42]. Very rarely, corticotroph tumor enlarges up to the occurrence of clinical signs related to compression such as headache, vision loss, ocular palsy, hyperpigmentation, and hypopituitarism [43]. Transsphenoidal surgery is usually the treatment of choice for most patients with Cushing disease [44]: in patients with Cushing disease, about 90% of pituitary gland tumors are microadenomas (<1 cm). It has been demonstrated a slow disappearance of ACTH levels from the circulation after a successful pituitary surgery in patients with Cushing disease [45]. Additionally, in these patients several cardiovascular abnormalities, i.e., atherosclerosis, clotting disorders, left ventricular hypertrophy, concentric remodeling, and diastolic dysfunction, have been documented. It has been reported a case of dilated cardiomyopathy without improvement of left ventricular ejection fraction despite normalization of serum cortisol levels [46]. Therefore, it should be underlined the importance of long-term monitoring and treatment of these complications, as well as in the long-term follow-up after Cushing syndrome remission. Cushing's patients present a two- to fivefold increase in mortality rates as compared to the general population, because of the higher risks of cardiovascular complications [47]. Antiglucocorticoid and antihypertensive agents can be administered in these patients to treat hypertension and related cardiovascular damage being the angiotensin I-converting enzyme inhibitors (ACEi) or an angiotensin receptor blockers (ARB) the most appropriate drugs [48]. Patients suffering from Cushing syndrome have increased sensitivity to endogenous vasoconstrictors such as angiotensin II, epinephrine, and norepinephrine. In addition, patients exhibit an increased pressor response to norepinephrine [49].

In this contest, particular attention must be given to the nasal mucosa preparation. In our opinion, it is unnecessary in most cases to infiltrate the nasal mucosa with large amount of epinephrine during endoscopic surgery. However, the hypertensive response can be treated with antihypertensive agents or by simply increasing the depth of anesthesia.

Again, also for patients with Cushing syndrome, a careful preoperative assessment of the patient's airway is fundamental. Cushingoid body features, indeed, render troublesome airway management and ventilation as well as anesthetic drug balance.

The systemic presentations of Cushing syndrome include osteoporosis which is present in nearly 40% of patients with an increased risk of pathological fractures. In fact, glucocorticoids inhibit bone formation in part by decreasing the number of osteoblasts and by increasing bone resorption by stimulating osteoclasts [50]. The anesthesiologist must take care during positioning and taping these patients in order to avoid bone fractures and sloughing with adhesive tape removal. Cannulation of superficial veins for intravenous access can be difficult, and minimal trauma may result in bruising: central vein cannulation may be preferable in some cases.

In the presence of an exophthalmos caused by the retro-orbital abnormal fat distribution [51], attention must be given in order to avoid a corneal abrasion. It is mandatory in all cases to protect the eyes with ocular ointments and/or by placing of paddle over the closed eyes.

Patients with Cushing syndrome commonly suffer from sleep disturbances, and they are nearly three times more prone to develop

obstructive sleep apnea syndrome (OSAS) [52]. It has been reported that as many as 33% of patients with Cushing disease have mild sleep apnea and 18% of patients have severe sleep apnea.

10.8 Postoperative Care

Usually, after undergoing an endoscopic endonasal procedure, patients don't require intensive care unit admission, unless in extraordinary conditions and/or depending on preexisting comorbidities. In these patients, the postoperative issues are mainly related to airway management, pain management, neurological and endocrine status, and fluid balance control. Endocrine disorders include hypopituitarism, diabetes insipidus, and inappropriate secretion of antidiuretic hormone (SIADH). As previously stated, acromegalic patients and those with Cushing syndrome suffering from sleep disturbances and OSAS have a higher risk of respiratory obstruction and should be closely monitored. In these patients nonsteroid anti-inflammatory drugs, paracetamol and opioids, only upon strict need are adopted for pain relief. Endocrine management in the immediate postoperative (perioperative) period represents a true example of multidisciplinary team approach, involving endocrinologists, anesthesiologists, and surgeons.

Diabetes insipidus (DI) and SIADH are common complications after pituitary surgery, especially for large intra-suprasellar mass, such as giant adenomas, craniopharyngiomas, and Rathke cleft cysts [53]: it is widely accepted that direct damage to the pituitary gland is the cause, but the mechanisms behind the response variability and the underlying pathophysiology remain unknown. DI is characterized by decreased secretion of antidiuretic hormone (ADH), and it leads to the output of large volumes (>3 L/24 h) of diluted urine (<300 mOsm/kg); it usually occurs between 24 and 48 h after the surgery and can last for several days to weeks or be permanent. Diabetes insipidus runs throughout the so-called triphasic pattern: a first phase in which AVP secretion is interrupted as consequence of disruption of the connections between the cell bodies of AVP-secreting neurons in the hypothalamus and their nerve terminals in the posterior pituitary gland; later on, a second phase of inappropriate antidiuresis, caused by an uncontrolled release of AVP into the bloodstream from the degenerating nerve terminals in the posterior pituitary gland, becomes evident; finally, upon loss of vital neuron cells synthesizing AVP, permanent diabetes insipidus develops. The treatment relies initially on intravenous desmopressin, according to the fluid balance, serum sodium levels, and serum and urine osmolality monitoring. During the second phase, desmopressin can be discontinued, and the fluid intake should be restricted [54].

SIADH is usually manifest a week after the surgery, and it features inappropriate secretion of ADH, which determines lower serum sodium (<135 mmol/L) and osmolarity (<280 mOsmol/L) while on the contrary concentrated urine. First therapeutic option is water restriction: at this stage continuing water administration may exacerbate hyponatremia and hypoosmolality, finally resulting in cerebral edema.

It has been shown that a low BMI can be considered the only clear predictor of delayed postoperative hyponatremia [55]. Treatment of hypotonic hyponatremia often challenges clinicians, and a management plan tailored to the clinical findings is required [56]: if significant hyponatremia (<120 mmol/L) occurs, hypertonic saline solution has to be administered; correction of serum sodium in case of severe symptoms should be done with extreme caution (1–2 mEq/L/h for 3–4 h and then 0.5 mEq/L/h over 24 h) in order to avoid central pontine myelinolysis [57, 58]. Recent developments in the understanding of hyponatremia pathophysiological regulatory mechanisms, along with epidemiologic insights, the introduction of vasopressin receptor antagonists and the identification of new adverse effects, allowed refinement of its diagnosis and thus improvement of its management [59].

Key Points

- Pituitary surgery requires skillful anesthetic technique because it raises several difficult issues related to the pituitary hormonal hyper-/hyposecretion and/or its mass effect.
- The main anesthetic issues are obstructive sleep apnea, difficult airway management, and associated endocrine disease.
- The endoscopic endonasal transsphenoidal approach is characterized by short and intense pain stimulation and rapid ending, i.e., at the removal of the endoscope.
- Anesthesiologist should focus to achieve mild hypotension for minimizing bleeding and optimizing operative conditions and prompt and rapid awakening at the end of surgery.

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Anesthesia for Epilepsy Surgery

11

Sujoy Banik and Lashmi Venkatraghavan

11.1 Introduction

Epilepsy is a chronic disorder characterized by recurrent seizures due to unknown etiology. The International League Against Epilepsy (ILAE) recognizes approximately 10 types of recurrent seizures and approximately 40 types of epilepsy syndromes [1]. With an estimated incidence of 34–76 per 100,000 new cases per year (median incidence of 50.4/100,000 per year), epilepsy affects about 70 million people worldwide [1]. The median incidence of epilepsy in developed countries is around 45.0/100,000 per year [interquartile range (IQR) 30.3–66.7], while for low- and middle-income countries, it is almost double with an incidence of 81.7/100,000 per year (IQR 28.0–239.5) [2]. The higher incidence of head trauma and central nervous system (CNS) infections (invasive bacteria, malaria, and neurocysticercosis) may be responsible for the difference [2].

Seizure control using antiepileptic drugs is the mainstay treatment of epilepsy; however, in around 30% of patients, seizures become refractory to treatment. Epilepsy is deemed to be refractory if seizures persist even after 2 years of optimal pharmacotherapy with two or three agents, considering that patient is compliant with medications. Also, this patient population is more prone to side effects and complications of combined therapy with multiple anti-seizure medications. Usually, normal function and/or development is also affected by seizures. Approximately 15–20% of these patients are candidates for surgical treatment [1, 2]. Benefits of surgery include freedom or a significant reduction in the frequency of seizures with improvements in both cognitive function and overall quality of life due to reduction or elimination of anticonvulsive drugs [3]. This review aims to discuss the various types of epilepsy surgery and anesthetic considerations for patients undergoing epilepsy surgery.

11.2 Types of Epilepsy Surgery

Epilepsy surgeries can be broadly classified into two types: (a) resective procedures, which involve removal of an epileptogenic focus [scar tissue, tumor, gliosis] or the cortex [frontal, temporal lobectomy, amygdalohippocampectomy], and (b) non-resective procedures, where modification of seizure pathways is done by either disconnection [corpus callosotomy, hemispherectomy, or subpial resections] or stimulation [deep brain stimulation (DBS) or vagal nerve stimulation (VNS)] procedures. The choice between different types of epileptic surgeries depends on the location of the epileptogenic cortex and its proximity with

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the eloquent areas of the brain. In general, disconnection procedures are mostly indicated in children; resection and stimulation procedures are performed in both adults and children.

11.2.1 Resective Procedures

Resection of epileptogenic foci can be performed for the patients with a well-defined epileptic lesion in non-eloquent area. It can be either temporal or extra-temporal resections, and there is a significant difference in the outcomes between these two groups. *Anterior temporal lobectomy with or without amygdalohippocampectomy* is the most commonly (60–70%) performed epilepsy surgery, which has the cure rate of up to 90% especially in patients with seizure foci localized to mesio-temporal sclerosis. Extra-temporal resections carry less favorable results and depend on whether a localizable lesion can be identified or not. Extra-temporal lesionectomy for tumors or vascular abnormalities has cure rate up to 66.6%. For the epileptic patients with multifocal origins, multiple resections involving different areas are generally not recommended [4–6]. Magnetic resonance imaging (MRI)-guided laser ablation of epileptogenic cortex is an upcoming modality of treatment where Nd-YAG laser is used to ablate the epileptogenic foci using stereotaxic MRI guidance [7].

11.2.2 Disconnection Procedures

Disconnection and stimulation are generally indicated for palliative purposes to reduce the seizure frequency and disability. Disconnection is mainly used when the seizure foci involve eloquent areas of the brain. The basic principle of the surgery is to prevent the spread of the electrical activity from the epileptic foci to other parts of the brain. Corpus callosotomy and functional hemispherectomy involve disconnections of two cerebral hemispheres. *Corpus callosotomy* is primarily performed to interrupt the spread of the epileptogenic discharges across the hemispheres in patients where the exact location of epileptogenic foci cannot be identified. It is generally indicated in patients with intractable epilepsy along with drop attacks. Due to the high complication rate and invasiveness of this procedure, it is mainly indicated in a few carefully selected patients. Almost 80% of patients have their seizure frequency halved and also experience decreased seizure intensity, with less traumatic falls, shorter generalized seizures, lesser akinetic spells, and episodes of status epilepticus also reduce in frequency [1, 6].

Hemispherectomy is a highly invasive surgery, usually indicated in patients with refractory epilepsy with significant brain injury such as hemiconvulsion hemiplegia epilepsy (HHE), Sturge–Weber syndrome, Rasmussen's encephalitis, and hemimegalencephaly [4]. Over time this surgery has been modified to a less-invasive procedure called hemispherotomy to prevent severe longer-term complications of hemispherectomy. In hemispherotomy, hemisphere with seizure foci is disconnected from the rest of the subcortical structures and the other hemisphere. After hemispherotomy, up to 80% patients remain seizure-free, and a further 15% show reduction in seizure frequency [4, 6].

Multiple subpial resections are indicated for partial seizure originating from eloquent cortical areas that cannot be resected. It involves transections of cerebral cortex in 5 mm interval and thus interrupts the horizontal spread of ictal activities while sparing the vertically oriented functional fibers. This technique is very time-consuming [8, 9]. Seventy-five percent of patients who had multiple subpial transection can be seizure-free or have a significant reduction in seizures [1, 4, 8].

11.2.3 Stimulation Procedures

Vagus nerve stimulation (VNS) is the Food and Drug Administration (FDA)-approved procedure to reduce the frequency of seizure in adults [10–12]. In this procedure, an electrode is inserted into the left vagus nerve which is then connected to the pulse generator placed in the chest wall. The exact mechanism of action of VNS is not clear, but it has been postulated that vagal nerve stimulation modulates the excitability of cerebral cortex either due to limbic system activation or via brain stem arousal [12]. In a retrospective review of 15-year follow-up in

60 patients with VNS, the mean seizure reduction was 31.37%. Twenty patients (34.48%) were considered responders (seizure reduction ≥50%); 7 patients (12.06%) had seizure reduction of ≥75%, and 2 patients had seizure control of ≥90% (3.4%) [13].

Deep brain stimulation (DBS) has also been used as one of the treatment modalities for medically refractory seizures. The exact mechanism of DBS is not known, but it has been shown to interfere with synchronized oscillations by neurotransmitter release [14]. Commonly targeted nuclei include the anterior nucleus of the thalamus, centromedian nucleus of the thalamus, subthalamic nucleus, substantia nigra pars reticulata, caudate nucleus, cerebellum, and hippocampus. However, the results have been quite variable with most studies reporting moderately reduction in seizure frequency. In addition, anterior thalamic nuclei DBS is associated with higher rates of self-reported depression and subjective memory impairment [14]. There is insufficient evidence on the efficacy and safety of hippocampal DBS, centromedian thalamic DBS, nucleus accumbens DBS, and cerebellar stimulation [14–16].

11.3 Anesthesia Considerations

Anesthetic management of patients undergoing surgery for epilepsy does pose significant challenges for anesthesiologist. They are enlisted in Table 11.1.

Table 11.1 Anesthetic considerations for epilepsy surgery

1. Patient related
a. Seizure disorder
Risks for perioperative seizures
b. Adult and pediatric patients
Special considerations for pediatric patients: airway management, altered pharmacokinetics and pharmacodynamics, inhalational induction, temperature control, and fluid management
c. Associated comorbidities
Developmental delay
Congenital syndromes with multisystem involvement
Depression and psychiatric illnesses
d. Antiepileptic medications
Side effects: sedation, ataxia, sedation, cognitive impairments, anemia, thrombocytopenia, gingival hyperplasia, cardiac toxicity
Interactions with anesthetic drugs: enzyme induction, faster metabolism of anesthetics especially nondepolarizing muscle relaxants, and opioid resistance
2. Procedure related
a. Different types of surgery
Diagnostic-presurgical localization-intracranial electrode insertion
Resection procedures: temporal lobectomy, amygdalohippocampectomy, excision of cortical scars, tumors, vascular malformations
Disconnection: corpus callosotomy, hemispherotomy
Stimulation procedures: vagal nerve stimulation, deep brain stimulation
b. Different anesthetizing locations
CT, MRI suites, PET scanner, MEG, neuroradiology suite
c. Anesthesia
Awake craniotomy
Craniotomy under general anesthesia (GA)
d. Intraoperative electrocorticography
Pharmacological activation of the epileptogenic focus
3. Others
a. Complications of surgery: slow/altered emergence, bradycardia/asystole, major blood loss, new deficits

CT computed tomography, *MRI* magnetic resonance imaging, *PET* positron-emission tomography, *MEG* magnetoencephalography

11.4 Preoperative Localization of Epileptogenic Focus

Success of the epilepsy surgery depends on the precise localization of epileptogenic foci. A multidisciplinary approach with both noninvasive and invasive investigations is performed to identify the location of the seizure foci as well to determine the feasibility to resect the epileptogenic foci safely without major neurological or cognitive deficits [17, 18].

The initial evaluation of the patient primarily focuses on the semiology of the seizure and its effective control with medical therapies. This include complete history related to the cause of seizure (infection, trauma, family history of seizures) and the treatment (current and past medications, side effects). In addition, general contraindications for surgery, namely, the presence of significant medical comorbidities, psychiatric illnesses, and neurodegenerative diseases, are identified. Presurgical evaluation is indicated for precise location of the epileptogenic foci and for identification of eloquent areas of the brain (Table 11.2) [19]. These include:

1. Imaging techniques, namely, computerized tomography (CT), high-resolution magnetic resonance imagining (MRI), positron-emission tomography (PET), single photon emission computed tomography (SPECT), and magnetoencephalography (MEG).
2. Electrophysiology studies that include with surface electroencephalogram (EEG) and/or intracranial electrocorticography (ECoG). In majority of patients, scalp EEG can accurately identify the seizure foci. However, in some cases especially in those with multiple seizure foci and/or those where seizure foci from deep subcortical tissues often need invasive procedures such as insertion of subdural strip or grid electrode insertion.
3. Functional assessments include neuropsychological assessment, functional MRI (fMRI), and Wada test. Neuropsychological assessments are performed to determine the patients' intelligent quotient (IQ), handedness, side of language and memory dominance, and presence of pre-existing neuropsychological deficits. fMRI is often used for identifying the eloquence of brain areas such as motor cortex, speech, and language areas [20]. Wada test (intracarotid sodium amytal injection) is done to identify memory and language dominance [21]. In this procedure, one hemisphere is "anesthetized" by injection of amobarbital into ipsilateral internal carotid artery and to verify if contralateral non-anesthetized brain can

Table 11.2 Presurgical localization of epileptic foci

Modalities	Technique	Description
Imaging	CT, MRI	Structural abnormality detection like mesial temporal sclerosis, focal cortical dysplasia, vascular malformations
	SPECT	Show focal increase in blood flow during seizures, identifying epileptogenic focus
	PET	Detect focal interictal reduction in metabolism of ^{18}F-labeled fluorodeoxyglucose; hypometabolic area depicts the probable seizure focus
	MEG	Shows magnetic field of epileptic locus in relation to seizure spikes to detect irritative zone
Electrophysiologic	Scalp EEG	Shows seizure activity during (ictal spikes) and between (interictal spikes) seizures
	Video EEG	Physical videographic correlation of seizures
	ECoG	Intracranial EEG recording
Functional	Wada test	Language dominance and memory reserve
	Functional MRI	Mapping of eloquent cortex—motor or language

CT computed tomography, *MRI* magnetic resonance imaging, *SPECT* single photon emission computed tomography, *PET* positron-emission tomography, *MEG* magnetoencephalography, *EEG* electroencephalography, *ECoG* electrocorticography

support the memory and language functions after surgery [22]. This test is usually performed without an anesthesiologist. However, due to nonavailability of sodium amytal, propofol and etomidate are now being used requiring the presence of an anesthesiologist [23].

Recent advances in imaging techniques have led to significantly reduction in the use of invasive evaluations for presurgical evaluation. Most patients with unilateral mesial temporal sclerosis as well as epileptogenic lesions that are well circumscribed, away from eloquent cortex such as benign neoplasms, vascular malformations, and atrophic scars, are evaluated by noninvasive studies [4]. Patients who require invasive and/or functional mapping include temporal lobe epilepsy with bilateral mesial temporal sclerosis, discordant electro-clinical data, normal imaging, extratemporal lesions close to eloquent area, and dual pathologies [4].

11.5 Anesthesia for Epilepsy Surgery

11.5.1 Preoperative Assessment and Preparation

Preoperative anesthetic assessment and preparation are similar to any patient undergoing craniotomy under general anesthesia. However, there are special considerations for patients requiring awake craniotomy, intraoperative ECoG, and cortical mapping. The preoperative evaluation should focus on patient's comorbidities and its optimization. Patients should continue their preoperative medications as indicated; however, the use of antiepileptic medications should be in discussion with the neurologist and/or surgeon. Sedative premedication is often not required as patients are usually well informed. In addition, benzodiazepines can affect the electroencephalographic activity of the brain and hence should be avoided especially if intraoperative electrocorticography (ECoG) is planned. Full explanation of the perioperative management should be given to patients, and any concerns from the patient should be addressed.

The awake patient usually facilitates better localization of epileptogenic foci and cortical mapping for functional preservation and provides continuous clinical neurologic monitoring [8, 24, 25]. A holistic approach involving the neurosurgeon, neuroanesthesiologist, neurologist, neuropsychologist, and other paramedical personnel is the key to success.

Children with epilepsy syndromes [Lennox-Gastaut syndrome, benign Rolandic epilepsy, childhood absence epilepsy (CAE), juvenile myoclonic epilepsy (JME), infantile spasms (or West syndrome)] often have developmental delay [5, 26]. In addition, some of these patients might also have congenital anomalies of cardiovascular system and the airway [27].

11.5.2 Anesthesia for Diagnostic Procedures for Seizure Localization

Most of diagnostic procedures for seizure localization are performed without the involvement of anesthesiologist. However, pediatric patients may need sedation for some of these procedures. Intracranial electrode placements for the localization of the epileptogenic focus often require general anesthesia. Anesthetic considerations for these procedures are similar to other craniotomies, and there is no specific concern with the choice of anesthetic agents used as the recordings are usually done at the end of the procedure or postoperatively. Electrode plates or large grids may need adequate brain relaxation with the use of mannitol or mild hyperventilation to decrease the arterial carbon dioxide level. Postoperative complications include cerebral edema and rarely may need removal of grids due to raised intracranial pressure [26, 27].

11.5.3 Anesthesia for Resective Procedures

Anesthesia for resective procedures may be with general anesthesia or an awake craniotomy [8, 9]. The decision is primarily dependent on the location of the seizure focus and whether

intraoperative ECoG for localization of the epileptic foci and/or cortical mapping of eloquent function is required or not. In addition, patient cooperation and his ability to tolerate awake procedure is also important.

11.5.3.1 Awake Craniotomy

The main challenges during awake craniotomy are to have the patient comfortable through a long procedure and also be alert and cooperative for intraoperative mapping of cortical function. The medications used must not interfere with stimulation testing and also electroencephalographic recordings.

The overall anesthetic preparation and management is like any other intracranial surgery except for the additional considerations of the effects of anesthetic agents on ECoG. Also, the duration of the procedure may be longer due to a larger craniotomy and more complex mapping. Regional scalp blocks are used to provide sufficient local anesthesia [28–30].

Standard monitoring includes an electrocardiogram, blood pressure, pulse oximetry, and end tidal capnography. Other monitors such as invasive arterial monitoring are indicated as per individual institutional practice and patients' comorbidities. Supplemental oxygen is administered by a face mask or nasal prongs with built-in port for CO_2 monitoring. Nasal prongs may be better for many patients, and it is more comfortable especially during language mapping.

Local anesthesia is used for head pin application and the incision. Scalp nerve blocks are performed using long-acting local anesthetics, like bupivacaine or ropivacaine with added epinephrine, sometimes in combination with lidocaine, with additional supplementation over the dura if needed [24, 29–31].

Common techniques for conscious sedation include propofol infusion with fentanyl and/or remifentanil and dexmedetomidine in conjunction with other agents [29–32]. In patients with epilepsy, opioids have been shown to induce epileptiform activity on ECoG and may cause myoclonic movements resembling clinical seizures [31, 32]. Propofol is the most commonly used agent for sedation during awake craniotomy [27, 29, 30]. However, depending on the dose, propofol can suppress the epileptiform discharges, and hence it must be stopped at least 15–30 min before electrocorticographic recordings [31]. Dexmedetomidine, a newer alpha-2 adrenoreceptor agonist, has become a popular choice for sedation and analgesia during awake craniotomy. Dexmedetomidine provides good analgesia with minimal respiratory depression [32, 33]. In addition, it has least effect on intraoperative EEG with better preservation of cognitive function [32, 33]. Sedative agents should be stopped before stimulation testing and restarted after all testing is completed. Ongoing patient reassurance is very important for the success of awake craniotomy. Patient should be pre-warned before painful and uncomfortable parts of the surgery such as burr holes, retraction of the scalp, and stretching of the dura. Small allowances like holding hands, moving intermittently, or sipping water may be more beneficial than sedation per se. Antiemetic agents may be indicated prior to intraoperative mapping and stimulation testing, and nonsedative antiemetics such as ondansetron or granisetron are preferred.

In some centers, "asleep awake asleep" technique is often used. Here, the patient undergoes full general anesthesia with a laryngeal mask airway (LMA) or endotracheal intubation with airway topicalization. Ease of placement and minimal coughing and gaging are the main advantages of LMA. At completion of craniotomy, the patient is woken up and the airway device removed to facilitate electrocorticographic recordings and stimulation testing. After intraoperative testing, patient may be re-induced with securing the airway as indicated [34]. Increased patient comfort and tolerance during craniotomy especially for longer procedures and a presence of airway device with ability to use hyperventilation are some of the main advantages of this technique.

Common intraoperative complications during awake craniotomy include seizure, hemodynamic instability, apnea, airway obstruction, agitation, restlessness, nausea and vomiting, and very rarely conversion to general anesthesia [28, 30, 31, 35]. Seizures are one of the most common complications during awake craniotomy in patients undergoing epilepsy surgery. Management of

Table 11.3 Management of intraoperative seizures

Before the dura is open
Propofol 10–30 mg boluses, multiple boluses, may be needed
Midazolam 1–2 mg boluses may interfere with electrocorticography
After the dura is open
Cold saline irrigation to brain
General supportive measures
Secure airway
Protect patient from injury
Phenytoin/levetiracetam/barbiturates may be needed

intraoperative seizure during different parts of the surgery is presented in table (Table 11.3). Airway obstruction, apnea, and hypoxia may be due to oversedation, seizures, mechanical obstruction, air embolism [35, 36], or loss of consciousness from an intracranial event. Careful planning and preparation are important to overcome these challenges. One should stop the sedation if the patient is overly sedated, and the airway should be supported with either a chin-lift, jaw thrust, or oral or nasal airway device. Assisted ventilation with a face mask may be needed. If a definite airway is needed especially for prolonged seizures or airway obstruction or apnea, the use of a laryngeal mask airway or endotracheal intubation with either video laryngoscope or fiber-optic bronchoscopy may be indicated. The choice depends on the individual anesthesiologist experience and skill. During airway management, the surgical field should be protected by sterile drapes [36].

The patient may also experience excessive pain and discomfort, which may need administration of appropriate analgesics. Perioperative nausea and vomiting may be multifactorial, like anxiety, drugs, and surgical stimulation, especially dural stripping and intracranial vessel movement, which may be treated by antiemetics like ondansetron. If the patient gets disinhibited, clinical judgment decides further course of action, as to reduce the sedation or convert to general anesthetic. The incidence of conversion to general anesthesia is low [33, 34]. Other less common complications include local anesthetic overdose, raised intracranial pressure, and hemodynamic fluctuations, which are managed as per standard protocol.

11.5.3.2 General Anesthesia

The choice of general anesthetic is due to preference of the surgeon and/or the inability of the patient to tolerate an awake procedure. The challenge for general anesthesia is provision of good conditions for electrocorticography and for motor testing, ensuring anesthetic influence is minimized, but also to avoid long periods of potential patient awareness. Patients must be informed of this possibility but also made aware that this risk is minimal and all efforts to avoid it will be done. Either inhalation anesthetics like sevoflurane or intravenous drugs like propofol may be used. Overall management of the patient is similar to other craniotomies. If testing is not done, usual general anesthetic technique may be used. Specifically, long-term anticonvulsant therapy in these patients may cause increased opioid and relaxant dosing [18, 25, 28]. Nitrous oxide should be avoided to prevent complications from an expanding pneumocephalus if recent surgery was done, considering the presence of intracranial air.

Delayed emergence may be a significant problem with general anesthesia for epilepsy surgery. The quality of emergence is pivotal to patient safety, as violent emergence may be occasionally seen in these patients. Emergence from anesthesia starts with activation of deep brain structures, namely, subcortical and limbic regions of the brain [37]. Later they become functionally coupled with other parts of the brain including the frontal and inferior parietal cortex. Arousal (spoken command)-induced brain activations during emergence from anesthesia are mostly localized in deep, phylogenetically old brain structures (limbic cortex or mesial temporal structures) than in the neocortex [37]. Due to asymmetry of temporal neocortical (dominant vs nondominant) and mesial temporal functional representations, the loss of these structures in epilepsy surgery and hence their functions in the postoperative period complicates emergence from anesthesia in these patients [38].

11.5.4 Anesthesia for Disconnection and Stimulation Procedures

Most of these procedures are done in children and usually under general anesthesia. The goals of anesthesia are to maintain normothermia,

normotension (age-appropriate), and normocapnia and to avoid the rise in intracranial pressure during induction, maintenance, and emergence [26, 27, 39, 40]. Parental presence at induction is practiced at many centers and may be desirable for kids with developmental delay for smooth induction of anesthesia [27, 39]. Some of the procedures like hemispherectomy may be particularly prone to massive blood loss [3, 41, 42], so blood and blood products should be readily available. Massive transfusion protocols should be activated promptly if indicated, and transfusion-related acute lung injury requires vigilant postoperative neurocritical care [3, 39, 42]. Homonymous hemianopia is common postoperatively [39, 42]. Endoscopic corpus callosotomy is being increasingly performed with minimal blood loss, minimal risk, and excellent visualization [43]. Corpus callosotomy may cause mutism, non-dominant arm and leg apraxia, bilateral Babinski signs, and urinary incontinence [39]. They usually resolve shortly after surgery; however, mutism can last for several weeks. In 8–12% of cases, weakness, apraxia, and language/behavior impairment may be permanent [39]. These complications are due to altered information processing across the cerebral hemispheres, often called as disconnection syndrome [41]. In some cases, neuropsychological testing may be required for detection of this condition as the changes may be very subtle. Staged surgery where initial partial callosotomy and followed by total callosotomy in 6–12 months later may minimize these complications [3, 41, 43].

Vagal nerve stimulation is performed under general anesthesia, usually with an endotracheal intubation [11, 44, 45]. Abnormal motion of vocal cords as a result of vagal stimulation can cause partial airway obstruction with a LMA. Intraoperative, bradycardia, and/or atrioventricular block can occur. Postoperative complications include laryngeal dysfunction including vocal cord paralysis, impaired respiration, aspiration risk, and worsening of obstructive sleep apnea [44].

Insertion of deep brain stimulators is usually done under conscious sedation followed by internalization and implantation of pulse generators under general anesthesia. Propofol and dexmedetomidine with or without opioids are commonly used as sedation during the procedure [30, 35, 46]. The use of benzodiazepines is usually avoided because they have a profound inhibitory effect on the neuronal discharges [35, 46]. General anesthesia for DBS surgery is an alternative in patients who cannot tolerate being awake. However, intraoperative mapping and stimulation testing are difficult under general anesthesia [46].

11.5.5 Postoperative Care

In the immediate postoperative period, patients should be closely monitored in the postanesthetic care unit and then transferred to surgical step-down unit when the patient is stable and discharge criteria are met [8, 9, 35, 39]. The patient should be nursed in 30-degree head-up position to improve ventilation; to reduce face, neck, and airway swelling; and to ease cerebral venous congestion. Neurological status should be assessed frequently. A CT scan may be needed to rule out an intracranial hemorrhage or cerebral edema, especially if there is a change in patient's neurological status. In addition, careful monitoring of hemodynamic parameters, ventilation status, fluid and electrolyte balance, temperature, blood glucose, and osmolality may all need to be addressed. Analgesic plan must be tailored to meet patient requirements. Short-acting opioids like fentanyl are a good choice [27, 39, 47]. Complications such as seizures require prompt administration of anti-seizure medications along with protection of patient from injuries as well as securing of airway early (Table 11.3).

11.5.6 Special Considerations

11.5.6.1 Intraoperative Electrocorticography and Pharmacological Activation

Intraoperatively, seizure focus can be localized using ECoG where direct recordings of the brain are performed from the area that has been predetermined to be epileptogenic foci (Fig. 11.1) [31].

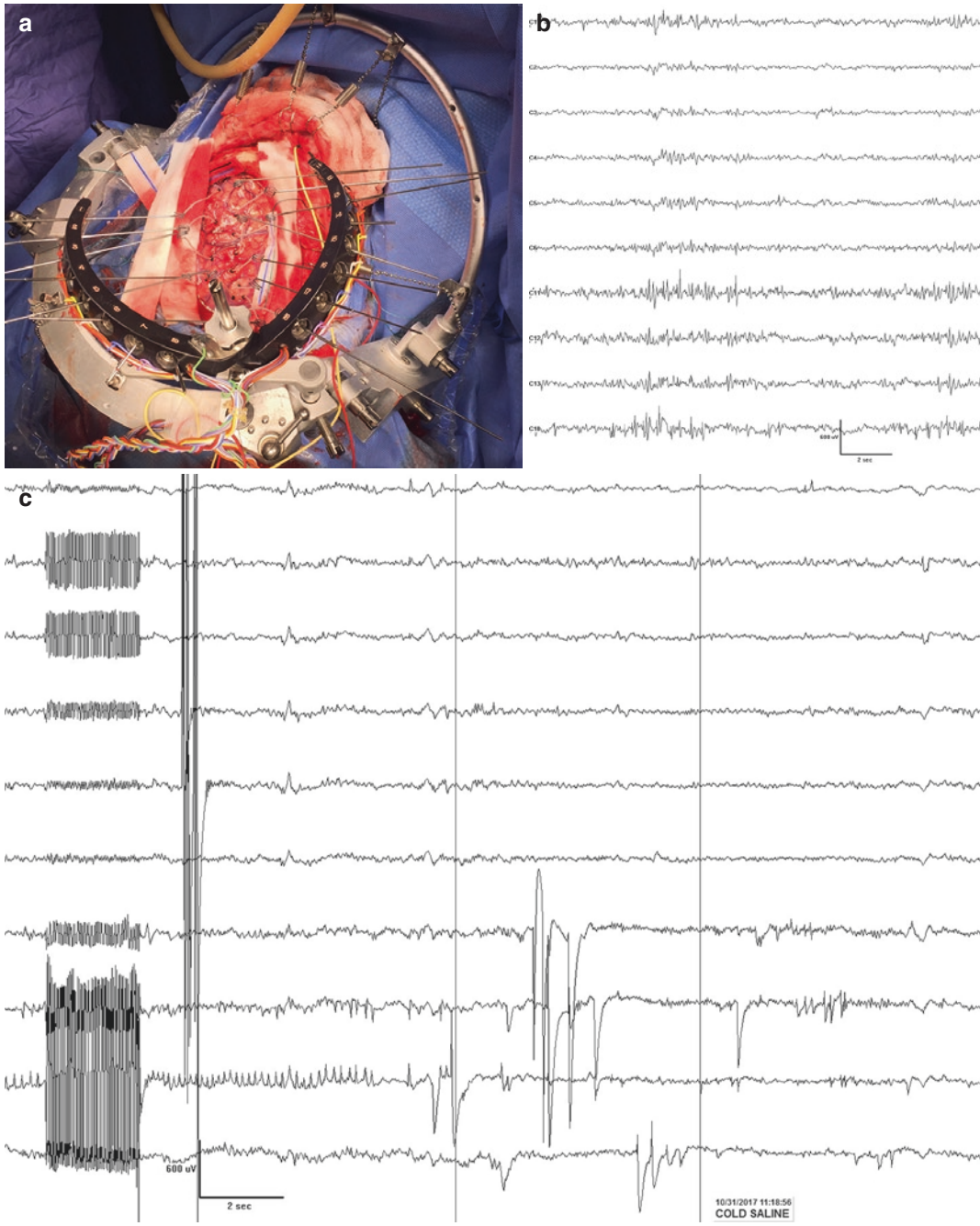

Fig. 11.1 Intraoperative electrocorticography (ECoG). The figure shows the intraoperative ECoG recording using Medusa headframe (**a**) depicting interictal spikes (**b**) and the electrographic seizure activity after cortical stimulation (**c**)

Background ECoG recording is similar to scalp EEG and represents basal cortical activity, with amplitude between 30 and 50 μV/mm [31]. In contrast, epileptiform potentials are sharp, transient discharges that are distinct from the background activity. A spontaneous seizure (ictal event) is usually uncommon during intraoperative ECoG, but interictal epileptiform activities

(IEAs) also known as interictal spikes are the most common finding during intraoperative ECoG. IEAs may be in the form of single spikes, polyspikes, sharp waves, spikes-and-waves, sharp-and-slow wave complexes, and/or any combination (Fig. 11.1) [31]. IEAs represent irritative zones; hence, they assist in localization of seizure focus. Anesthetic agents have a significant effect on intraoperative ECoG [28, 31], and hence awake craniotomy is the preferred anesthetic technique. However, pharmacological activation of IEAs may be indicated if sufficient information cannot be obtained during intraoperative ECoG. Commonly used agents for pharmacological activation include methohexital (10–50 mg), etomidate (2–4 mg), alfentanil (500–1000 μg), propofol (10–20 mg), or remifentanil (50–100 μg) or thiopental (25–50 mg) (Table 11.4) [24, 31, 48, 49]. Intraoperative ECoG can be performed under general anesthesia with intraoperative pharmacological activation using alfentanil, remifentanil, or inhalation agents such as enflurane and sevoflurane with or without hypocapnia [31, 48–51].

Table 11.4 Anesthetic considerations for intraoperative electrocorticography (ECoG)

Awake craniotomy
Benzodiazepines avoided
Propofol—skull pins, maintenance
Stop infusion 20 min before ECoG
Dexmedetomidine
0.5–1 μg/kg loading dose followed by 0.2–0.7 μg/kg/h infusion
Stop or decrease dose during ECoG
Opioids—fentanyl (bolus or infusion) or low-dose remifentanil infusion
Craniotomy under general anesthesia
Benzodiazepines avoided
Warn about the risk of awareness during ECoG
IV induction
Maintenance with TIVA or inhalational agents
Before ECoG
1. Both IV and inhalational agents stopped
2. Low-dose remifentanil or dexmedetomidine may be continued
During ECoG
1. Muscle relaxants to stop movement
2. Pharmacological activation for enhancement of epileptiform discharges

Key Points

- Epilepsy is a chronic disorder characterized by recurrent seizures due to unknown etiology.
- Success of the epilepsy surgery depends on the precise localization of epileptogenic foci and its complete removal. Surgery for epilepsy may be diagnostic (seizure localization) or therapeutic (resection of epileptogenic foci or modify the discharges).
- Anesthetic management of patients undergoing surgery for epilepsy does pose significant challenges for anesthesiologist.

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12 Anesthesia for Functional Neurosurgery

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12.1 Introduction

Functional neurosurgery is a subspecialty that deals with the surgical treatment of those neurological conditions where the central nervous system (brain and spinal cord) physiology is altered but the anatomy may or may not be normal. It includes mainly the surgical treatment for movement disorders as Parkinson's disease, essential tremor, dystonias, medically refractory epilepsy, psychiatric disorders, chronic pain syndromes, and drug addiction. In this chapter we will have a brief overview of deep brain stimulation, focused ultrasound, and treatment of the refractory epilepsy.

12.2 DBS Implantation

DBS implantation has been approved by the FDA for the treatment of Parkinson disease, essential tremor, dystonia, and refractory epilepsy [1]. It is being increasingly used for obsessive-compulsive disorder, tremor caused by multiple sclerosis, Tourette syndrome, chronic pain, and Alzheimer disease. Recently, deep brain stimulation (DBS) of the thalamic reticular nuclei has been tried to improve the level of consciousness in TBI. Chudy et al. found that if a patient in minimally conscious state or vegetative state has intact somatosensory-evoked potentials from upper extremities and motor- and brainstem auditory-evoked potentials, DBS could be considered as a treatment option [2, 3].

Contraindications to DBS implantation mainly include uncontrolled hypertension, use of antiplatelet medication, or underlying coagulopathy. Procedures requiring electrocautery should be avoided after DBS insertion. If there is a need for the use of electrocautery, a preoperative and postoperative program alteration of the DBS generator is done, the use of monopolar cautery is avoided, and there should be the use of the lowest energy for the minimum possible time.

During deep brain stimulation, the target nuclei are determined by the underlying pathological conditions, the subthalamic nucleus and globus pallidus internus (GPi) are the targets in Parkinson's disease, the ventral intermediate nucleus of the thalamus for essential tremor, globus pallidus internus for dystonia, Brodmann area for depression, and anterior limb of internal capsule for obsessive-compulsive disorder.

The exact mechanism by which DBS acts is not completely understood. The various suggested effects are hyperpolarization,

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inhibition of neuronal activity, and stimulation of gamma-aminobutyric acidergic neuronal activity [4, 5]. The most common DBS hardware manufactured by Medtronic (USA) has four main components: (1) the multicontact intracranial quadripolar electrodes, (2) a plastic ring and cap seated onto a burr hole to fix the electrodes to the skull, (3) a single- or dual-channel internal pulse generator, and (4) an extension cable that is tunneled subcutaneously from the cranial area to the chest or abdomen, connecting the DBS electrode(s) to the internal pulse generator.

Deep brain stimulator placement is a two-staged procedure. The first stage involves the placement of the intracerebral electrode. This is followed by the lead internalization and insertion of the pulse generator which may be done during the same sitting or at a later stage as a separate surgical procedure [6]. With the introduction of intraoperative magnetic resonance imaging, it is possible to image the stereotactic targeted nuclei. The real-time magnetic resonance imaging reduces the errors from brain shift making the planning and the execution of the whole procedure very accurate. The procedure starts by placing the patient in the MRI scanner. This is followed by T1- and T2-weighted MR images to identify the target nuclei and by planning of a safe trajectory. After making a burr hole, the stylet is advanced to the desired target under MR guidance followed by insertion of the DBS lead through the stylet. This is followed by a final MRI to confirm the optimal lead placement and to detect any possible complication as brain edema or hemorrhage [7]. The conventional method of DBS involves the use of microelectrode recording (MER) for precise localization of the target area. In MERs, the electrode is advanced 0.5–1 mm increment along a predefined trajectory toward the target nuclei. As the electrode is advanced, a recording of the spontaneous neuronal discharges is made. The target area is identified via generation of a distinctive pattern of neuronal discharges. Previous MRI and CT images may be helpful. This is followed by securing of the electrodes and wound closure.

Focused ultrasound (FUS) has been introduced for the treatment of minimally invasive management of essential tremor. Initially the use of ultrasound was limited due to significant attenuation and scattering of the intact bony skull [8]. However, with the introduction of hemispheric multielement, phased array transducers, it has been possible to deliver a targeted cavitation therapy without doing a craniotomy. The use of MR thermography has made it possible to evaluate the temperature of the target tissue.

FUS involves three main steps: (1) a preprocedure imaging with a computerized tomography and MRI to determine the skull thickness and the desired anatomical targets, (2) targeted use of low-power sonications to increase the initial temperature to 40–45° Celsius with a simultaneous confirmation by real-time magnetic resonance thermal imaging, and (3) after target confirmation, the final temperature is raised to 55 and 63° Celsius by sonications that result in the desired tissue ablation [9].

12.3 FUS for Essential Tremor

FUS is being increasingly used for essential tremor that does not respond to medical management. A lesion is made in the ventral intermediate nucleus of the thalamus to cause a disruption in the tremor circuits [10, 11]. The use of FUS has been found to have minimal complications as intracranial bleeding or infection. FUS may have a promising role in the future treatment of tremor-dominant Parkinson's disease, essential tremor associated with multiple sclerosis, and brain tumors [12, 13].

12.4 Laser Therapy for Refractory Epilepsy

Temporal lobe epilepsy may be refractory to medical therapy and may need temporal lobectomy. Laser ablation is a newer minimally invasive surgical technique which involves placement of a laser probe near the lesion. The seizure focus is then ablated by MRI-guided thermal imaging in real time. This technique ensures that there is minimal damage to the surrounding normal brain tissues [14]. With advances in technology, it is now possible to treat irregular lesions (conformal treatment) which were not possible with earlier

systems which allowed only destruction of globular area (concentric treatment). Conformal treatment is helpful to treat the epilepsy due to hamartomas and heterotopia.

12.5 Anesthetic Considerations for Functional Neurosurgery

12.5.1 Preoperative Concerns

In the preoperative period, the decision on whether to operate on a patient is made by a multidisciplinary team in which the anesthetic, medical, neurological, and psychiatric issues are addressed to determine the suitability of the patient for the surgical procedure. Surgery is mainly considered when a patient with Parkinson's disease develops moderate to severe motor fluctuations, medication-induced dyskinesia, and refractory tremor not responding to medication. It is important to differentiate whether the disabling symptoms in parkinsonism are dopa-sensitive or dopa-induced. Dopa-sensitive symptoms usually respond to the DBS rather than dopa-induced symptoms.

It is necessary to evaluate whether the patient will be able to tolerate the awake craniotomy. Old patients may have minimal motor improvement accompanied by an increased incidence of cognitive dysfunction after DBS. Welter et al. [15] found that Parkinsonian motor disability with a younger age and shorter disease duration had a more marked clinical improvement with DBS. Saint et al. [16] observed that elderly patients older than 69 years have a risk of cognitive impairment with worsening of their dementia after DBS. They suggested that advanced age may lead to a reduced neurological functional reserve at the cortical level. This may be a result of the inability to reprogram the cognitive operations once the basal ganglia circuitry is blocked by DBS. A Mini-Mental Status Exam (MMSE) score $\leq$24 or a Mattis Dementia Rating Scale (MDRS) total score of $\leq$120 is suggested as a poor marker of surgery [17].

In patients undergoing traditional DBS anti-Parkinsonian drugs are to be stopped the evening before surgery to allow the clinician to observe any change in symptoms during the macrostimulation testing [18]. However, in patients undergoing MRI-guided DBS surgery, the anti-Parkinsonian drugs are continued to prevent worsening of the symptoms [19].

Antiplatelet agents should be withheld if possible before and immediately after surgery. A good hypertensive control is mandatory; hence, antihypertensive medications should be continued on the day of surgery.

Orthostatic hypotension may result from Parkinson's disease itself or anti-Parkinson medications and might be further aggravated by the vasodilating effects of anesthetics and perioperative hypovolemia. Glossop and Dobbs [20] reported two patients who experienced chest pain, tachycardia, hypertension, and oxygen desaturation during insertion of a DBS under local anesthesia. This was accompanied with ST segment changes and increased troponins. They attributed the symptoms to abnormal vasoactive responses resulting in coronary vasospasm.

In patients who are undergoing FUS for essential tremor, the use of dexmedetomidine, opioids, and benzodiazepines should be avoided as they may cause suppression of the tremor [21]. In patients who are on prolonged antiepileptic drug therapy, there may be resistance to non-depolarizing neuromuscular blocking agents due to induction of hepatic drug metabolism, increased protein binding of the non-depolarizing neuromuscular blockers, and/or upregulation of acetylcholine receptors [22].

12.5.2 Anesthetic Techniques (General Versus Local Anesthesia)

DBS Surgery For the traditional DBS surgery, awake craniotomy was preferred as an awake patient was needed for optimal results during intraoperative macrostimulation testing and microelectrode recordings of the target nucleus. MRI-guided DBS is based on neuroimaging rather than awake neurophysiological testing, so general anesthesia is desirable particularly in pediatric population.

Focused Ultrasound For the treatment of essential tremor, it is performed in awake patients, without the need for general anesthesia.

Epilepsy surgery with intraoperative cortical mapping is done under awake craniotomy. For awake craniotomy a regional anesthesia of the scalp is given by blocking the supraorbital, supratrochlear, auriculotemporal, zygomaticotemporal, greater occipital, and lesser occipital nerves. It may be supplemented by a field block, in which the local anesthetic is infiltrated along incision lines of the scalp flap. The local anesthetic may be mixed with sodium bicarbonate solutions to minimize the burning sensation during injection of the local anesthetic. *Asleep-awake-asleep* technique may be used for awake craniotomy. It involves the use of general anesthesia in the initial part and the final stages of the surgery. However, during neurophysiological testing and macrostimulation, the patient is awake. In case of a seizure activity during awake craniotomy, iced saline irrigation by the surgeon should be done to stop seizure activity. The use of propofol may be considered by the anesthesiologist to terminate the seizure keeping a close vigil on the airway. *Laser therapy* for refractory seizures is done under general anesthesia. It is associated with minimal blood loss, minimal alteration of cerebral and systemic hemodynamics, and minimal risks of intraoperative seizures. Standard anesthesia monitoring is sufficient in the form of electrocardiogram, pulse oximetry, end-tidal capnogram, and noninvasive blood pressure with no need for arterial line and central venous line.

12.5.3 Intraoperative MRI Considerations

With the use of intraoperative MRI for functional neurosurgery, the anesthetic concerns for an MRI suite should be considered while carrying out these procedures. An updated practice advisory on anesthetic care for magnetic resonance imaging was published by the American Society of Anesthesiologists in 2015 [23]. These guidelines address the issues of patient screening, preparation of the patient, patient management during MRI (including airway management and monitoring), post-procedure care, and management in case of (1) medical emergencies (e.g., cardiopulmonary arrest) and (2) environmental emergencies (e.g., quench, fire, and projectiles).

12.6 Intraoperative Complications

Khatib et al. [24, 25] found that coughing, sneezing, aspiration, pulmonary edema, combative behavior and agitation/confusion, bronchospasm, angina, intracranial hemorrhage, hypertension, and seizures were some of the complications that were observed during deep brain ablation. Age greater than 64 years was found to be an independent risk factor for complications during DBS.

12.7 Venous Air Embolism

Two important predictors during functional neurosurgery that may lead to air embolism are patient positioning and the occurrence of coughing. Whenever the surgical site is above the right atrium, a negative pressure gradient is created. As venous sinuses are fixed to dural attachment, they do not collapse when a negative pressure gradient is created. This facilitates air entrainment into the right atrium resulting in air embolism. Clinically significant air embolism has been seen in spontaneously breathing patients and is mainly preceded by an episode of cough. In addition to coughing, awake patients may complain of acute chest pain or nausea during air embolism [26].

Transesophageal echo (TEE) which is the most sensitive monitor to detect air embolism will not be tolerated by awake patients. Precordial Doppler ultrasound may help in detection of air embolism. Changes in vital signs as hypoxemia, hypercapnia, and decreased end-tidal CO_2 may aid in the diagnosis coupled with an increase in end-tidal nitrogen. Hypotension, cardiac dysrhythmias, and cardiovascular collapse can occur in severe cases.

Treatment is mainly supportive. The surgeon is informed, surgical field is irrigated with saline, open veins are cauterized, and exposed bone surfaces are waxed. An LMA may be inserted if the oxygen saturation is falling and used as a bridge until the headframe can be removed and a definitive airway is secured. The use of N_2O is avoided to prevent an increase in the size of the entrained bubbles. The blood pressure is supported with fluids and vasopressors. The operative site is positioned below the level of the heart by tilting

the table into the Trendelenburg position. Air is aspirated through the central venous catheter that is placed in the right atrium [26, 27].

Coronary vasospasm may result due to abnormal vasoactive responses, resulting in chest pain, tachycardia, hypertension, oxygen desaturation accompanied with ST segment changes, and increased troponins during DBS [20].

Respiratory depression or loss of airway may occur during functional neurosurgery in an awake patient, due to oversedation, seizures, or intracerebral hemorrhage. If access to the airway is limited due to the presence of headframe, a laryngeal mask airway may be used to maintain the oxygenation.

Acute airway obstruction may result, leading to an emergency, when an awake patient moves his body but the head remains fixed to the headframe. The equipment to release the head from the headframe should be readily available to deal with this emergent situation.

12.8 Postoperative Complications

Intracranial hemorrhage may be commonly seen in the postoperative period. Hypertension during emergence has been implicated as a major factor in causation of intracranial hemorrhage [28].

There is little evidence available to guide intraoperative blood pressure management. It was suggested that significant risk factors for intracerebral hemorrhage were chronic arterial hypertension and acute intraoperative hypertension. The authors found that maintaining a systolic blood pressure of less than 140 mm Hg is associated with a lower risk of intracerebral hemorrhage [28]. Metoprolol, esmolol, labetalol, and propranolol should not be utilized for blood pressure control as they can attenuate the essential tremor [21], while hydralazine, nicardipine, clevidipine, and enalaprilat may be used with no effects on essential tremor. All patients who have an altered mental status, new focal neurological deficits, and focal or generalized seizures in the postoperative period should undergo immediate neuroimaging to rule out any intracranial bleed or neurologic injury.

Seizures have been seen in 0.5–4.5% of patients during DBS. They may be seen mainly during macroelectrode stimulation testing or may occur in the postoperative period due to reactive edema or pneumocephalus. Though most of the seizures are self-limited, they are treated by irrigation with cold saline. Few patients may require small doses of midazolam or propofol [25].

Neuroleptic malignant syndrome characterized by hyperthermia, autonomic dysfunction, altered mental state, hemodynamic dysregulation, elevated serum creatine kinase, and rigor has been reported due to discontinuation of anti-Parkinson medication [29].

12.9 Conclusions

Functional neurosurgery has undergone major technological advancements in the last decade with the introduction of focused ultrasound and MR thermography. These changes have reduced the need for awake craniotomy and intraoperative neurophysiological monitoring. An understanding of these procedures and the effects of various anesthetic agents and neuropharmacological agents is vital for the successful functional outcome of these procedures and will help in the early recognition and treatment of any complications.

Key Points

- Functional neurosurgery is a subspecialty that includes mainly the surgical treatment for movement disorders as Parkinson's disease, essential tremor, dystonias, medically refractory epilepsy, psychiatric disorders, chronic pain syndromes, and drug addiction.
- General anesthesia is preferred for magnetic resonance imaging-guided DBS placement as the electrode localization is guided by the imaging rather than awake neurophysiologic testing.
- Functional ultrasound procedures for treatment of essential tremor or dystonia are minimally invasive procedures. Hence, general anesthesia is avoided in these procedures.
- Epilepsy surgery with intraoperative cortical mapping is done under awake craniotomy. Scalp block is given for craniotomy in awake state.

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13 Anesthesia for Endoscopic Third Ventriculostomy

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13.1 Introduction

Endoscopic third ventriculostomy (ETV) is one of the most recent advances in the treatment of obstructive hydrocephalus. Subsequently there have been a number of publications which have established its role in neurosurgical practice, particularly in hydrocephalus. ETV is a standard surgical procedure for treatment of non-communicating hydrocephalus. This procedure requires a general anesthetic and necessitates manipulation of the brain neural structures to access the floor of the third ventricle. In this chapter we are going to focus on ETV sciences in terms of history of ventriculoscopy, endoscopic ventricular anatomy of the third ventricle, surgical technique, and anesthetic considerations of ETV.

13.2 History of Ventriculoscopy

In the early 1900s, Walter E. Dandy was one of the first surgeons to use a primitive endoscope to perform choroid plexectomy in a patient with communicating hydrocephalus [1]. The first ETV was performed by William Mixter, a urologist, in 1923. Mixter used a urethroscope to examine and perform the ETV in a child with obstructive hydrocephalus [2]. Putnam then borrowed this urethroscope and optimized its use for the ventricular system. His ventriculoscope was specifically designed for cauterization of the choroid plexus in children with hydrocephalus [3]. Nevertheless, the arrival of valve-regulated shunt systems and the simplicity of the technique resulted in minimal advances in ETV for 30 rs. In 1947, McNickle introduced a percutaneous method of performing ETV that decreased the complication rate and improved the success rate [4]. There has since been renewed interest in the use of ETV for the treatment of obstructive hydrocephalus. This has been related to advanced fiberoptic and lens technology. There are now small neuroendoscopes available that have deflectable tips, working ports, and good optic resolution, in addition to the rigid endoscopes with their excellent optic resolution. In recent series of ETV performed for the treatment of obstructive hydrocephalus, success rates between 50% and 94% have been reported [5]. Improvements in the technique will surely come as more clinicians perform ETV and communicate their experiences.

13.3 Endoscopic Ventricular Anatomy

It is important to be familiar with the ventricular anatomy. The foramen of Monro is the first structure visualized. The foramina are paired structures serving to connect the lateral ventricle with

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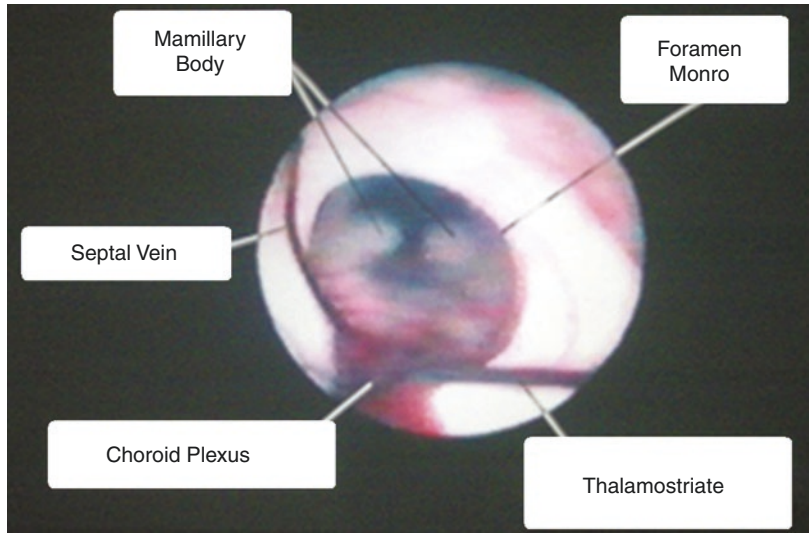

Fig. 13.1 Endoscopic anatomy of the foramen of Monro (live case from our setting)

the third ventricle. The head of the caudate is situated laterally and the septum pellucidum is located medially. The choroid plexus of the lateral ventricle projects forward to the foramen, through which it passes before turning posteriorly to lie under the roof of the third ventricle. The vein of septum pellucidum, located anteromedially, joins the thalamostriate vein, located posterolaterally, at the posterior rim of the foramen of Monro. These vessels join and ultimately form the internal cerebral vein, which runs in the tela choroidea of the third ventricle (Fig. 13.1).

These veins should become larger in caliber as they approach the foramen of Monro. The fornix is intimately related to the foramen. The C-shaped fornices are paired, efferent-output bundles projecting from the hippocampus to the mammillary bodies, passing from the medial margin of the foramen anteriorly before diving into the medial wall of the third ventricle. Inside the third ventricle, there are several anatomical landmarks. Two hypothalamic mammillary bodies are intersected by the basilar artery and most anteriorly the pituitary infundibulum (Fig. 13.2). The lateral walls consist of the anterior two thirds of the thalamus and hypothalamus, continuous with the gray matter of the floor. The lateral walls are joined by a band of gray matter, the massa intermedia. The posterior border consists of the pineal body, the habenular commissure, the posterior commissure, and the cerebral aqueduct. The aqueduct is a narrow channel approximately 15 mm long and 1 mm wide that connects the third ventricle with the fourth ventricle. A clear view of the floor of the third ventricle is provided once the endoscope is passed through the foramen of Monro. The floor is formed mainly by hypothalamic nuclei. In an anteroposterior direction, these are the optic recess, the optic chiasm, the infundibulum, the infundibular recess, the tuber cinereum, and the mammillary bodies. In the majority of cases,

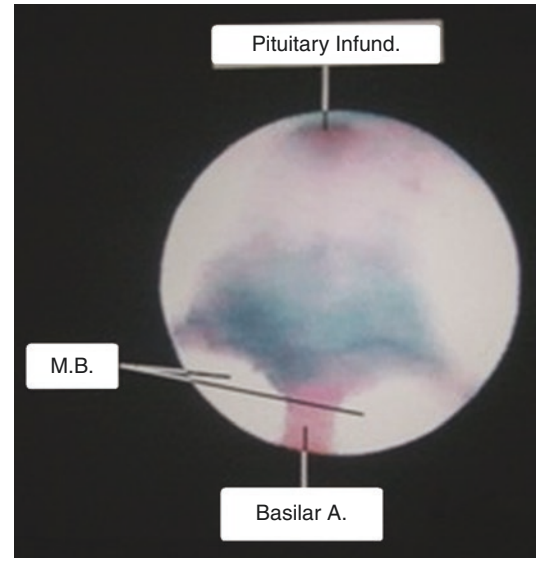

Fig. 13.2 Floor of the third ventricle (live case from our setting). *MB* mammillary bodies

the floor (tuber cinereum) of the third ventricle is often thinned out and translucent.

13.4 Surgical Technique and Technical Considerations

The scope is introduced through the anterior fontanelle or a burr hole (according to the patient age) just anterior to the coronal suture in the midpapillary line. The scope then passes from the lateral ventricle through the foramen of Monro toward the floor of the third ventricle. The floor of the third ventricle is punctured posterior to the infundibular recess with the tip of the scope. The fenestration is enlarged slightly with gentle movement of the tip of the scope and passed through the hole. Irrigation with saline at body temperature at different rates as required is used for the clarity of the field only if hemorrhage occurs. The cerebrospinal fluid was then allowed to drain into the basal cistern, bypassing the aqueduct stenosis to the surface of the brain (Fig. 13.3) [6]. Jallo et al described his technique using different tools as follows: after general anesthesia is induced, the patient is placed supine with the head in the neutral position on a doughnut pillow. The head is then elevated approximately 30°. The coronal burr hole 3 cm lateral to midline, 6–10 mm in diameter, is created on the side of the normal foramen of Monro, larger lateral ventricle, or right side. The dura mater is then opened in a cruciate fashion, and a No. 14 French peel-away catheter is then used to cannulate the lateral ventricle. The stylet is then removed to ensure the proper placement into the ventricular system, and the two leaves are peeled away and stapled to the drapes. This maneuver prevents inadvertent passage of the sheath deep into the ventricles. The advantages of this sheath include an egress pathway for irrigation fluid or CSF and repeated passage of the endoscope without traction on or injury to the brain. The foramen of Monro is at mean distance of 6 cm from the dura mater via this coronal approach in an adult and less than that in children. The endoscope is passed through the sheath and the lateral ventricle is visualized. The foramen of Monro is identified, and the scope is navigated into the third ventricle. The floor of the third ventricle is, on average, 9 cm from the dura mater, but this is highly variable depending on age and extent of hydrocephalus. The mammillary bodies and infundibular recess are identified in the attenuated floor. It is often possible to see the basilar artery through the diaphanous floor of the third ventricle. At this juncture, the surgeon should be certain that the intended fenestration will be anterior to the BA. It is wise to have confirmed this on the sagittal MR image obtained before surgery. A Bugbee wire, without electrocoagulation, is used bluntly to puncture the floor of the third ventricle midway between the mammillary bodies and the infundibular recess. The Bugbee wire is then removed, a No. 3 French Fogarty balloon catheter is advanced through the opening in the floor, and 0.2 ml of fluid is instilled into the balloon, inflating it, to widen the newly created aperture. This maneuver widens the fenestration to a width of approximately 5 mm. We do not inflate the balloon under the floor and pull back through the stoma. The scope is then carefully guided into the prepontine cistern. Any arachnoid bands or imperforate membrane of Liliequist that seem to be impeding the free flow of CSF are bluntly disrupted with the Fogarty catheter. After the stoma is created, the to-and-fro oscillations of the ventricular floor indicate good CSF communication

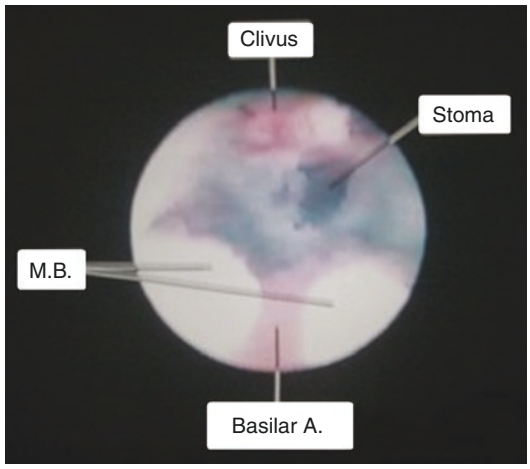

Fig. 13.3 Fenestration stoma in the floor of the third ventricle (live case from our setting)

between the ventricles and subarachnoid space. Besides Bugbee wire other methods to create the fenestration include using the endoscope as a blunt trocar and using laser, bipolar, and monopolar instruments. Doppler devices are available that can help locate the basilar artery prior to the thermal fenestration. At completion of the fenestration, the endoscope and sheath are removed, Gelfoam is placed in the burr hole, and the scalp is sutured. The galea is closed with a Vicryl suture and the skin with surgical staples. If any bleeding has occurred, a ventricular drain is commonly left in place for 1–2 days. A ventricular drain is left in place in patients who have previously undergone shunt insertion. In these patients, the shunt system will be observed for several days [7].

13.5 Indications of Neuroendoscopy

ETV is ideal for candidates with an obstructive etiology due to a variety of possible causes, including primary congenital anomalies such as aqueductal stenosis, myelomeningocele, and idiopathic causes [8–10]; obstruction secondary to pineal region tumors for which ETV and biopsy may be coupled [11–13]; aqueductal stenosis secondary to tectal gliomas [14]; and giant retrocerebellar cysts [15]. Some have found ETV to be effective in managing hydrocephalus in children with posterior fossa tumors prior to tumor resection [16, 17]. ETV also provides great utility in managing patients with obstructive hydrocephalus who present with shunt failure secondary to obstruction, infection, abdominal CSF pseudocyst, or other complications [18, 19]. In cases where shunting can give rise to slit ventricle syndrome, ETV has also been proven effective in assessing brain compliance. Specifically, if the brain is sufficiently compliant, the existing shunt is removed, and ETV is performed during the same operation [20]. Preformed cavities filled with crystal-clear CSF, such as the ventricular system, subarachnoid space, and some cystic lesions, provide most favorable conditions for the application of endoscopes. Therefore, hydrocephalus, intraventricular lesions, and space-occupying arachnoid or parenchymal cysts are perfect indications for the use of an endoscopic approach. Due to the further improvement of endoscopic hemostasis even highly vascularized tumors can be resected. Management of hydrocephalus represents the classic indication for a neuroendoscopic approach. Currently, hydrocephalus remains the most frequent intracranial disease treated endoscopically. ETV has become a well-established procedure for the treatment of non-communicating hydrocephalus. ETV has been successful in controlling obstructive hydrocephalus caused by tumors, aqueductal stenosis, hemorrhages, and infarctions. Although the procedure is commonly considered to be safe and straightforward, severe and, rarely, fatal complications may occur. One of those complications, namely, acute respiratory failure, happened in our setting. The authors report an 8-month-old patient with obstructive hydrocephalus secondary to posterior fossa cyst and Chiari malformation. After ETV he developed difficulty in breathing, and the trachea had to be reintubated and ventilated. The infant recovered fully after craniocervical decompression and insertion of cystoperitoneal shunt. We speculate that respiratory failure is related to relative expansion of the posterior fossa arachnoid cyst, causing significant compression on the brain stem. Supportive care with mechanical ventilation and brain stem decompression were the mainstay of treatment [21]. In our setting and in a larger study on 52 children younger than 1 year who underwent ETV for treatment of hydrocephalus. The overall success rate was 69.4% with mean follow-up period of 68.2 months. Patients with aqueduct stenosis had a higher success rate of ETV which was 77.4%. Seven infants were born preterm, six of them required a permanent VPS; $p = 0.003$. There was one death from intracranial hemorrhage, two cerebrospinal fluid leaks, and one meningitis [22]. We concluded from this study that ETV can be considered a possible treatment procedure alternative to VPS for the treatment of occlusive hydrocephalus in infants. ETV was effective in full-term infants, while the results in low-birth-weight, preterm infants were poor. Success of ETV is not only age dependent but also etiology dependent.

Infants with occlusive hydrocephalus treated with VPS, who present with shunt failure, could be treated by ETV and removal of the shunt device. The correct placement of the fenestration in the floor of the third ventricle is of utmost importance to avoid vascular and neural damage. The perforation of the floor should be made halfway between the infundibular recess and mammillary bodies in the midline, just behind the dorsum sellae. In this way, hypothalamic injury, oculomotor palsy, and vascular injury are unlikely to occur. Careful inspection of a CT scan or sagittal MR image to assess the individual relation of the basilar artery and the floor of the third ventricle is advisable.

13.6 Anesthetic Considerations

13.6.1 Preoperative Evaluation and Premedication

The evaluation must include history and physical examination pertaining to the conditions requiring special anesthetic considerations. Patient's neurological status is noted before accepting the case. Associated bulbar palsy and sleep disturbance are also noted. Assessment of neurological status should include evidence of raised intracranial pressure (ICP), altered sensorium, and cranial nerve palsies. Infants with ICP might present with irritability, lethargy, decreased consciousness, failure to feed, bulging fontanel, and cranial enlargement [23]. In children, it may present with early morning headache, vomiting without nausea, diplopia, and papilledema and, in late stage, with Cushing's triad. Frequent vomiting episodes may lead to dehydration and electrolyte imbalances and increase the risk of aspiration. Hence, serum electrolytes should be determined to identify abnormalities of sodium and potassium following vomiting. Dehydration and electrolyte abnormalities if present need to be corrected before surgery. Other laboratory investigations should include hemoglobin or hematocrit level and typing and crossmatching of blood if the loss is expected to be considerable. Additional studies should include electrocardiogram (ECG), coagulation profile, and renal and hepatic function, as deemed necessary. Patients are at higher risk of urinary tract infections or impaired renal function as a part of multisystem congenital syndromes. In our setting, patients with depressed mental status received no premedication. Otherwise, trimeprazine syrup 0.5 ml/kg b.w. 30 min preoperatively was given to children less than 2 years. Older children receive oral midazolam 0.5 mg/kg b.w. 30 min preoperatively.

13.6.2 Pediatric vs. Adult Airway

The key principle to understand about the pediatric vs. adult airway is that it is smaller in diameter and shorter in length than the adult's. That airway resistance is primarily influenced by the diameter of the airway, and resistance can be dramatically increased with subtle changes (such as soft tissue swelling) in an already small system. It should be noted also that children younger than 10 have the narrowest portion of the airway below the glottis at the level of the cricoid cartilage. This is why uncuffed endotracheal tube is preferred in pediatric vs. adult airways. A cuffed tube during a prolonged intubation can increase soft tissue swelling, and again this can decrease the radius and narrow the airway significantly increasing resistance; a clinical example of this is a child with stridor. In a patient with stridor, the airway is swollen to the point that air being drawn past the narrowing makes an audible sound. The larynx in infants and young children is located more anteriorly making it potentially more difficult to obtain a complete view during laryngoscopy. The epiglottis in infants and young children is relatively long, floppy, and narrow, and it can be difficult to navigate your laryngoscope around it. Children with large occiput and large tongue will lead to upper airway obstruction especially during times of apnea or hypoventilation. These factors are often relieved by placing a properly sized oral airway device and gently manipulating the head of the patient to achieve the proper sniffing position (Fig. 13.4). We had a hydrocephalic child poster to undergo ETV with cleft lip and palate

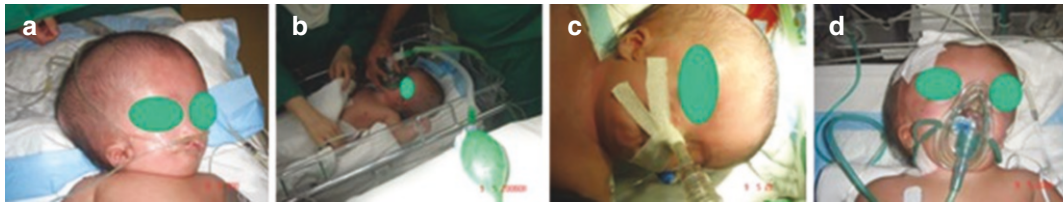

Fig. 13.4 A hydrocephalic patient with laryngeal mask airway (LMA). (**a**) Before induction. (**b**) At induction. (**c**) LMA inserted. (**d**) At recovery

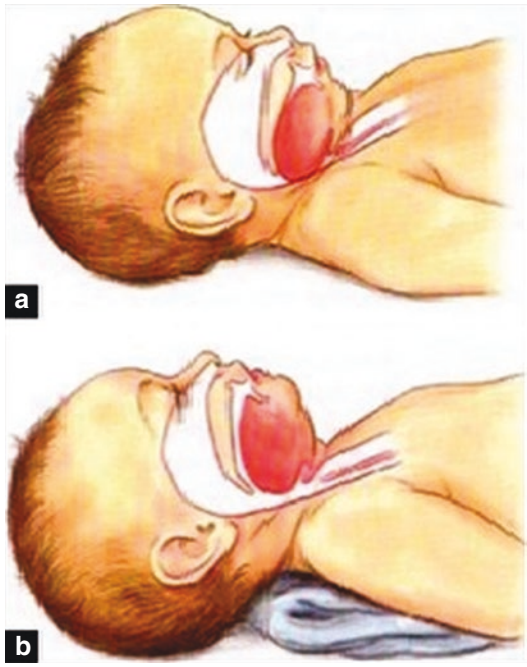

Fig. 13.5 (**a**) Head position. (**b**) Corrected head position

where laryngeal mask airway (LMA) is the only preferred choice used to maintain the airway intraoperatively (Fig. 13.5). Children and neonates are also prone to faster rapid oxygen desaturation. The pediatric vs. adult airway has a higher metabolic rate, increased closing volumes, and higher minute ventilation to functional residual capacity ratios all contributing to a more rapid desaturation. The infant diaphragm is the major muscle of ventilation and fatigues much easier than the adult airway during times of distress. The pliable rib cage of infants and children diminishes the efficacy of infant's attempts to increase ventilation. Sedative and narcotic premedication should be avoided in all the children suspected of increased ICP as these medications decrease respiratory drive which may result in hypercapnia and further increase in ICP [24]. However, patients with normal ICP, such as those scheduled for repair of vascular lesions, may be sedated so as to allay preoperative anxiety and avoid hypertension, thus preventing rupture of vascular abnormality. Oral benzodiazepines (midazolam) may be beneficial for small children as they provide sedation without respiratory depression and should be administered under supervision [25].

13.6.3 Induction and Maintenance of Anesthesia

The goal of anesthetic induction is to avoid increase in ICP owing to associated hypoxia, hypercapnia, and volatile anesthetic-induced increases in CBF. An intravenous (IV) induction with propofol and neuromuscular block to facilitate endotracheal intubation is best in children with raised ICP. However, in children without IV access, inhalational induction by face mask with sevoflurane should be preferred as crying or struggling may lead to further increase in ICP. After the IV access is secured, the inhalational technique may subsequently be changed to an IV induction. All volatile anesthetics cause an increase in CBF and thence the ICP. Therefore, ventilation should be controlled as early as possible and mild hyperventilation be instituted to prevent rise in ICP. Children at risk for aspiration should undergo rapid-sequence anesthetic induction with thiopentone or propofol followed by rapid-acting muscle relaxants such as suxamethonium or rocuronium. Maintenance of anesthesia is achieved with

inhalation anesthetic sevoflurane in 50% air in oxygen for all patients. Analgesia is achieved with 1 mcg/kg of fentanyl, and muscle relaxation maintained with incremental doses of rocuronium when required. At the end of surgery, IV reversal agents for muscle relaxants were given in usual doses (atropine 20 mcg/kg and neostigmine 80 mcg/kg), and the trachea is extubated. Patients then were sent to the recovery room and later to the ward [26]. Large exchange of irrigation fluid and wetting of surgical drapes expose the child to the risk of life-threatening perioperative hypothermia. The use of thermal blanket and warm irrigation fluids or fluid warmer is strongly advocated. The largest possible catheter should be used to establish peripheral venous line, and access should be ensured throughout the procedure. The aim of IV fluid administration is to maintain normovolemia. In general, there is no requirement for blood transfusions. Routine and emergency drugs must be labeled and kept. Eyes should be protected from external pressure and surgical cleaning solutions. While positioning the child, care must be taken to ensure adequate ventilation and avoidance of venous congestion.

13.6.4 Intraoperative Monitoring

A consensus on standard monitoring requirements has not yet established in the literature. Basic monitoring includes electrocardiography, pulse oximetry, capnography, temperature, and urine output monitoring. In our setting and due to the hemodynamic changes occurring during the procedure, we use to increase the tone of the ECG monitor to be audible to both the surgeon and the anesthesiologists for early recognition and diagnosis of any changes and prompt management without delay. There are many authors who recommend invasive blood pressure monitoring by indwelling arterial catheter in all patients, irrespective of their age [27]. In our setting we don't recommend insertion of arterial cannula. Abrupt changes in CBF due to changes in ICP are possible during the procedure. Transcranial Doppler is the fastest and most reliable method to detect any fluctuations in CBF due to changes in ICP [28]. It has got high sensitivity to changes in CBF. However, practical objections restrict it as a routine use in neuroendoscopic procedures even though many consider it as a routine monitor in neuroendoscopy. The use of ICP monitoring and the methods employed is another debatable point. Even though several strategies to ICP monitoring are described, measuring through the rinsing channel of the endoscope is preferred in literature. In one of our studies, we have used intraoperative ICP monitoring intraoperatively, but currently we are not using it as a routine. Although the experimental animal models favorably suggested the use of mild hypothermia in neurosurgical patients, it has not been extrapolated to humans. The intraoperative goal is to maintain normothermia and avoid both hypothermia and hyperthermia with application of different methods.

13.6.5 Fluid Management

Warmed Ringer's lactate or normal saline is used for irrigation during ETV. Normal saline is the most commonly administered crystalloid during pediatric neurosurgical procedures as it is mildly hyperosmolar and hence prevents cerebral edema [29]. However, infusion of large quantities (>60 ml/kg) of normal saline may cause hyperchloremic metabolic acidosis and hypernatremia [30]. Ringer's lactate is slightly hypo-osmolar and may increase cerebral edema if infused in large quantities. Hyperglycemia worsens reperfusion injury, and so glucose-containing fluids should not be used during these procedures. However, in neonates and premature infants, the danger of hypoglycemia should be borne in mind. Blood glucose should be closely monitored in these patients, along with continuous infusion of glucose at 5–6 mg/kg/min [31, 32]. Children do not need exogenous glucose administration and are able to maintain normal levels along with the associated surgical stress. Blood transfusion should be guided by the degree of blood loss and initial hematocrit values.

13.6.6 Complications

ETV is the method of choice in the treatment of obstructive hydrocephalus [33]. The reported complications of ETV include hemiparesis [34] and transient third cranial nerve paresis [35]. At the same time, patients might develop transient fever because of aseptic irritation of the ependyma or manipulation of the hypothalamus [33]. Life-threatening complications such as hemorrhage from traumatic basilar artery aneurysm and cardiac arrest have also been reported [36, 37]. Experimentally, the stimulation of the hypothalamic nuclei can cause a variety of sympathetic and parasympathetic responses [38, 39]. In an attempt to identify the possible mechanisms of the hemodynamic changes, namely, bradycardia during ETV under anesthesia, we compared the intracranial pressure and the hemodynamic changes with negative correlation [40]. Manipulation of delicate structures around the third ventricle (hypothalamus and brain stem) can occasionally lead to intraoperative bradyarrhythmias, hypotension, hypertension, and even cardiac arrest [41]. In one of our study series on complications of ETV and its effect on hemodynamics on 49 pediatric patients, bradyarrhythmia was reported in 20 patients (41%), which warranted the surgeon to temporarily stop the procedure. Withdrawing the scope away from the floor of the third ventricle successfully resolved the bradycardia. However, once the heart rate was stabilized and the floor of the third ventricle was perforated, the bradycardia resolved immediately. None of the patients required atropine [6]. Fabregas et al. reported 1% mortality rate among 100 neuroendoscopy cases. Also they reported intraoperative complications in 36 patients with arterial hypertension being the most frequent (53%) and postoperative complications in 52 patients, anisocoria (31 %) and delayed arousal (29%) [42]. Intraoperative hemodynamic changes during ETV have been extensively studied with conflicting results. In one study tachycardia was found more frequently than bradycardia and was attributed to an increase in ICP and systemic hypertension and was caused by high-speed fluid irrigation or kinking of the outflow tube [41]. Atypical Cushing response was given to explain the frequency of tachycardia during ETV. The classic response as described by Cushing includes apnea, hypertension, and bradycardia. However, in the literature, tachycardia consistently preceded bradycardia in the Cushing response and was attributed to compression of the hypothalamus by dilated third ventricle [43, 44]. Baykan et al. reported bradycardia intraoperatively alone in 28.1% and the respective rates for asystole and for bradycardia following tachycardia as 0.5% and 12.4% with an overall incidence of arrhythmia involving bradycardia as 41% [45]. Derbent et al. encountered bradycardia in only 1 of the 24 patients for a short period during balloon inflation with possible temporary brain stem ischemia and subsequent bradycardia [46]. Fatal complications described in the literature are rare. However, injury of the basilar artery is the most feared intraoperative complication. This can lead to massive intraventricular and subarachnoid hemorrhage, hemiparesis, and midbrain damage. Other reported neurological complications are paralysis of III and VI nerves, delayed awakening, transitory mental confusion, headache, loss of memory, infection, convulsions, and pneumocephalus [47]. In a retrospective study on 223 adult and pediatric patients, the reported complications were hypothermia (25.1%), and cardiovascular complications (such as tachycardia 18.8%, bradycardia 11.3%, hypertension 16.1%, and hypotension 16.6%) were the commonly observed complications during intraoperative period both in pediatric and adult patients. At the end of the procedure, delayed arousal was observed in 17 patients and 19 patients requiring postoperative ventilatory support. Postoperative frequent complications included fever (34.1%), tachycardia (32.7%), and nausea and vomiting (18.8%). Potentially fatal complications such as intraoperative hemorrhage, air embolism, etc. were rare. Most of the complications were transient and self-limiting [48]. Hypothermia is a potential complication that can result in delayed awakening and disordered coagulation. However, some of the commonly observed postoperative complications

such as vomiting and respiratory problems are not specific to the procedure. Overall, a good long-term outcome after ETV is between 70% and 80% in most case series [49]. Another issue of interest following ETV is the postoperative electrolyte imbalance. Postoperative hyperkalemia has been reported following ETV [50]. The authors attributed hyperkalemia to a disturbance related to the hypothalamic nuclei situated in the floor of the third ventricle. However, the hyperkalemic response in these patients has been noticed in isolation, without any change in the serum sodium level. Also it was transient and late in onset which suggests a hormonal dysfunction. In that report we found that the authors were using lactated ringer solution for irrigation, which we believe has contributed to the hyperkalemic response following ETV. Derbent et al. reported in their study that although they were using lactated ringer solution for irrigation and 0.9% normal saline for intravenous fluid replacement during ETV, there was no significant difference between the pre- and postoperative serum sodium and potassium [46]. In our setup we are using normal saline and not lactated ringer for irrigation, and in spite of that, we have reported hypokalemia and hypernatremia in the second and third postoperative days following ETV with no clinical significance [51].

13.7 Conclusions

We conclude that ETV has become the most common procedure for treatment of obstructive hydrocephalus. With improvements in technology, neuroendoscopy in pediatric population is now routinely performed in more centers. Anesthesiologists should be aware of the intra- and postoperative complications secondary to ETV. Intraoperative bradycardia is the commonest arrhythmia that occurs during the procedure. Precautions like alerting the surgeon and pulling out the scope away from the floor of the third ventricle are enough procedures to revert bradycardia if it occurs. Any fluid and electrolyte abnormalities should be corrected before taking up for procedure. Attention should be given to problems specific to pediatric age group such as hypothermia and fluid overload. Though postoperative electrolyte imbalance occurs, we believe it has no clinical significance. We believe that either normal saline or lactated ringer solutions could be safely used for intraoperative irrigation with minimal postoperative clinical impact. Though it is a minimally invasive procedure, close observations of vital signs, serum electrolytes, as well as volume and temperature of the irrigation fluid besides close communication between anesthesiologist and surgeon are important precautions for better outcome.

Key Points

- Endoscopic third ventriculostomy is the surgical treatment of choice for obstructive hydrocephalus.
- Understanding the anatomy of the third ventricle floor is important to manage the intraoperative complications.
- General anesthesia is indicated for endoscopic third ventriculostomy.
- The most often reported intraoperative complication is bradycardia which occurs during the fenestration of the third ventricle floor.
- Alerting the surgeon and withdrawal of the endoscope are the preferred precautions to revert bradycardia.

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Anesthesia for Spine Surgery

14

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14.1 Principles

Spine surgery is often of critical importance for improvement in patients with traumatic or neoplastic disease that compromises neurologic function [1]. Although successful surgery has often been designated by the suggestion of improvement in quality of life due to functional gains, overall patient satisfaction can often be poor given the risk of acute deterioration after such procedures. It is paramount, therefore, to perform sufficient patient assessment for the prevention of intra- and postoperative complications as well as application of a circumspect informed consent to acknowledge the surgical risks in attempting to preserve the neurological autonomy of patients. Although a number of best practice protocols have been utilized to reduce complications and improve outcomes, efforts have been forged by individual surgeons or service lines and often based upon largely anecdotal experience rather than high-grade evidence. More recently, enthusiasm has grown for the development of enhanced recovery after surgery (ERAS) programs, which are both multidisciplinary and patient-centered and involve bundles of surgery-specific process measures evidenced to improve patient outcome following major surgery. Individual elements include preoperative education, multimodal analgesia management, early mobilization, and coordination of care, among others [2]. The anesthesiologist plays a vital role in spine surgery as a key facilitator to preoperative optimization, intraoperative anesthetic technician, and postoperative consultant. In this light, this chapter summarizes the evidence regarding anesthesia for patients undergoing spine surgery.

14.2 Enhanced Recovery Pathways

Surgery imposes significant stress and is associated with numerous complications. Despite best intentions, traditionally perioperative care has failed to comprehensively prevent injury following major surgery. In the last few decades, there has been an increased emphasis on patient-focused care. This has led to the development of multidisciplinary perioperative programs designed to reduce the length of hospitalization by integrating evidence-based process measures tailored to both the surgery and the patient alike. Although ERAS programs were originally created for abdominal surgery, multiple surgical disciplines have since integrated similar ERAS program efforts [2]. An ERAS program for lumbar spine surgery has also been created, utilizing hallmark objectives such as

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employment of measures known to both reduce surgical stress and provide multimodal analgesia [3]. The protocol implemented minimally invasive surgical techniques (endoscopic and percutaneous procedures) in combination with regional anesthesia. Prior trials have suggested that the use of ERAS programs for spine surgery decreases the average length of hospital stay from 6 to 2.9 days, reduces readmission rate from 7% to 3%, provides adequate analgesia while being opioid-sparing, and increases overall patient satisfaction [4, 5]. The assertion is that these results can be achieved by improving upon the selection and compliance with process measures at each stage of the patient's surgical journey, including the preadmission (comprehensive education in smoking cessation, nutritional screening, and more), preoperative (liberation of traditional fasting periods and routine carbohydrate loading), intraoperative (regional anesthetics, opting for sedation over general anesthesia, endoscopic decompression and percutaneous instrumentation, maintenance of normothermia and euvolemia), and postoperative (effective pain control, early mobilization, early oral intake, systematic auditing) phases [3]. Importantly, the application of these protocols has also been shown to reduce costs associated with surgical interventions and acute care, thereby increasing the value of care provided to each patient [2]. Despite the relatively small number of studies specific to spine surgery, early results are encouraging nonetheless, and centers around the world continue to institute ERAS programs for spine surgery.

14.3 Preoperative Assessment

One of the most important preoperative steps is the provision of clear oral and written descriptions of what the patient should expect and what role they play in recovery and of course informed patient consent for spine surgery. This interaction has been shown to have a significant impact on the effectiveness of perioperative care [6]. Surgery is offered to a patient based upon the presence of one of five common pathologies, which include traumatic lesions (vertebral fracture or penetrating injury), malignancy (either primary disease or metastatic with spinal instability or neurological compromise), infection (epidural abscess), congenital diseases (scoliosis acquired or secondary to hereditary diseases such as Duchenne syndrome, Becker syndrome), and degenerative diseases. Different surgical approaches are utilized for the correction of a particular spine defect, and a comprehensive understanding of the intended procedure is essential for appropriate preoperative assessment.

Zheng and Angst [7] have established three classes of surgical procedures—minor, major, and complex—based upon the magnitude of the procedure. Table 14.1 shows the procedures for each class of spine surgery and their most common indications. Much of the anesthetic management stems from this classification.

Preoperative detection of patients at high risk for developing short-term complications is useful to decrease the impact of factors that influence a delayed recovery. It is important to have presented the independent risk factors for perioperative complications that include age (>69 years), duration of surgery (>4 h), estimated blood loss (>1990 mL), ASA physical status (≥3), Charlson comorbidity index (>2), and fusion levels (≥10) [8]. All of these factors were integrated in a recent simple sliding scale to prioritize high-risk patients and to guide preoperative interventions. In that scale Yoshida et al. [8] recommended maximum acceptable operation times and blood losses for each age group and ASA (3 h and 500 mL for >75 y/o patients with ASA physical status ≥3; 4 h and 1000 mL for 70–79 y/o patients; 6 h for <70 y/o patients). Predictors of long-term outcomes have also been studied, the most commonly described being the duration of chronic low back pain and peroperative radiologic findings such as the Modic changes (types 1 and/or 2) [9]. Recent evidence have also shown that gradual preoperative reduction of opioid consumption should be included in protocols of patient optimization.

14.3.1 Airway Assessment

All patients undergoing spine surgery should have a preoperative evaluation of their airway regardless of the type of anesthesia. In particular, close attention should be paid to those with cervical spine diseases (e.g., cervical spine

Table 14.1 Description of the classes of spine surgery and common indications

Classes of surgery	Common indications
Minor spine surgery	
• ≤2 level decompression or microdiscectomy	Lumbar herniated disc
• 1–2 level anterior cervical discectomy and fusion	Cervical herniated disc or remove bone spurs
Major spine surgery	
• 3–4 level anterior or posterior cervical discectomy	Extensive cervical disc herniation
• 1–3 level anterior or lateral lumbar interbody fusion	Degenerative lumbar disc disease and revision of failed posterior fusion
• 1–2 level transforaminal lumbar interbody fusion	All degenerative pathologies (spondylolisthesis)
• Degenerative corpectomy	Decompress the spinal cord in degenerative, traumatic, or neoplastic conditions
Complex surgery	
• 6–18 level surgery with instrumentation	Idiopathic scoliosis and major deformity
• ≥3 level anterior and posterior fusion	High degree of spinal instability (e.g., fractures)
• Pedicle subtraction osteotomy	Hyperkyphosis, ankylosing spondylitis, flatback syndrome
• Vertebral column resection	Severe hyperkyphosis or scoliosis
• Resection of spinal cord tumor	Intramedullary tumors or spinal cord compression

lesions, degenerative disease) and other rheumatologic diseases such as rheumatoid arthritis and ankylosing spondylitis. These comorbidities may restrict head extension and therefore lead to difficulty with intubation or manual ventilation. Beyond a simple physical examination, one may consider imaging for assessment of cervical stability such as lateral or flexion/extension radiographic plain films. Magnetic resonance imaging can also be used to determine ligament damage that is not detectable by X-rays alone. These have often been obtained in preparation for surgery. The main objective is to identify patients who may represent those with "difficult airways" and to determine the appropriate intubation technique (direct laryngoscopy, video laryngoscopy, fiber-optic-assisted, or awake intubation). More details regarding intubation are found in the section entitled "Tracheal Intubation."

14.3.2 Cardiorespiratory System

All patients should have a complete assessment of their medical history, including formal inquiry regarding functional status. This is particularly important for spine surgery as many patients undergoing spine surgery have concomitant pulmonary comorbidities of obstructive or restrictive pathology. The primary screening method for structural deformities is a chest X-ray, and if necessary, one may consider obtaining computed tomography for better assessment. The indications for solicitation of pulmonary function tests include scoliosis, major thoracic spine deformity (severe thoracic kyphosis), moderate to severe pulmonary comorbidities (chronic obstructive disease, asthma, sleep apnea), and morbid obesity. Other specific preoperative cardiopulmonary considerations include patient education on the following aspects: (1) cessation of smoking at least 6 weeks prior to surgery is associated with quicker bone fusion and lower complication rates [10]; (2) improving enteral nutrition in underweight patients by increasing protein intake as well as the use of routine carbohydrate loading prior to surgery is recommended [3]; and (3) routine use of thromboembolic prophylaxis in the form of compression stockings or sequential compression devices is encouraged.

14.3.3 Neurological System

Neurological examination is necessary to record the patient's baseline clinical conditions to monitor for further deterioration during surgical and anesthetic planning and to prevent aspiration secondary to swallowing abnormalities. Additionally, it is important to evaluate the risk of developing intraoperative neurogenic

shock (tends to be present within 3 weeks of initial injury) and autonomic dysreflexia defined as an increase in systolic blood pressure of 25 mmHg when the injury has occurred above the T6 level.

14.4 Anesthesia Management

On the day of surgery, there are several important pre-anesthetic considerations. In the pre-anesthetic area, the anesthesia team should ensure the following: (1) adequate intravenous (IV) access, it is suggested that a 20G peripheral catheter is appropriate for minor surgery, 18G for major surgery, and central venous access may be considered for complex surgery with large volume resuscitation [7]; (2) antibiotic prophylaxis is administered 30 min prior to skin incision along with appropriate cleaning of the incision site (three betadine scrub brushes, six alcohol wipes on incision area, betadine ointment application) (this may be coupled with other routine antibiotic prophylaxis that adheres to regional or institutional profiles) [11]; (3) recent laboratory results are reviewed and interpreted, and appropriate blood products have been crossed and reserved if needed; (4) multimodal analgesia is administered in the form of preoperative acetaminophen, tramadol [5], and/or gabapentin, with consideration given to the addition of dexamethasone; and (5) appropriate equipment and expertise are available to perform selected spinal cord monitoring (sensory- or motor-evoked potential monitoring).

14.4.1 Induction

Induction agents should be selected based upon a number of considerations, including the patient's age, clinical condition, and comorbidities [12]. Induction with IV medications (e.g., propofol, fentanyl) is suitable for most patients. In patients without overt risk factors necessitating rapid sequence intubation (full stomach, severe gastric reflux), muscle relaxation may be obtained through the use of a short acting non-depolarizing neuromuscular blocking agent [1]. For procedures in which electrophysiologic monitoring of the spinal cord is necessary (e.g., lumbar interbody fusion due to scoliosis, correction of major deformity or spinal cord tumors), succinylcholine is preferred at intubation over non-depolarizing neuromuscular blocking agents as the latter may interfere with early monitoring of evoked potentials. Despite the utility of succinylcholine in terms of stability and rapid-onset action, it should be avoided in patients with muscular dystrophies (e.g., Duchenne syndrome, Becker syndrome, myotonic dystrophy), and its use should be cautioned in patients with denervation as a result of spinal cord lesions. These patients may have an increased number of perijunctional nicotinic receptors (with a peak at 8 days after injury) that can be hyper-stimulated with succinylcholine leading to hyperkalemia [13]. It is safe to administer this drug within 48 h of initial injury to the spinal cord, and evidence suggests risk dissipates around 9 months following injury [14].

14.4.2 Tracheal Intubation

Respiratory complications are the major cause of death after surgery in patients with severe myelopathy [15]. Therefore, airway security is extremely important in patients undergoing major surgery. There are three groups shown to have high frequency of difficult tracheal intubation, and the use of flexible fiber-optic laryngoscope with light sedation and topical anesthesia should be considered: (1) patients with severely limited range of cervical motion (e.g., rheumatoid arthritis, cranio-cervical fixation device); (2) significant cervical or upper thoracic spine deformity; and (3) excessive oropharyngeal swelling and deformity [15]. In cases where difficult tracheal intubation was not expected, fiber-optic intubation through the laryngeal mask airway is useful. Highly invasive cervical procedures (i.e., with maxillectomy or mandibular splits) may result in significant swelling of the soft tissues postoperatively, and, in some of those cases, an elective tracheostomy should be considered at the outset to secure the airway [15].

14.4.3 General Anesthesia

Balanced anesthesia is the most commonly used technique to provide general anesthesia for spine surgery. This combines intravenous agents (i.e., remifentanil) with volatile anesthetics (i.e., halogenates such as sevoflurane or desflurane and nitrous oxide). The combination of nitrous oxide and any halogenate is appropriate in order to reduce the impact of volatile anesthetics on spinal cord monitoring. General anesthesia is recommended for complex surgeries (≥4 h), patients with increased risk of bronchial aspiration, moderate to severe mental retardation, and a history of cerebrovascular diseases with motor sequela. Additional intraoperative measures such as the use of an intravenous infusion of ketamine (0.5 mg/kg bolus followed by an infusion rate of 0.25 mg/kg/min) or acetaminophen (15 mg/kg) have been shown to improve postoperative pain scores, reduce perioperative opioid consumption, and facilitate better extubation conditions [5, 16, 17].

14.4.4 Neuraxial Anesthesia

A safe alternative to anesthesia for lumbar spine surgery is the injection of local anesthetics into the subarachnoid space, one form of neuraxial anesthesia also known as a spinal block. A recent meta-analysis demonstrated that spinal anesthesia used for lumbar spine surgery is associated with a lower incidence of postoperative nausea and vomiting, lower intraoperative blood loss, and a shorter length of hospital stay [18]. Despite these advantageous characteristics, this technique requires a skilled approach when performing it on patients with spine pathologies as well as special attention to hemodynamics due to the potential for spinal block-induced hypotensive events [19]. Some reports advocate for the use of 3 mL of plain 0.5% bupivacaine, a modest dose by many standards, for lumbar discectomies in order to have fewer episodes of hypotension [15]. Intraoperative thoracic epidural anesthesia is an excellent adjuvant technique for spinal surgery or general anesthesia in lumbar and thoracic spine surgery and has been demonstrated to reduce intra- and postoperative use of opioids, decrease patient reported pain scores for up to 72 h, and facilitate earlier achievement of functional capacity after surgery [20–22].

14.4.5 Peripheral Blockage

The cervical plexus block, which has been recently demonstrated to have utility in anterior cervical discectomy, is gaining popularity for urgent cervical spine surgeries (i.e., odontoid fracture) [23]. This technique consists of performing a deep block of the muscular branches of the cervical plexus (i.e., three of the four straps of muscles of the neck, geniohyoid, paravertebral muscles, sternocleidomastoid, levator scapulae, scalenes, trapezius) and a superficial block of the innervation of the skin of the anterolateral aspect of the neck. An important advantage of this peripheral block is that it allows continuous neurologic monitoring and better hemodynamic stability in comparison to general anesthesia. Results from a trial comparing cervical plexus block to general anesthesia for anterior cervical discectomy concluded that combined (deep and superficial) cervical block is associated with a more rapid recovery and lower patient reported pain scores after surgery. Despite this, patients were also shown to prefer general anesthesia, which may be explained by the stress associated with awareness during the surgery itself rather than the success of the outcomes of the technique. Cervical block and general anesthesia may be combined, and studies have shown that this strategy is effective for improving the early quality of recovery, reduction in dose of various anesthetics, facilitation of hemodynamic stability, and relief of postoperative pain [24–26].

14.5 Intraoperative Considerations

14.5.1 Blood Loss

A robust amount of evidence advocates for the use of tranexamic acid (TXA) to reduce intraoperative blood loss [27, 28]. TXA, an antifibrinolytic agent, is recommended for major spine

surgeries or minor spine surgeries (See Table 14.1) with significant patient risk factors for transfusion (i.e., age ≥50 years, smokers, preoperative hemoglobin <12 g/dL, fusion of more than 2 levels, metastatic lesions from renal cell carcinoma and multiple myeloma). Dosing requires a medication load (10 mg/kg bolus), followed by intravenous maintenance (1 mg/kg/h). Evidence has shown this strategy to be both safe and effective to reduce intraoperative and postoperative blood loss as well as to decrease blood transfusions without the presence of significant adverse events (e.g., deep venous thrombosis, hematoma, infection) [28, 29]. In anemic patients, the most widely accepted threshold to consider preoperative blood transfusion is a hematocrit (Hct) of 24% or hemoglobin (Hb) of 8 g/dL for major and complex spinal surgeries. During surgery it is also important to calculate the allowable blood loss (based on the formula: weight*average blood volume*[initial Hct – threshold Hct]/mean Hct) in order to prepare additional blood transfusion when real blood loss exceeds the allowable blood loss. Other considerations include the use of other blood products (fresh frozen plasma, platelets, and cryoprecipitate).

Preoperative identification of anemia has been shown to be an independent predictor of pulmonary complications (i.e., pneumonia, unplanned reintubation, and prolonged duration of ventilator-assisted respiration, return to operating room, and extended length of stay >5 days after posterior cervical fusion) [30]. Therefore, preoperative correction of anemia may serve to prevent such complications. There are several methods that have demonstrated efficacy to reduce the requirement for allogeneic blood such as the administration of erythropoietin (if anemia due to chronic kidney disease) or iron loading. Intraoperatively, the most frequently used methods to decrease allogeneic blood transfusions include pharmacologic therapy with tranexamic acid or aminocaproic acid, the use of pre-deposit autologous transfusion [31], and the use of intraoperative normovolemic hemodilution in which blood volume is removed at the beginning of surgery and replaced with crystalloid. This is theorized to both hemodilute the patient's blood (lower red cell mass is lost with subsequent bleeding) and allow for autologous transfusion with preserved factors and platelets at the end of the surgery [32]. Postoperatively, fibrin sealants, shed blood salvage, or intravenous iron can be used for postoperative anemia, especially when patients refuse or have contraindication to blood product transfusions [31]. Usually the recommended threshold for postoperative transfusion is lower (Hb < 7) but also tends to depend on the patient comorbidites.

14.5.2 Hemodynamic Parameters

Hypotension is one of the most common anesthetic-induced events in spine surgery and an important cause of intra- and postoperative complications (e.g., cardiac arrest, perioperative visual loss, acute kidney injury). Although there is controversy regarding the optimal blood pressure, a minimum systolic blood pressure of 84 mmHg or maintenance and mean arterial blood pressure within 24% of the estimated baseline pressure are accepted recommendations based upon prior study [33]. A stricter (and more elevated) blood pressure goal is likely necessary for patients with traumatic spine lesions (goal of mean arterial blood pressure should be 80–90 mmHg, especially if the injury is located at upper thoracic segments or cervical spine). Intraoperative blood pressure management can be achieved through three sequential steps: (1) use of a minimal amount of volatile anesthetic as is necessary (0.7–1.0 MAC is often sufficient); (2) use of sufficient fluids to restore euvolemia and maintain adequate preload (see next item "Fluid Management"); and (3) consideration of a low-dose vasopressor (phenylephrine at a rate ≤0.4 mcg/kg/min). Providers should be reminded to urgently treat anaphylactic reactions to surgical materials, (e.g., gelatin-containing hemostatic agents) characterized by a sudden, marked hemodynamic changes, with epinephrine [34].

As for many types of surgery, deliberate hypotension has been utilized for spine surgery to both reducing the blood loss and transfusion requirements [35, 36]. This technique often requires invasive continuous blood pressure monitoring and access to a rapid laboratory assay to monitor hematocrit and markers of tissue hypoperfusion

(e.g., base deficit or lactate). General recommendations for deliberate hypotension are to maintain the systolic blood pressure 20–30% below baseline (in the range of 80–90 mmHg) or a mean arterial blood pressure between 60–65 mmHg during surgical dissection [36]. The most commonly used drugs to achieve this blood pressure goal are increased doses of volatile anesthetics and continuous infusion of rapid-acting vasodilator such as nitroglycerin, esmolol, nicardipine, or fenoldopam [37]. Although this technique has a long record of safety, it is not advisable in patients with chronic hypertension or those likely to be vulnerable to ischemic complications (e.g., diabetics, coronary artery disease, stroke, chronic renal failure, etc.) [36].

14.5.3 Fluid Management

Maintenance fluid therapy and recovery of intraoperative fluid losses are critical aspects to prevent delayed recovery and poor postoperative outcomes [38]. The goal of a comprehensive fluid management strategy is maintenance of euvolemia. This is reasonably achieved through the use of crystalloids (principally ringer's lactate and plasmalyte for maintenance fluid therapy). One may consider the judicious use of colloids (e.g., albumin 5%) to expand intravascular volume and theoretically avoid soft tissue edema, especially in major and complex surgeries. Intraoperative fluid losses during surgery depend on the degree of surgical trauma (minor, 2–3 mL/kg; major, 4–6 mL/kg; complex, 7–8 mL/kg) and blood losses. Fluid status can be measured invasively (i.e., transesophageal echocardiography) or noninvasively with cardiac output monitors, and studies in other surgical specialties have demonstrated the effectiveness of minimizing fluid loss when these types of monitoring are implemented in conjunction with a goal-directed fluid protocol [39]. A similar algorithm for goal-directed fluid therapy has been shown to be beneficial in spine surgery and consists of a rapid infusion of Ringer's lactate (maximum 10 mL/kg) if the patient's stroke volume variation (SVV) >12% with concomitant hypotension [40]. This technique is associated with a reduction in blood transfusions, better postoperative respiratory performance, shorter ICU stay, and faster recovery. Esophageal Doppler has also been used to optimize fluid management during spine surgery, and this has shown a significant reduction in intraoperative hypotensive episodes [41]. More studies are needed to provide formal recommendations regarding the use of a specific device or intraoperative fluid management protocol.

14.5.4 Monitoring Spinal Cord

The risk of nervous injury and subsequent neurological complications during spine surgery (e.g., paraplegia, paresis, cauda equina) makes monitoring spinal cord functions for early detection of functional deterioration crucial to the procedure [42]. There are five monitoring techniques that can be used to evaluate spinal cord function. These techniques include a test for intact pyramidal tracts (using motor-evoked potentials), spinothalamic tracts (somatosensory-evoked potentials), or integrity of any segmental spine (spinal cord-evoked potentials), while the two remaining techniques (wake-up test and ankle-clonus test) have low utility due to inherent limitations. Although there is no consensus regarding which specific spine surgeries require cord-specific monitoring, it is highly recommended that monitoring be employed in spinal fusion for scoliosis (class IIA of evidence for the prevention of neurologic deficits) [43], correction of major deformities, and resection of spinal cord tumors. In these procedures it is also recommended to use ≤0.5 MAC of any halogenate anesthetic combined with nitrous oxide 50% to avoid the dose-dependent reduction in somatosensory-evoked potential amplitude. Total intravenous anesthesia has lesser impact on the spinal cord monitoring and is recommended for surgery during which continuous somatosensory-evoked potentials are to be recorded. Mean arterial blood pressure less than 60 mmHg is another factor that could result in false-positive signal changes. Please refer to Table 14.2 for the types of monitoring techniques, common indications, advantages, and disadvantages.

Table 14.2 Summary of common indications, advantages, and disadvantages of various monitoring techniques

Type of monitoring	Indications	Advantages	Disadvantages
Somatosensory-evoked potentials	Short-latency technique is first choice during spine surgery	Unaffected by anesthesia and good indicator of spinal cord function	Antinoise measures are necessary because of the small amplitude of the signal
Motor-evoked potentials	Complement spinal function monitoring	Minimum interruption of surgery and indicates the function of the pyramidal tract	Easily affected by general anesthesia and muscle relaxants (train stimulation method required)
Spinal cord-evoked potentials	Need for real-time information of spinal function	Evaluates spinal segments function	Invasive technique with electrode catheter into the yellow ligament and epidural space
Stagnara wake-up test	In cases of difficult intraoperative electrophysiological monitoring	Definitive method for spinal function monitoring	Sufficient comprehensive is necessary, can only be assessed when patients are awake, excessive movements can be detrimental for spinal injuries
Ankle clonus test	If electrophysiological monitoring is not available	Easy to administer and very high sensitivity and specificity	Applicable only during emergence from anesthesia

14.6 Postoperative Considerations

During the immediate postoperative period, frequent neurological assessment of the patient is necessary in order to detect early deterioration. Cognitive impairment is the most common postoperative complication. It can persist for several days after spine surgery, and chief among the potential triggers is thought to be short periods of intraoperative brain oxygen desaturation. In recent years, randomized trials have shown promising results through the use of intraoperative cerebral oximetry as measured by near-infrared spectroscopy (NIRS) [44]. Intraoperative treatments designed to reduce rates in intraoperative brain desaturation have shown reductions in subsequent postoperative cognitive impairment [45]. Others have suggested the avoidance of prone positioning in cervical spine surgery due to the risk of desaturation in elderly patients [46]. Postoperative delirium is another common complication, affecting between 12 and 24% of elderly patients undergoing spine surgery. This complication is typically reversible and has a multifactorial etiology (prolonged surgery >3 h, greater blood loss, intraoperative hypercapnia, and hypotension). Several preventive therapies have been reviewed, including the use of dexmedetomidine as a sedative agent, reduction in the frequency/duration of intraoperative hypotension, limitation of blood loss, and reduction of anesthetic duration [47]. At least one study has suggested that a single dose of preoperative nimodipine may prevent delirium [48]. Treatment of acute postoperative delirium is complex, but there is evidence to show that the combination of haloperidol and quetiapine may allow for faster recovery, decreased agitation, and decreased length of hospital stay compared to the use of haloperidol alone [47].

A rare but catastrophic postoperative complication is visual loss, which occurs in less than 0.2% of spine surgeries [33]. This is usually secondary to ischemic optic neuropathy (89% of the cases) or central retinal artery occlusion (11% of the cases) [49]. High-risk patients are defined as those who experience substantial blood loss (>1 L) during prolonged spine procedures (>6 h) in a prone positioning (posterior surgical approach) [33]. Therefore, it is suggested that in order to effectively avoid perioperative visual loss, the reduction in surgical time and blood loss is necessary [50]. Excessive crystalloid administration in prone

positioning may also increase the risk of perioperative visual loss; the volume is recommended to be to no more than 40 mL/kg for the entire operative procedure, regardless of duration [51]. If additional fluid is necessary, providers may consider the administration of colloids or vasopressors to augment perfusion pressure. An additional factor that is attributable to visual loss is prolonged pressure on the eye while in a prone position. The practice advisory from the American Society of Anesthesiologists (ASA) recommends that for high-risk patients, intravascular volume should be monitored continually, anemia should be corrected preoperatively, and direct pressure on the eye should be avoided [33]. Another rare complication is the development of an anterior cervical hematoma. This should always be suspected in patients with postoperative dysphagia, stridor, or dyspnea after anterior cervical spine surgeries. The airway of these patients must be secured quickly, often through awake intubation in a sitting position, and patients are likely to remain intubated for >24 h to facilitate surgical exploration and recovery.

Another important objective for the postoperative period is to achieve adequate analgesia. Multimodal analgesia, whereby several medications are acting upon unique receptor types, can facilitate discontinuation of intravenous opioids while achieving effective pain control. This practice has been shown to facilitate early mobilization and accelerated postoperative recovery [52]. One of the recommended analgesic regimens includes preoperative gabapentin and acetaminophen, intraoperative low-dose ketamine and acetaminophen, and postoperative patient-controlled analgesia supplemented with gabapentin, acetaminophen, and a nonsteroidal anti-inflammatory agent such as ketorolac [4].

14.7 Summary

Anesthesiologists are a critical part of the multidisciplinary perioperative team for spine surgery. In order to provide evidence-based care, anesthesiologists are encouraged to perform a rigorous preoperative assessment, a comprehensive, goal-directed intraoperative anesthetic, and a thoughtful, multimodal postoperative regimen. This chapter has introduced the growing evidence in support of ERAS for spine surgery, the use of neuraxial anesthetic techniques in spine procedures, and the movement toward limitation of opioids in routine care. A graphical anesthetic framework is proposed in this chapter to provide the readers an updated summary on how to approach patients undergoing spine surgery (Fig. 14.1).

Key Points

- General anesthesia is currently the mainstay anesthetic option for major and complex spine surgeries, while neuraxial anesthesia has shown to be a safe and advisable alternative for minor lumbar spine surgeries.
- Succinylcholine is preferred for muscle relaxation at intubation over nondepolarizing neuromuscular blocking agents if electrophysiologic monitoring is planned.
- Intraoperative neuromonitoring plays a critical role for neurological success in spinal fusion for scoliosis, correction of major deformities, and resection of spinal cord tumors.
- Tranexamic acid is recommended for major spine surgeries or minor spine surgeries with significant patient risk factors for transfusion (i.e., age ≥50 years, smokers, preoperative hemoglobin <12 g/dL, fusion of more than two levels).
- Avoid postoperative visual loss by limiting crystalloid infusion (no more than 40 mL/kg for the entire surgery) and reducing pressure on the eye while in a prone position.

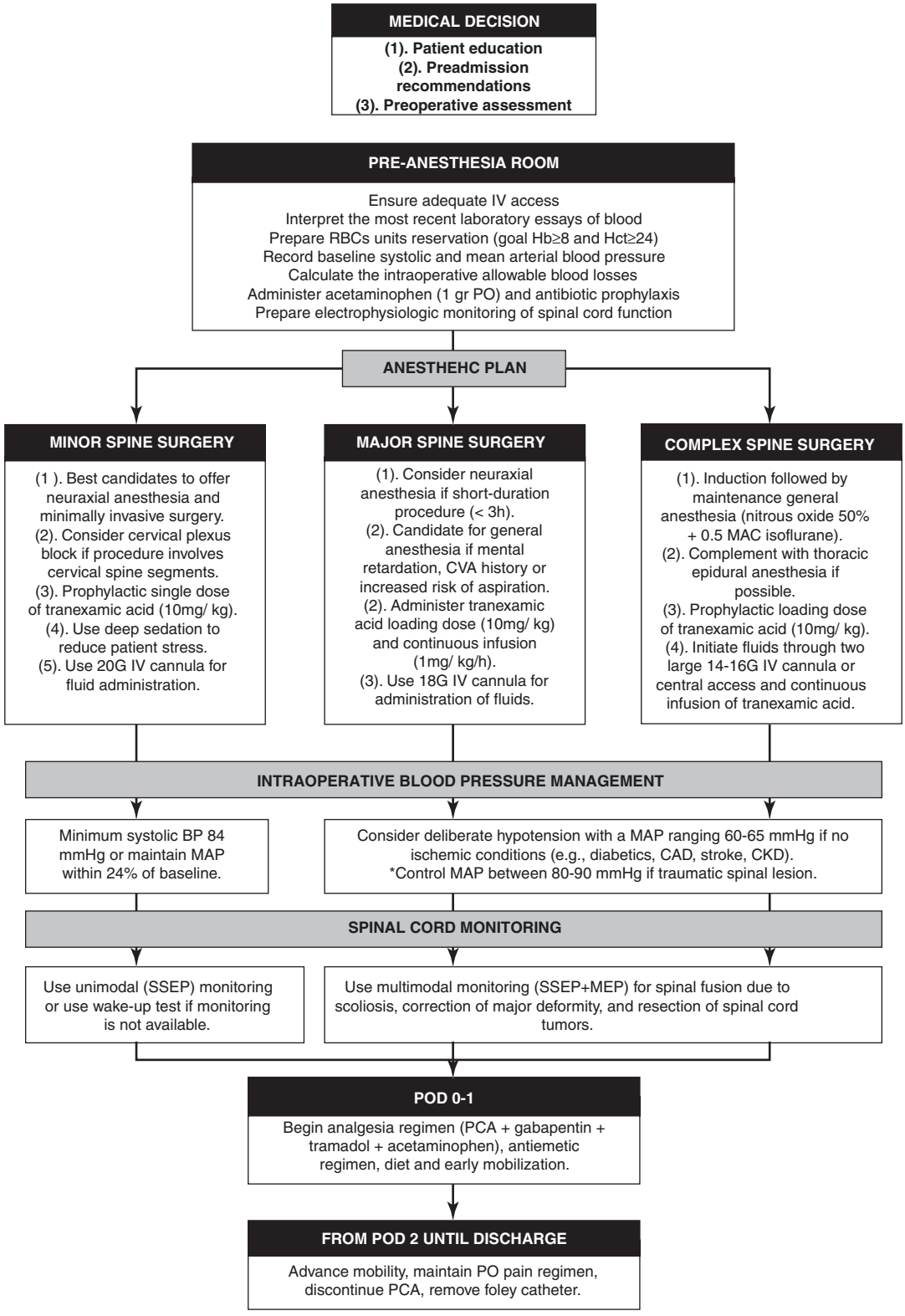

Fig. 14.1 Summary of anesthetic management of patients undergoing spine surgery based upon ERAS programs

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Anesthesia for Traumatic Brain Injury

15

Rachel Kutteruf

15.1 Introduction

Traumatic brain injury (TBI) is a significant public health issue and a leading cause of death and disability worldwide [1]. In the United States, TBI contributes to approximately 30% of all injury-related deaths and places a substantial burden on the healthcare system [2]. In 2013, roughly 2.8 million people in the United States were diagnosed with TBI, resulting in approximately 282,000 hospitalizations and 56,000 deaths [2]. TBI occurs most commonly in young children (age 0–4 years), adolescents and young adults (age 15–24 years), and the elderly (age ≥ 75 years) [2]. Across all ages, males are more likely to suffer TBI than females [2]. The most common mechanisms of TBI in the United States are falls, being struck by or against an object, and motor vehicle collisions [2]. Recently, there has been increased awareness and concern about concussions (also referred to as mild traumatic brain injury), especially in regard to athletes and the pediatric population [3]. In the United States, it is estimated that up to 3.8 million concussions occur per year during recreational activities and competitive sports [4], and as many as 50% of concussions may go unreported [4].

Given the prevalence of TBI and the significant morbidity and mortality associated with these injuries, anesthesia providers will frequently be faced with the management of these patients. The main goals of caring for this patient population are to stabilize the patient and prevent secondary neurologic injury [5]. This chapter will focus on the perioperative management of patients with traumatic brain injury, including initial evaluation, intraoperative management, prevention of secondary injury, and anesthetic considerations for patients with concussions. The critical care management of patients with traumatic brain injury is discussed in a separate chapter.

15.2 Pathophysiology

There are numerous mechanisms of TBI, including motor vehicle collisions, falls, gunshot wounds, athletics, and combat injuries [6]. TBI severity ranges from mild to severe, with variations in associated morbidity and mortality across this spectrum [7]. The severity of a head injury can be classified based on the Glasgow Coma Scale (GCS), which defines neurologic impairment in terms of eye opening, speech, and motor function (Table 15.1) [8]. Severe TBI is defined as an initial GCS score ≤8 persisting for 6 h or more [8]. Trauma may result in a variety of neurologic injuries, ranging from subtle changes in molecular

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Table 15.1 Modified Glasgow Coma Scale[a]

Feature	Point(s)
Eye opening	
Spontaneously	4
To verbal command	3
To pain	2
None	1
Best verbal response	
Oriented, conversing	5
Disoriented, conversing	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	1
Best motor response	
Obeys verbal commands	6
Localizes to pain	5
Flexion or withdrawal	4
Abnormal flexion (decorticate)	3
Extension (decerebrate)	2
No response (flaccid)	1

From Phan RD, Bendo AA. Perioperative management of adult patients with severe head injury. In: Cottrell JE, Patel P, editors. Cottrell and Patel's neuroanesthesia. 6th ed. New York: Elsevier; 2017. Used with permission from Elsevier

[a]Total scores: mild head injury = 13–15 points; moderate = 9–12 points; severe ≤8 points

signaling and cellular function to extensive tissue injury, such as hemorrhage and contusions [6]. Primary brain injury is due to the mechanical impact itself, and when severe, results in increased intracranial pressure (ICP) and reduced cerebral perfusion [9]. TBI also causes blood-brain barrier (BBB) dysfunction and impaired neurologic homeostasis [5], which lead to inflammation, cerebral edema, and further increases in ICP and reductions in cerebral perfusion pressure (CPP) [9]. The primary neurologic injury can also lead to alterations in the function of other organ systems, such as acute kidney injury, respiratory failure, and cardiac injury (Table 15.2) [5, 9–11]. Trauma patients often have other injuries, such as orthopedic fractures, intra-abdominal injuries, and spinal cord compromise [5]. These coexisting injuries, coupled with BBB dysfunction and neurologic inflammation, contribute to the development of secondary neurologic injury [5, 6].

Table 15.2 Effects of traumatic brain injury on other organ systems

Cardiovascular
• Sympathetic nervous system overactivity – Hypertension, tachycardia, increased cardiac output – Electrocardiogram changes mimicking myocardial ischemia • Neurogenic stunned myocardium/Takotsubo stress cardiomyopathy – Left ventricular dysfunction – Electrocardiogram changes: ST-segment elevation, T-wave inversion – Elevated cardiac enzymes: CK-MB, troponin • Cushing response: hypertension, bradycardia • Arrhythmias • Hemorrhagic shock • Hypotension
Respiratory
• Upper airway obstruction/inability to protect airway • Abnormal respiratory patterns: apnea, hypoventilation • Neurogenic pulmonary edema • Acute respiratory distress syndrome (ARDS) • Pneumonia • Pulmonary embolism • Pulmonary injuries: pneumothorax, hemothorax, pulmonary contusion, flail chest, aspiration, atelectasis
Musculoskeletal
• Cervical spine injury • Long bone or pelvic fractures
Gastrointestinal
• Aspiration risk due to "full stomach" • Stress-induced gastric ulcers (Cushing's ulcers) • Intra-abdominal injuries • Alterations in mucosal permeability and gastrointestinal absorption
Metabolic/endocrine
• Hyperglycemia, insulin resistance • Hypokalemia • Hyponatremia • Pituitary dysfunction • Diabetes insipidus • Syndrome of inappropriate antidiuretic hormone secretion (SIADH) • Increased catecholamine levels • Increased caloric demand
Hematologic
• Coagulopathy • Disseminated intravascular coagulation (DIC)
Other
• Sepsis, septic shock • Acute kidney injury • Autonomic dysfunction: hypertension, tachycardia, tachypnea, fever

Table 15.3 Time course and mechanisms of secondary insults in traumatic brain injury (Reprinted from Perioperative management of adult traumatic brain injury. Sharma D, Vavilala MS, pages 333–46, 2012, with permission from Elsevier/Anesthesiology Clinics 2012 June;30(2):333–46)

Secondary insult	Early causes	Delayed causes
Hypoxemia	Aspiration Apnea Pneumothorax Pulmonary contusion Endobronchial intubation Neurogenic pulmonary Edema	Adult respiratory distress syndrome Ventilator-acquired pneumonia Transfusion-related acute lung injury Pulmonary embolism
Hypotension	Associated high spinal cord injury Long bone fracture Thoracic/abdominal bleeding	Shock Sepsis
Hypercarbia	Apnea Brainstem injury Inadequate ventilation	Iatrogenic (opioids) Pneumonia
Hypocarbia	Unwanted hyperventilation	Unwanted hyperventilation
Hyperglycemia	Stress	Persistent/new onset
Seizures	Electrolyte abnormalities Hypoglycemia	Syndrome of inappropriate antidiuretic hormone
Vasospasm	–	In patients with traumatic subarachnoid hemorrhage
Intracranial hypertension	Mass effect of hematoma Herniation	Cerebral edema

15.2.1 Secondary Neurologic Injury

Secondary neurologic injury is neurologic compromise not directly caused by the mechanical trauma of TBI but rather resulting from physiologic perturbations following the initial injury that result in cerebral hypoxia and ischemia [8, 9]. Hypotension and hypoxemia are the two most important secondary insults that can worsen patient prognosis [9]. Systolic blood pressure (SBP) <90 mmHg in adults and PaO_2 <60 mmHg are independently associated with increased morbidity and mortality in TBI patients [9]. Additional secondary insults include hyper- and hypoglycemia, hyper- and hypocapnea, and elevated ICP (Table 15.3) [9].

Secondary injury can occur hours to days to months after the initial trauma and adversely affects outcomes [5, 6, 8, 9]. While surgery and anesthesia are often necessary components of TBI management, they can also predispose to additional secondary insults [9]. Thus, the perioperative period is a critical time for optimizing outcomes in TBI patients. Goals in the perioperative period include resuscitation and stabilization of the patient, as well as correcting and preventing additional physiologic perturbations that can lead to secondary neurologic injury [5, 9].

15.3 Head Injury Guidelines

In 1995, in an effort to standardize care and improve outcomes in TBI, the Brain Trauma Foundation collaborated with the American Association of Neurological Surgeons to create guidelines for the management of patients with severe traumatic brain injury [12]. The fourth, and most recent, edition of these guidelines was published in 2016 [13]. It provides 28 evidence-based recommendations to help guide TBI management in regard to treatment, monitoring, and thresholds (Tables 15.4, 15.5, and 15.6). Recommendations were made only when there was sufficient evidence to do so, and as such, the guidelines are not meant to serve as a complete clinical protocol. Rather, these guidelines are meant to supplement consensus and clinical judgment in the development of treatment protocols [13]. Adherence to these guidelines is variable, but research has demonstrated a causal relationship between guideline adherence and improved outcomes [14]. With the

Table 15.4 Updated treatment recommendations[a] (From Carney M, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Brain Trauma Foundation. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017 Jan 1;80(1):6–15. Used by permission of Oxford University Press/Congress of Neurological Surgeons)

Topic	Recommendations
Decompressive craniectomy	Level IIA
	• **Bifrontal DC is not recommended to improve outcomes as measured by the GOS-E score at 6 month post-injury in severe TBI patient with diffuse injury (without mass lesions) and with ICP elevations to values >20 mmHg for more than 15 min within a 1-h period that are refractory to first-tier therapies. However, this procedure has been demonstrated to reduce ICP and to minimize days in the ICU**
	• **A large frontotemporoparietal DC (not <12 × 15 cm or 15 cm diameter) is recommended over a small frontotemporoparietal DC for reduced mortality and improved neurologic outcomes in patients with severe TBI**
	*The committee is aware that the results of the RESCUEicp trial were released soon after the completion of these guidelines. The results of this trial may affect these recommendations and may need to be considered by treating physicians and other users of these guidelines. We intend to update these recommendations if needed. Updates will be available at https://braintrauma.org/coma/guidelines
Prophylactic hypothermia	Level IIB
	• **Early (within 2.5 h), short-term (48 h post-injury), prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury**
Hyperosmolar therapy	Recommendations from the prior (third) edition not supported by evidence meeting current standards
	Mannitol is effective for control of raised ICP at doses of 0.25–1 g/kg body weight. Arterial hypotension (systolic blood pressure <90 mmHg) should be avoided
	Restrict mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes
Cerebrospinal fluid drainage	Level III
	• **An EVD system zeroed at the midbrain with continuous drainage of CSF may be considered to lower ICP burden more effectively than intermittent use**
	• **Use of CSF drainage to lower ICP in patients with an initial GCS <6 during the first 12 h after injury may be considered**
Ventilation therapies	Level IIB
	• Prolonged prophylactic hyperventilation with $PaCO_2$ ≤25 mmHg is not recommended
	Recommendations from the prior (third) edition not supported by evidence meeting current standards
	Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP
	Hyperventilation should be avoided during the first 24 h after injury when CBF is often reduced critically
	If hyperventilation is used, SjO_2 or $BtpO_2$ measurements are recommended to monitor oxygen delivery
Anesthetics, analgesics, and sedatives	Level IIB
	• Administration of barbiturates to induce burst suppression as measured by EEG as prophylaxis against the development of intracranial hypertension is not recommended
	• High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy
	• Although propofol is recommended in the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes. Caution is required as high-dose propofol can produce significant morbidity

Table 15.4 (continued)

Topic	Recommendations
Steroids	Level I
	• The use of steroids is not recommended for improving outcomes or reducing ICP. In patient with severe TBI, high-dose methylprednisolone was associated with increased mortality and is contraindicated
Nutrition	Level IIA
	• **Feeding patients to attain basal caloric replacement at least by the fifth day and at most by the seventh day post-injury is recommended to decrease mortality**
	Level IIB
	• **Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia**
Infection prophylaxis	Level IIA
	• Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit is thought to outweigh the complications associated with such a procedure. However, there is no evidence that early tracheostomy reduces mortality or the rates of nosocomial pneumonia
	• **The use of PI oral care is not recommended to reduce ventilator-associated pneumonia and may cause an increased risk of acute respiratory distress syndrome**
	Level III
	• Antimicrobial-impregnated catheters may be considered to prevent catheter-related infections during extraventricular drainage
Deep vein thrombosis prophylaxis	Level III
	• LMWH or low-dose unfractioned heparin may be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage
	• In addition to compression stockings, pharmacologic prophylaxis may be considered if the brain injury is stable and the benefit is considered to outweigh the risk of increased intracranial hemorrhage
	• There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis
Seizure prophylaxis	Level IIA
	• Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS
	• Phenytoin is recommended to reduce the incidence of early PTS (within 7 days of injury), when the overall benefit is thought to outweigh the complications associated with such treatment. However, early PTS have not been associated with worse outcomes
	• **At the present time, there is insufficient evidence to recommend levetiracetam compared with phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity**

$BtpO_2$ brain tissue O_2 partial pressure, *CBF* cerebral blood flow, *CSF* cerebrospinal fluid drainage, *DC* decompressive craniectomy, *EEG* electroencephalogram, *EVD* external ventricular drainage, *GCS* Glasgow Coma Scale, *GOS-E* Glasgow Outcome Scale-Extended, *ICP* intracranial pressure, *ICU* intensive care unit, *LMWH* low-molecular-weight heparin, *$PaCO_2$* partial pressure of arterial carbon dioxide, *PI* povidone-iodine, *PTS* posttraumatic seizures, *RESCUEicp trial* Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP trial, *SjO_2* jugular venous oxygen saturation, *TBI* traumatic brain injury

[a]Bold: New or revised recommendations

Table 15.5 Updated monitoring recommendations[a] (From Carney M, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Brain Trauma Foundation. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017 Jan 1;80(1):6–15. Used with permission from Oxford University Press/Congress of Neurological Surgeons)

Topic	Recommendations
Intracranial pressure monitoring	Level IIB
	• **Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality**
	Recommendations from the prior (third) edition not supported by evidence meeting current standards
	ICP should be monitored in all salvageable patients with a TBI (GCS 3–8 after resuscitation) and an abnormal CT scan. An abnormal CT scan of the head is one that reveals hematomas, contusions, swelling, herniation, or compressed basal cisterns
	ICP monitoring is indicated in patients with severe TBI with a normal CT scan if ≥2 of the following features are noted at admission: age >40 years, unilateral or bilateral motor posturing, or SBP <90 mmHg
Cerebral perfusion pressure monitoring	Level IIB
	• **Management of severe TBI patients using guideline-based recommendations for CPP monitoring is recommended to decrease 2-week mortality**
Advanced cerebral monitoring	Level III
	• Jugular bulb monitoring of $AVDO_2$, as a source of information for management decisions, may be considered to reduce mortality and improve outcomes 3 and 6 months post-injury

$AVDO_2$ arteriovenous oxygen content difference, *CPP* cerebral perfusion pressure, *CT* computed tomography, *GCS* Glasgow Coma Scale, *ICP* intracranial pressure, *SBP* systolic blood pressure, *TBI* traumatic brain injury
[a]Bold: New or revised recommendations

Table 15.6 Updated recommendations: thresholds[a] (From Carney M, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Brain Trauma Foundation. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017 Jan 1;80(1):6–15. Used with permission from Oxford University Press/Congress of Neurological Surgeons)

Topic	Recommendations
Blood pressure thresholds	Level III
	• **Maintaining SBP at ≥100 mmHg for patients 50–69 years old or at ≥110 mmHg or above for patients 15–49 or >70 years old may be considered to decrease mortality and improve outcomes**
Intracranial pressure thresholds	Level IIB
	• **Treating ICP >22 mmHg is recommended because values above this level are associated with increased mortality**
	Level III
	• A combination of ICP values and clinical and brain CT findings may be used to make management decisions
	*The committee is aware that the results of the RESCUEicp trial were released after the completion of these guidelines. The results of this trial may affect these recommendations and may need to be considered by treating physicians and other users of these guidelines. We intend to update these recommendations if needed. Updates will be available at https://braintrauma.org/coma/guidelines

Table 15.6 (continued)

Topic	Recommendations
Cerebral perfusion pressure thresholds	Level IIB
	• **The recommended target CPP value for survival and favorable outcomes is between 60 and 70 mmHg. Whether 60 or 70 mmHg is the minimal optimal CPP, threshold is unclear and may depend upon the autoregulatory status of the patient**
	Level III
	• Avoiding aggressive attempts to maintain CPP >70 mmHg with fluids and pressors may be considered because of the risk of adult respiratory failure
Advanced cerebral monitoring thresholds	Level III
	• Jugular venous saturation of <50% may be a threshold to avoid in order to reduce mortality and improve outcomes

CPP cerebral perfusion pressure, *CT* computed tomography, *ICP* intracranial pressure, *RESCUEicp trial* Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP trial, *SBP* systolic blood pressure
[a]Bold: New or revised recommendations

Table 15.7 Canadian CT head rule (Reprinted from The Lancet, volume 357, Stiell IG, Wells GA, Vandemheen K, Clement C, Lesiuk H, Laupacis A, et al. The Canadian CT head rule for patients with minor head injury, pages 1391–6, 2001, with permission from Elsevier)

CT head rule is only required for patients with minor head injuries with any one of the following:
High risk (for neurologic intervention) – GCS score <15 at 2 h after injury – Suspected open or depressed skull fracture – Any sign of basal skull fracture (hemotympanum, "raccoon" eyes, cerebrospinal fluid otorrhoea/rhinorrhoea, Battle's sign) – Vomiting ≥2 episodes – Age ≥ 65 years
Medium risk (for brain injury on CT) – Amnesia before impact >30 min – Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 ft or five stairs)
Minor head injury is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13–15

fourth edition of these guidelines, the Brain Trauma Foundation is transitioning to a "Living Guidelines model" in which the literature will be constantly evaluated and updates to the recommendations will be made as the evidence warrants, rather than publishing updated editions every few years [13]. Specific recommendations from these guidelines will be discussed throughout this chapter.

15.4 Evaluation

Trauma patients undergo initial assessment and stabilization upon arrival to the emergency department. Not all patients with minor head injuries (GCS 13–15) require radiographic evaluation. Two slightly different sets of criteria, the Canadian CT Head Rule and the New Orleans Criteria, are widely used to determine which of these patients require computed tomography (CT) scanning based on clinical findings, patient factors, and the mechanism of injury (Tables 15.7 and 15.8) [15, 16]. All patients with moderate or severe head injuries require radiographic evaluation. Noncontrast multidetector CT is the test of choice in TBI because it is widely available, fast, and highly accurate for detecting injuries that require urgent or emergent neurosurgical intervention, such as hemorrhage, herniation, and hydrocephalus [17]. MRI is generally not used for the initial evaluation of TBI because it is less widely available, less sensitive for fractures, more time-consuming, relatively

Table 15.8 New Orleans criteria [16]

CT is recommended for patient with head trauma and any of these factors
– Headache
– Vomiting
– Age > 60 years
– Drug or alcohol intoxication
– Short-term memory deficits
– Physical evidence of trauma above the clavicles
– Seizure

CT computed tomography

more expensive, and incompatible with some medical devices and metallic foreign bodies [17]. Intravenous contrast is only indicated in cases of suspected vascular injury. Risk factors for traumatic vascular injury, many of which can be identified on noncontrast CT, include skull base fractures, LeFort II and III facial fractures, high cervical spine fractures, epistaxis, GCS ≤8, and traumatic axonal injury [17].

Indications for neurosurgical intervention in TBI include evacuation of mass lesions (e.g., hematomas), repair of vascular injuries, removal of foreign bodies, and decompressive craniectomy for elevated ICP. "Primary" decompressive craniectomy is performed in the early phase after TBI for evacuation of intracranial hematomas. "Secondary" decompressive craniectomy is part of a tiered therapeutic protocol used in the intensive care unit (ICU) to control elevated ICP [18]. The 2016 Brain Trauma Foundation guidelines make two recommendations regarding decompressive craniectomy [13]. First, bifrontal decompressive craniectomy is not recommended to improve outcomes in patients with severe TBI with diffuse injury (without mass lesions) and ICP >20 mmHg for more than 15 min in a 1-h period that is refractory to first-tier therapy. This procedure has been shown to decrease ICP and minimize ICU length of stay, but there are no outcome benefits 6 months post-injury, as measured by the Glasgow Outcome Scale-Extended (GOS-E) score [13]. Second, a large frontotemporoparietal decompressive craniectomy (at least 12 × 15 cm or 15 cm diameter) is recommended over a small craniectomy for reduced mortality and improved neurologic outcomes in patients with severe TBI [13]. The RESCUEicp trial [18] was published shortly after the release of the 2016 TBI guidelines. This study compared outcomes of secondary decompressive craniectomy plus medical therapy versus continued medical management alone in patients with TBI and refractory intracranial hypertension. Patients with ICP >25 mmHg despite medical management were randomly assigned to last-tier secondary decompressive craniectomy or continued medical management. At 6 months post-injury, patients who had undergone craniectomy had significantly lower mortality but higher rates of vegetative state and severe disability than those managed medically. Rates of moderate disability and good recovery were similar between the two groups [18]. These results seem to bolster the findings of other studies that have shown that while secondary decompressive craniectomy reduces mortality, it does not translate into survival with good quality of life [19]. Whether living with severe disability or in a vegetative state is preferable to death is subjective. The authors of the 2016 Brain Trauma Foundation guidelines have not amended their recommendations regarding decompressive craniectomy in light of the findings of the RESCUEicp trial [13].

If it is determined that surgical intervention is warranted, another focused, rapid evaluation should be conducted by the anesthesia provider prior to surgery [9]. The patient's airway, breathing, and circulation should be assessed, in addition to a brief neurologic exam evaluating level of consciousness (via GCS score) and pupillary responses [5, 9]. The patient should be evaluated for the presence of anemia, coagulopathy, appropriate blood glucose control, and adequate vascular access [9]. The presence of extracranial injuries should be assessed and considered as factors in the development of hypoxemia, anemia, and hemodynamic instability in the perioperative period [9].

15.5 Management

15.5.1 Airway

Airway management in TBI patients can be challenging due to a number of complicating factors. Urgent intubation may be needed due to hypoxia

or a patient's inability to protect his airway [9]. It may be difficult to assess the airway due to altered consciousness, the presence of a cervical collar, facial injuries, or blood or debris in the oral cavity [9]. All trauma patients should be assumed to have a cervical spine injury until proven otherwise [5] and should be considered at risk for aspiration due to a full stomach [5, 9]. Many patients with TBI will have intracranial hypertension, and care must be taken to avoid further elevations in ICP while securing the airway [5]. Tenuous hemodynamic status must also be considering when selecting the method of intubation, as many anesthetic agents can cause hypotension and cardiovascular depression that may not be tolerated by hypovolemic patients [5].

The appropriate technique for endotracheal intubation depends on the patient's injuries, the practitioner's expertise, and available resources [9]. Most patients can be managed with a rapid sequence intubation (RSI) using cricoid pressure and manual in-line stabilization to maintain neutrality of the cervical spine [9]. Newer airway devices, such as video laryngoscopes and lighted stylets, may improve visualization of the glottis, especially in difficult airway scenarios [5, 9, 20]. Fiber-optic laryngoscopy remains the "gold standard" for difficult airway management, particularly in the setting of cervical spine injury [5]. Nasal intubation is contraindicated in patients with basilar skull fractures, sinus injuries, midfacial fractures, and bleeding diatheses [5, 9]. In some cases, proceeding directly to cricothyroidotomy without attempting to instrument the airway may be appropriate [5]. Regardless of the initial technique selected, a backup plan should also be established in the event of a difficult intubation, as TBI patients will poorly tolerate increases in cerebral blood flow (CBF) and ICP that accompany hypoxemia and hypercarbia [9].

As all trauma patients are assumed to have cervical spine injuries until cleared, manual in-line stabilization should be used regardless of intubation technique [5]. Once manual in-line stabilization is established, the anterior portion of the cervical collar can be removed to allow for greater mouth opening [21]. The goal during manual in-line stabilization is to apply forces that are equal in force and opposite in direction to those generated by laryngoscopy, thereby reducing overall movement of the cervical spine during airway manipulation [21]. However, care must be taken to avoid the application of traction forces, which can cause excess distraction at the site of ligamentous compromise [21].

The first step in selecting an appropriate technique for airway management is to determine if an awake intubation is necessary. Awake intubations may be possible in severely head-injured patients but will be challenging in combative or uncooperative patients [8]. If the need for an awake intubation is ruled out, careful consideration should be given to the appropriate pharmacologic agents for anesthesia induction and muscle relaxation. The main goal during induction of anesthesia is to maintain CPP by avoiding hypotension and reducing ICP [5]. Propofol and etomidate are two commonly used induction agents for RSI, which reduce the cerebral metabolic rate of oxygen ($CMRO_2$) and decrease ICP by inducing cerebral vasoconstriction and reducing cerebral blood flow [9]. Propofol causes hypotension, especially in hypovolemic patients. The resulting decrease in CPP may be worse for the patient than would be a transient increase in ICP as the result of intubation [5]. While etomidate maintains hemodynamic stability during induction, even single doses have been shown to cause adrenal suppression, which may result in delayed hypotension and increased need for vasopressors [22]. This finding led many institutions to curtail the use of etomidate for emergency airway management [23, 24]. However, subsequent research has failed to demonstrate worse outcomes with single-dose etomidate [23–25], and it remains an appropriate agent for RSI in hypovolemic and hemodynamically unstable TBI patients. Ketamine has become a popular induction agent for RSI, especially in emergency departments, as it has been shown to provide excellent intubating conditions while inducing limited cardiovascular compromise [23]. Traditionally, brain injury has been considered a relative contraindication to the use of ketamine due to its ability to increase mean arterial blood pressure (MAP), leading to increases in CBF and ICP [9, 26]. However, more recent

research has questioned this belief, and new data suggest that ketamine can safely be used in patients with intracranial hypertension [26, 27]. The judicious use of adjuvants, such as narcotics and antihypertensive agents, may be necessary to control tachycardia, hypertension, and increased ICP during intubation [5]. These agents should be used cautiously due to the risk of decreased CPP if hypotension ensues. Esmolol can be used to rapidly control heart rate with less potential for hypotension than longer-acting agents. Nicardipine is an easily titratable calcium channel blocker that is frequently used for blood pressure control in patients with brain injury [5].

A muscle relaxant should be administered to prevent coughing and facilitate intubation [5]. Use of neuromuscular blockade during airway instrumentation is associated with improved intubating conditions, including improved laryngeal view and fewer number of intubation attempts, as well as reduced procedure-related complications [28, 29]. The choices for neuromuscular blockade for RSI are rocuronium and succinylcholine [30]. Traditionally, succinylcholine has been the drug of choice for rapid sequence intubation due to its rapid onset of action and short duration of action [30, 31]. However, now that sugammadex is widely available for the rapid reversal of rocuronium, the superiority of succinylcholine is no longer obvious [32]. Nondepolarizing neuromuscular blockers have been shown to prevent significant increases in ICP during stimulation of the airway, such as endotracheal suctioning [33]. The effects of succinylcholine on ICP are less clear. Some studies demonstrate a transient increase in ICP with the use of succinylcholine [34, 35], possibly related to increased carbon dioxide production or cerebral stimulation from fasciculations [5]. Other studies show no effect of succinylcholine on ICP [31, 36, 37]. Additionally, the clinical significance of succinylcholine-related changes in ICP is questionable, and pretreatment with a defasciculating dose of nondepolarizing muscle relaxant has not been shown to influence outcomes [31]. The need to rapidly and effectively secure the airway in order to prevent aspiration, hypoxemia, and hypercarbia outweighs the risk of transient increases in ICP with the use of succinylcholine [5, 8, 9].

15.5.2 Maintenance of Anesthesia

The ideal anesthetic for TBI patients is one that maintains hemodynamic stability and CPP, preserves cerebral autoregulation and carbon dioxide reactivity, optimizes surgical conditions, and allows for a smooth and rapid emergence to facilitate early postoperative neurologic assessment [38]. A variety of anesthetic agents can be employed to meet these goals, including total intravenous anesthesia, volatile anesthetics, or a combination of the two. Under normal conditions, CBF is coupled to $CMRO_2$. When the metabolic demands of the brain increase, CBF increases to deliver more oxygen and glucose and to remove carbon dioxide. When cerebral metabolism decreases, so too does CBF [39]. In general, intravenous anesthetics decrease $CMRO_2$ and CBF in parallel, leading to a reduction in ICP [39]. The exception is ketamine, which increases both CBF and $CMRO_2$ [39]. As mentioned previously, despite the increase in CBF, ketamine does not appear to cause an increase in ICP [26, 27]. In fact, a recent review by Zeiler et al. [40] found no studies demonstrating an increase in ICP following ketamine administration and three that showed a reduction in ICP. Opioids do not affect cerebral hemodynamics when ventilation is controlled [9]. Volatile anesthetics are cerebral vasodilators and "uncouple" CBF from cerebral metabolism, resulting in an increase in CBF despite a reduction in $CMRO_2$ [39]. This increase in CBF has the potential to cause increased ICP. However, at <1 minimum alveolar concentration (MAC), the vasodilatory effects of volatile anesthetics are minimal, and low concentrations can be safely used in the setting of intracranial hypertension [9]. Nitrous oxide increases CBF, cerebral metabolism, and ICP [39] and thus should be avoided in brain-injured patients.

Several studies have investigated the impact of anesthetic technique on intraoperative and postoperative conditions; however, recent reviews of

the literature have failed to uncover evidence of the superiority of specific anesthetic agents [38, 41]. Equivalent brain relaxation can be achieved with either propofol or volatile anesthetics [38]. Time to emergence is similar with sevoflurane and propofol-based anesthetics [41]. Rates of postoperative nausea and vomiting are lower with propofol than volatile anesthetics, but other postoperative complications and recovery profiles are similar [38, 41]. There are insufficient data to determine the effects of anesthetic technique on neurologic morbidity and mortality in TBI [9, 38, 41]. Hence, selection of a specific anesthetic agent is less important than tailoring management to achieve the overarching principal of preventing secondary neurologic injury. The 2016 Brain Trauma Foundation guidelines do not make recommendations regarding the intraoperative use of anesthetic agents. However, barbiturates and propofol are recommended for control of ICP in the ICU (Table 15.4) [13].

15.5.3 Ventilation

Controlled ventilation can help avoid secondary neurologic injury by maintaining normocarbia ($PaCO_2$ 35–45 mmHg) and adequate oxygenation (PaO_2 > 60 mmHg) and, when necessary, by facilitating surgical exposure and the short-term treatment of intracranial hypertension via hyperventilation [9]. Arterial PaO_2 and $PaCO_2$ should be closely monitored to ensure adequate gas exchange and to evaluate the effectiveness of hyperventilation [9, 12]. End-tidal CO_2 may not accurately reflect arterial CO_2 if a large alveolar-arterial CO_2 gradient exists [8]. The 2016 Brain Trauma Foundation guidelines recommend against prolonged prophylactic hyperventilation with PaCO2 <25 mmHg due to the risk of cerebral ischemia from cerebral vasoconstriction [13]. Prophylactic hyperventilation should be avoided during the first 24 h after injury when CBF is often critically reduced [13]. When employing hyperventilation, cerebral oxygen delivery should be monitored via measurements of jugular venous oxygen saturation or brain tissue oxygen partial pressure [9, 13]. Normocarbia should be restored prior to dural closure to allow for an accurate assessment of cerebral swelling [9]. A temporary scalp closure with a loose dural patch may be required in the setting of persistently elevated ICP [8].

Most patients with TBI that require surgical intervention are taken to the intensive care unit intubated and sedated postoperatively. Postoperative brain swelling peaks 12–72 h after injury, and thus a period of postoperative controlled ventilation is reasonable even after uncomplicated craniotomy [8]. Postoperative sedation and controlled ventilation can also be helpful to avoid hypertension and coughing or bucking on the endotracheal tube, which can cause intracranial bleeding or increased ICP [8]. However, accurate neurologic examination is critical in the perioperative period, and thus sedative agents should be short-acting and easily titratable [5].

15.5.4 Monitoring

Standard American Society of Anesthesiology (ASA) monitors should be employed for all TBI patients that require surgical intervention. Additionally, arterial catheterization is recommended to allow for continuous blood pressure monitoring and sampling for blood gas analysis, glucose control, and monitoring of coagulation status [9]. Central venous catheterization can be considered to aid in resuscitation, but emergent surgery should not be delayed in order to obtain central access [9]. Adequate vascular access in the form of multiple large-bore peripheral intravenous catheters should be established prior to surgery.

The 2016 Brain Trauma Foundation guidelines make several recommendations for cerebral monitoring. ICP monitoring is indicated for all patients with severe TBI to reduce in-hospital and 2-week post-injury mortality. Treatment is recommended for ICP >22 mmHg, as this is the threshold for increased mortality. Management decision should be based on a combination of ICP values and clinical and brain CT findings. Additionally, CPP should be monitored in all

patients with severe TBI and maintained at a minimum threshold of 60–70 mmHg. Due to the risk of respiratory failure, practitioners may consider avoiding aggressive attempts to maintain CPP >70 mmHg with fluids and vasopressors [13].

Advanced cerebral monitoring allows for evaluation of global and regional blood flow and oxygenation. Modalities include transcranial Doppler (TCD) ultrasonography, measurement of arteriojugular venous oxygen content difference ($AVDO_2$), and measurements of focal cerebral oxygenation. Although rarely used outside of research settings, microdialysis can be employed to evaluate brain metabolism, and electrocorticography can determine cortical spreading depression [13]. The 2016 Brain Trauma Foundation guidelines recommend jugular bulb monitoring to assess global cerebral oxygenation and provide information for management decisions. Jugular venous saturations of >50% should be maintained to reduce mortality and improve outcomes [13]. Saturations of <50% indicate the need to improve cerebral oxygen utilization, either by increasing oxygen supply or decreasing cerebral metabolic demands. Cerebral oxygen delivery can be improved by increasing the inspired oxygen concentration (FiO_2), increasing hemoglobin via blood transfusion, and increasing CPP by increasing MAP or decreasing ICP [9, 42]. Based on new, higher-quality evidence, the 2016 Brain Trauma Foundation guidelines removed the previous recommendation for the use of local brain tissue oxygen monitors to assess for focal ischemia [13]. Despite insufficient evidence for a formal recommendation, the noninvasive nature of TCD and near-infrared spectroscopy (NIRS) monitoring leads to their frequent use in the ICU in the care of patients with severe TBI [9]. NIRS allows for assessment of regional cerebral oxygenation without the need for invasive probes. TCD ultrasonography provides information regarding cerebral autoregulation, vasospasm, and blood flow velocity [9]. Regardless of which monitoring modalities are chosen, it is important to remember that outcomes are not affected by the monitoring per se but rather by the treatment decisions based on the information generated from those monitoring techniques [13].

15.5.5 Blood Pressure Management and Vasopressors

Hypotension following TBI is known to contribute significantly to secondary neurologic injury and adversely affects outcomes [9, 43]. In patients with intact cerebral autoregulation, systemic hypotension results in a compensatory cerebral vasodilation in an attempt to maintain adequate brain perfusion. This results in increased cerebral blood volume and a resultant increase in ICP [13]. In patients with compromised autoregulation, adequate cerebral perfusion is dependent on systemic blood pressure, with hypotension resulting in ischemia [13]. Traditionally, hypotension has been defined as systolic blood pressure (SBP) <90 mmHg, and this was the minimum threshold recommended in previous editions of the Brain Trauma Foundation guidelines [13]. However, more recent research supports a higher SBP threshold that varies by age. The 2016 Brain Trauma Foundation guidelines recommend maintaining SBP ≥100 mmHg for patients aged 50–69 years old and ≥110 mmHg for patients aged 15–49 or ≥70 years old [13].

While hypotension can contribute to secondary neurologic injury at any point following TBI, anesthesiologists are most concerned about intraoperative blood pressure management. Research by Sharma et al. [43] revealed that intraoperative hypotension occurs commonly during craniotomy for TBI, and risk factors include multiple and large brain lesions on preoperative CT scan, subdural hematoma, and longer duration of general anesthesia. Hypotension commonly occurs at the time of dural opening and may be a result of the sudden reduction in ICP and cessation of the Cushing response [44]. Risk factors for hypotension following dural opening include low GCS score, lack of mesencephalic cisterns on preoperative CT scan, and bilateral dilated pupils [44]. Knowledge of the risk factors for intraoperative hypotension allows the anesthesiologist to anticipate, and hopefully avoid, this complication.

Data comparing the effectiveness of various vasopressors in TBI are limited. A few small studies comparing norepinephrine to dopamine found similar effects on cerebral blood flow

velocity [45, 46] and cerebral oxygenation and metabolism [47], but the effects of norepinephrine were more consistent and predictable [46]. Dopamine was also found to increase ICP [45]. A larger single-center retrospective study found that phenylephrine is commonly used in TBI patients and generates greater increases in MAP and CPP compared to dopamine and norepinephrine, without a concomitant increase in ICP [48]. There is insufficient evidence to recommend the use of a specific vasopressor in the setting of TBI, and the choice should be guided by individual patient characteristics and clinical circumstances.

15.5.6 Intravenous Fluids

Fluid resuscitation in TBI patients is a delicate balance between avoiding and treating hypotension, replacing intravascular losses, and avoiding cerebral edema and worsening intracranial hypertension. The BBB is relatively impermeable to sodium, and thus water moves between the serum and brain tissue depending on the osmolality of each. When serum osmolality is lower than that of the brain, water exits the vasculature and crosses the BBB, resulting in cerebral edema. While this process occurs even with an intact BBB, the risk of cerebral edema is worsened in the setting of TBI and BBB disruption [8]. In this setting, warm, non-glucose containing, isotonic crystalloid solutions, such as 0.9% saline, PlasmaLyte, or Normosol, are preferable. Hypotonic solutions, such as hypotonic saline or lactated Ringer's, should be avoided because they decrease serum osmolality and promote cerebral edema.

Peripheral tissue edema occurs with large-volume fluid resuscitation with isotonic crystalloids due to the reduction in colloid oncotic pressure. However, the colloid oncotic pressure gradients in cerebral vasculature are weaker than those generated by osmolar gradients, and cerebral edema does not occur in normal brain tissue in the setting of reduced colloid oncotic pressure as long as serum osmolality is maintained [8]. The use of colloids in TBI is controversial. A post hoc analysis of the Saline versus Albumin Fluid Evaluation (SAFE) study demonstrated increased mortality and worse neurologic outcomes at 24 months in TBI patients who were resuscitated with 4% albumin versus those who received 0.9% saline [49]. An additional post hoc analysis demonstrated that the use of albumin was associated with elevated ICP and an increased need for additional interventions to treat intracranial hypertension, which was postulated to be responsible for the increased mortality in this patient population [50]. Based on these findings, the use of albumin in TBI patients was widely discouraged. However, Van Aken et al. [51] questioned the validity of this conclusion. They evaluated the physicochemical characteristics of the albumin solution used in the SAFE trial and found it to be hypo-osmolar compared to serum. The authors suggest that, rather than avoiding all colloid solutions, a more appropriate conclusion to the SAFE trial is to avoid the use of hypo-osmolar solutions in patients with TBI.

Hypertonic saline may be considered for low-volume resuscitation of TBI patients due to its ability to improve cerebral perfusion while reducing ICP, replenish intravascular volume, improve tissue perfusion, and modulate the inflammatory response to trauma, which may reduce the development of multiorgan failure [52]. However, two randomized controlled trials of prehospital resuscitation with hypertonic saline versus conventional fluids in trauma patients showed no difference in survival or neurologic outcome at 6 months post-injury [52, 53].

In summary, the goals of fluid resuscitation of the head-injured patient include avoiding and treating hypotension, replenishing intravascular volume, and maintaining serum osmolality to prevent cerebral edema and worsening intracranial hypertension. Based on available evidence, glucose-free isotonic crystalloids should be administered to achieve these goals.

15.5.7 Management of ICP

The 2016 Brain Trauma Foundation guidelines recommend maintaining ICP $\leq$22 mmHg, as values above this threshold are associated with increased mortality [13]. ICP management intraoperatively is often very different than that

undertaken in the ICU setting. Patients with severe TBI may present emergently for decompressive craniectomy or hematoma evacuation without an indwelling ICP monitor. In these situations, evidence of intracranial hypertension may be evident from CT scan (e.g., midline shift, ventricular effacement) and physical exam findings (e.g., fixed and dilated pupils, posturing). For patients at imminent risk of cerebral herniation, the goal is to reduce ICP until the dura is opened, at which point ICP becomes zero. Intraoperative techniques that may be employed to acutely reduce ICP include hyperventilation, hyperosmolar therapy, CSF drainage, head elevation, and maintenance of venous cerebral drainage.

Hyperventilation reduces ICP by causing cerebral vasoconstriction, which results in reduced cerebral blood volume. While the prophylactic use of hyperventilation is discouraged by the 2016 Brain Trauma Foundation guidelines [13] due to the risk of cerebral ischemia, it is a reasonable technique for short-term, acute ICP management in patients with evidence of intracranial hypertension. Hyperosmolar therapy, using either mannitol or hypertonic saline, reduces ICP by creating an osmotic gradient that draws water from brain tissue, reduces cerebral edema, and stimulates osmotic diuresis. Additionally, these agents reduce blood viscosity, improve microcirculatory flow, and improve cerebral tissue oxygen delivery, which induces a reflexive vasoconstriction of cerebral arterioles, leading to reduced cerebral blood volume and ICP [13, 54]. Mannitol also decreases CSF production and reabsorption, thereby reducing ICP by decreasing CSF volume [54]. There is insufficient evidence on clinical outcomes for the 2016 Brain Trauma Foundation guidelines to make a specific recommendation or support a specific hyperosmolar agent for use in patients with severe TBI [13]. The authors of the 2016 guidelines state that "[the] Committee is universal in its belief that hyperosmolar agents are useful in the care of patients with severe TBI. However, the literature does not currently support recommendations that meet the strict criteria for contemporary evidence-based medicine approaches for guideline development" [13]. Despite the lack of a specific recommendation, existing literature suggests mannitol is effective at reducing ICP at doses of 0.25–1 g/kg body weight [9]. Hypovolemia and hypotension can result from osmotic diuresis, and practitioners should be prepared to treat this potential side effect.

An external ventricular drainage (EVD) system allows for both ICP measurement (while in the closed position) and CSF drainage (when in the open position). This can be advantageous for both the intraoperative and ICU management of patients with severe TBI. The 2016 Brain Trauma Foundation guidelines recommend continuous CSF drainage from an EVD leveled at the midbrain for more effective ICP control than that achieved with intermittent drainage [13]. The guidelines also recommend the use of CSF drainage to lower ICP during the first 12 h after injury in patients with an initial GCS <6 [13]. Care must be taken not to remove an excessive amount of CSF, which can lead to complications such as intracranial hemorrhage and brainstem herniation [55].

Simple techniques to aid in ICP reduction include head elevation and maintenance of cerebral venous drainage. Elevating the head of the bed up to 30° aids in venous drainage and reduces passive cerebral blood flow due to gravity. However, head elevation intraoperatively exposes the patient to the risk of venous air embolism during craniotomy, and proper precautions should be taken for the monitoring and treatment of this potential complication. Proper head and neck positioning should be ensured to maintain adequate cerebral venous drainage. Compromised jugular venous drainage, which can be caused by extreme neck flexion, external compression from malpositioned endotracheal tube or tracheostomy ties, or internal obstruction by venous catheters, can result in cerebral vascular congestion and increased ICP.

Barbiturates and other sedatives are routinely used to control ICP in the ICU setting. However, these drugs are not commonly used intraoperatively due to the preference for short-acting, easily titratable anesthetics that allow for accurate postoperative neurologic assessment. A detailed

discussion of the use of barbiturates and sedatives for ICP control in the ICU is outside the scope of this chapter.

15.5.8 Blood Transfusion

Anemia is common in patients with severe TBI and may contribute to secondary neurologic injury due to decreased cerebral oxygen delivery [56, 57]. The causes of anemia in critically ill patients include primary blood loss (e.g., trauma, gastrointestinal bleeding, surgical blood loss), hemodilution secondary to fluid resuscitation, phlebotomy, altered red blood cell production, and decreased red blood cell lifespan [58]. In the face of anemia, the body attempts to maintain cerebral oxygen delivery by increasing sympathetic tone via activation of aortic and carotid chemoreceptors, which results in increased heart rate and left ventricular stroke volume, leading to increased cardiac output and CBF [58, 59]. Anemia is associated with decreased blood viscosity, which improves microvascular perfusion and promotes venous return [58]. Additionally, tissue oxygen extraction is enhanced in the setting of anemia, and endothelial and neuronal production of nitric oxide increases, resulting in cerebral vasodilation and increased CBF [58]. At the cellular level, anemia stimulates the production of neuroprotective factors, such as hypoxia-inducible factor, erythropoietin, and vascular endothelial growth factor, which protect cells from ischemia and stimulate adaptation to chronic hypoxia [58, 59]. Despite these compensatory mechanisms, anemia is associated with increased in-hospital mortality [57] and poor outcomes in patients with severe TBI [58, 60]. Cerebral injury in anemic patients may be due to a number of factors, including tissue hypoxia, anemic cerebral hyperemia, embolic events, damage from reactive oxygen species, inflammation, and BBB disruption [59].

Twenty years ago, liberal transfusion parameters were commonly used in the ICU due to the belief that critically ill patients would poorly tolerate anemia [61]. More recent research, however, has shown improvements in morbidity and mortality with a more restrictive transfusion strategy [62, 63]. Blood transfusion is associated with complications such as infection, organ dysfunction, respiratory failure, increased ICU and hospital length of stay, and increased mortality [62, 63]. Current guidelines recommend a transfusion threshold of hemoglobin <7 g/dL for hemodynamically stable adult patients, including those who are critically ill [64]. For patients undergoing orthopedic or cardiovascular surgery or those with preexisting cardiovascular disease, the recommended transfusion threshold is hemoglobin <8 g/dL [64]. However, given how detrimental anemia is to patients with severe TBI, researchers have questioned whether these recommendations should be applied in the setting of acute brain injury. Theoretically, transfusion of red blood cells should increase oxygen delivery to the brain, thereby reducing the risk of secondary neurologic injury from hypoxia. However, studies have not consistently demonstrated that increased hemoglobin is associated with improved brain tissue oxygenation ($PbtO_2$) [65, 66]. Additionally, elevated hematocrit from blood transfusion may reduce CBF due to an increase in blood viscosity, potentially increasing the risk of cerebral ischemia [67]. Blood transfusion in patients with severe TBI is associated with poor long-term outcomes [56, 60, 68], including increased mortality [60]. Thus, the risks of anemia in the setting of TBI must be weighed against those of blood transfusion. There is insufficient evidence to recommend a specific transfusion threshold in this patient population. However, based on available data, a liberal transfusion threshold (hemoglobin <10 g/dL) is not recommended for most patients [58, 60]. Transfusion triggers should be individualized and guided by risk factors for poor tolerance to anemia (e.g., ischemic heart disease) or evidence of cerebral hypoxia. In patients without these characteristics, a restrictive transfusion strategy (hemoglobin <7 g/dL) is likely appropriate [58].

15.5.9 Glycemic Control

Hyperglycemia is common in critically ill patients and is associated with increased morbidity and mortality in patients with severe TBI [69–71].

Following head injury, circulating levels of catecholamines increase due to a systemic stress response. This, in turn, results in elevated serum glucose [70]. Additional causes of hyperglycemia in acute illness include insulin insufficiency, insulin resistance, and impaired glucose utilization [72]. Whether hyperglycemia is merely a marker of TBI severity or directly contributes to poor outcomes has been debated, with several studies identifying hyperglycemia as an independent risk factor for poor outcomes in TBI [70, 71]. Hyperglycemia contributes to secondary neurologic injury via a variety of complex mechanisms, including oxidative injury from free radical formation, activation of *N*-methyl-D-aspartate (NMDA) receptors, increased intracellular calcium, activation of inflammatory and apoptotic pathways, and altered lactate metabolism and tissue acidosis [69]. Additionally, BBB disruption leads to dysregulation of CBF, alterations in cerebral glucose transport and utilization, and excitotoxicity [72].

Given the association between hyperglycemia and poor outcomes in critically ill patients, researchers have sought to elucidate the optimal range of glycemic control for this patient population. An early study found that intensive insulin therapy to maintain blood glucose <110 mg/dL resulted in reduced morbidity and mortality for surgical ICU patients [73]. Subsequent studies, however, have demonstrated increased complication rates and no mortality benefit with intensive insulin therapy compared to conventional glycemic control (blood glucose <180 mg/dL) [74–76]. Hypoglycemia is of particular concern in brain-injured patients, as even moderate reductions in serum glucose may induce cerebral metabolic distress and neuroglycopenia [77]. Following TBI, there is a profound increase in glucose utilization (hyperglycolysis) and an inability to utilize ketone bodies as an energetic substrate [78]. As such, hypoglycemia could have devastating consequences in this setting. Several researchers have investigated the use of intensive versus conventional glycemic control in TBI patients [69, 77, 78]. In these studies, intensive insulin therapy was associated with more frequent episodes of hypoglycemia, although no differences in mortality or long-term neurologic outcomes were found [69, 77, 78]. There is a paucity of data regarding the best strategy for intraoperative glycemic control in TBI patients. As such, the previously cited data from ICU patients is extrapolated to the operative environment. Based on available data, no formal recommendation for glycemic control was included in the 2016 Brain Trauma Foundation guidelines [13]. Intermediate glucose control, avoiding both hyper- and hypoglycemia, appears to be a reasonable approach.

15.5.10 Temperature Control

Induced hypothermia has been successfully used to improve neurologic outcomes in the settings of cardiac arrest and neonatal hypoxic-ischemic encephalopathy [79]. Hypothermia has also been employed in the management of other types of brain injuries, such as ischemic strokes and TBI, although there is less evidence supporting its use in these settings [79, 80]. The mechanisms by which hypothermia provides neurologic protection include decreased cerebral metabolism, augmentation of apoptotic cell death, attenuation of inflammation and free radical production, decreased release of excitatory neurotransmitters, restoration of BBB integrity, and decreased vascular permeability [79, 81]. Hypothermia reduces cerebral metabolism by 5% for every 1 °C reduction in core body temperature, resulting in cerebral vasoconstriction, a reduction in cerebral blood volume, and a decrease in ICP [81]. Although induced hypothermia appears to offer several possible neurologic benefits, the technique is not without risks. Complications include coagulopathy, infection, hypotension, and cardiac dysrhythmias [13, 82], as well as complications associated with rewarming, including rebound intracranial hypertension and shock [82].

Despite its proven utility in other settings, hypothermia has not been consistently demonstrated to reduce mortality or improve outcomes in TBI. A Cochrane Review of 37 randomized trials found no high-quality evidence of benefit

from the use of hypothermia in patients with TBI [80]. Although hypothermia is often used as a method to control intracranial hypertension in the ICU, there is no evidence of improved neurologic outcomes in TBI compared to standard methods of ICP reduction [83]. There is insufficient evidence to recommend widespread use of hypothermia for neuroprotection after TBI [82]. In fact, the 2016 Brain Trauma Foundation guidelines recommend against the use of early (within 2.5 h), short-term (<48 h post-injury), prophylactic hypothermia [13].

Spontaneous temperature dysregulation is common in the setting of brain injury [84]. Fever following TBI is associated with increased mortality and worse neurologic outcomes [84, 85]. Both the degree and duration of post-injury pyrexia are correlated with long-term neurologic outcomes in TBI; even brief, mild hyperthermia (37.3–38 °C) is associated with worse outcomes and higher mortality [84]. Temperature regulation and avoidance of hyperthermia are an important aspect of TBI management.

15.5.11 Corticosteroids

BBB disruption following TBI can lead to the development of cerebral edema. Corticosteroids, particularly dexamethasone, are commonly used to control cerebral edema in other settings, such as intracranial tumors. In the case of tumor-induced cerebral edema, steroids act to regulate tumor mediators, stabilize the BBB, and decrease vascular permeability [86]. For decades, steroids were administered in head injuries with the goal of reducing cerebral edema via similar mechanisms, although there was little supporting evidence [13]. However, the Corticosteroid Randomization After Significant Head Injury (CRASH) trial demonstrated increased risk of 2-week and 6-month mortality, as well as severe disability, in TBI patients who had received high-dose methylprednisolone [87, 88]. Steroid administration in TBI is also associated with higher rates of infection and gastrointestinal bleeding [89]. According to the 2016 Brain Trauma Foundation guidelines, steroids are not recommended to improve outcomes or reduce ICP, and high-dose methylprednisolone is contraindicated in severe TBI [13].

15.5.12 Seizure Prophylaxis

Post-traumatic seizures are a common complication of TBI, affecting over 20% of patients in the ICU [90] and up to 25% of patients chronically [91]. Post-traumatic seizures promote secondary neurologic injury and are associated with poor outcomes [90]. Seizures increase ICP, promote cerebral edema, and result in cerebral metabolic crisis, which is characterized by reduced oxidative metabolism and increased glucose consumption, resulting in an increased lactate/pyruvate ratio and decreased extracellular glucose level [90]. Seizures also induce excitotoxicity, leading to cell membrane disruption and cell death [90].

Post-traumatic seizures are defined as immediate (occurring <24 h after injury), early (occurring 24 h to 7 days after injury), or late (occurring >7 days after injury). The majority of early seizures are nonconvulsive and thus go unrecognized unless continuous electroencephalography (EEG) is used [92, 93]. Prophylactic anticonvulsants are routinely administered following TBI in order to prevent post-traumatic seizures and reduce the potential for secondary neurologic injury and post-traumatic epilepsy. However, studies have shown that anticonvulsant prophylaxis is only effective in preventing early seizures and does not impact morbidity or mortality following severe TBI [94, 95]. Thus, the current recommendation is to discontinue prophylaxis 1 week after injury [13].

Traditionally, phenytoin has been the drug of choice for post-traumatic seizure prophylaxis. However, phenytoin is associated with numerous side effects, including significant drug-drug interactions due to its induction of the hepatic cytochrome P450 system [96]. Additionally, phenytoin is known to cause cutaneous hypersensitivity reactions, fever, and altered level of consciousness in some patients [97]. Phenytoin also has a narrow therapeutic window and

requires close monitoring of serum drug levels [96, 97]. Several studies have found levetiracetam to be equally effective as phenytoin at preventing early post-traumatic seizures [96–98]. Levetiracetam is an attractive alternative due to its better side effect profile and wider therapeutic index, which obviates the need to monitor serum drug levels [98]. Although the use of levetiracetam in this setting is increasing, the available comparative studies were insufficient for the Brain Trauma Foundation to recommend its use over phenytoin in the 2016 guidelines [13].

Data regarding intraoperative seizures following TBI is lacking. Prophylactic anticonvulsants should be continued for 7 days following injury, and care must be taken that scheduled doses are not missed while patients are in the operating room. Conversion of enteral dosages to intravenous administration may be required depending on surgical timing. Intraoperative prophylactic anticonvulsants may be indicated outside the window of early post-traumatic seizures in select patients. For example, a patient undergoing decompressive craniectomy >1 week after injury may be at risk of intraoperative seizures due to intracranial pathology and cerebral stimulation during surgery. The use of prophylactic anticonvulsants in such settings should be a collaborative determination between the surgeon and anesthesia provider. As discussed previously, phenytoin can alter the metabolism of many medications. Phenytoin use has been associated with resistance to the effects of nondepolarizing muscle relaxants, including pancuronium, vecuronium, and rocuronium [99]. Phenytoin may also precipitate in some electrolyte solutions [100] and should not be administered through the same intravenous line as continuous intravenous anesthetics.

15.6 Concussion

The terms mild traumatic brain injury and concussion are often used interchangeably. Mild traumatic brain injury is defined as a GCS score of 13–15 within 24 h of head injury. Concussion, on the other hand, is a clinical syndrome that describes the neurological, cognitive, and behavioral symptoms that result from a transient disruption of normal brain function by a biomechanical force [3]. Public awareness of the risks and ramifications of concussions, particularly in the setting of organized sports, has increased dramatically in recent years. It is estimated that between 1.6 million and 3.8 million athletes suffer concussions each year [101], and up to 50% of concussion may go unreported [4]. Studies have found that the vast majority of patients who visit the emergency department for sports- and recreation-related TBI are treated and released, suggesting that their injuries are mild [102]. However, up to 25% of such patients have persistent signs and symptoms 1 year after injury, which suggests that the term "mild TBI" may be a misnomer in these cases [102]. Risk factors for prolonged recovery after concussion include history of prior concussions; younger age; preexisting learning disability, attention deficit, or psychiatric diagnoses; symptoms of migraine headache, fogginess, or dizziness; and on-field mental status change [101].

Similar to the pathogenesis described for severe TBI, head injury in mild TBI results in a metabolic crisis due to a massive flux of ions and excitatory neurotransmitters within the brain. This crisis is characterized by transmembrane ion imbalance, hyperglycolysis, and mitochondrial dysfunction. Decreased cerebral perfusion exacerbates this process by creating a metabolic mismatch of high glucose demand and impaired delivery. The acute hypermetabolic state is followed by a prolonged subacute hypometabolic phase, characterized by inflammation and microstructural injury [3]. These changes result in a disturbance of brain function and produce symptoms from physical, cognitive, and emotional domains. Unlike severe TBI, however, gross structural injuries are absent [103]. It is theorized that the symptoms of concussion are related to the metabolic mismatch created by reduced cerebral blood flow in the setting of cerebral hypermetabolism [3, 103]. Symptoms of concussion include headache, dizziness, photophobia, phonophobia, nausea, drowsiness, difficulty concentrating, slowed processing, slowed

reaction time, and amnesia [3, 103]. Concussed patients are also at higher risk of subsequent concussions, a phenomenon known as "second impact syndrome" [103]. Repetitive concussions can result in cognitive and behavioral dysfunction, ranging from mild memory impairment to gross dementia, as well as pituitary dysfunction, most commonly hyposomatism and hypogonadism [101].

Given the prevalence of concussions, particularly in recreational activities that may be associated with other injuries, anesthesia providers may frequently encounter these patients. There is a lack of definitive experimental or clinical data regarding the impact of anesthesia on the concussed brain. Management of these patients requires a balance of concern regarding the potential for impaired neurologic recovery versus suboptimal surgical or orthopedic outcomes due to unnecessary surgical delays. Although the impact of anesthesia and surgery on concussion recovery is unknown, several physiologic changes have been shown to occur following concussion that may have ramifications for the administration of anesthesia. Within 3 days of injury, alterations in vascular myogenic tone and vagal tone occur [103]. Autonomic nervous system dysfunction, particularly in the first 7–10 days after injury, may lead to inappropriate hemodynamic responses and reduced capacity to appropriately react to increased metabolic demands [103]. Additionally, cerebrovascular response to CO_2 may be impaired [103]. Autoregulation of cerebral blood flow may be impaired or even abolished, exposing the injured brain to risk of secondary neurologic injury during periods of even mildly reduced cerebral perfusion pressure [104]. Thus, although it is not yet possible to definitively show the impact of anesthesia on concussion recovery, the injured brain is clearly vulnerable to additional harm. Avoidance of elective anesthetics, particularly in the acute postconcussive phase, seems prudent. Thus, it is reasonable to postpone elective procedures at least until postconcussive symptoms have resolved. When anesthesia cannot be avoided in these patients, utmost care must be taken to prevent secondary neurologic injury.

15.7 Summary

TBI is very prevalent and is associated with significant morbidity and mortality. Anesthesia providers will often be faced with the management of these patients, and the primary goals of care are patient resuscitation and avoidance of secondary neurologic injury. The 2016 Brain Trauma Foundation guidelines for the management of severe traumatic brain injury represent an effort to improve outcomes in this patient population through the implementation of evidence-based practices and standardized care. Anesthesia providers play a critical role in optimizing outcomes and decreasing mortality in these vulnerable patients. Further research is needed to elucidate additional means by which the care of patients with brain injury can be improved.

Key Points

- Traumatic brain injury (TBI) is an important public health concern associated with significant morbidity and mortality. In the United States, nearly three million people are diagnosed with TBI annually, and almost four million concussions occur each year.
- The primary goals of anesthetic care for patients with TBI are patient resuscitation and avoidance of secondary neurologic injury. Hypotension and hypoxemia are the two most important secondary insults that can worsen patient prognosis. Systolic blood pressure should be maintained ≥100 mmHg for patients aged 50–69 years old and ≥110 mmHg for patients aged 15–49 or ≥70 years old.
- The ideal anesthetic for TBI patients is one that maintains hemodynamic stability and cerebral perfusion pressure, preserves cerebral autoregulation and carbon dioxide reactivity, optimizes surgical conditions, and allows for a smooth and rapid emergence to facilitate early postoperative neurologic assessment.

- The goals of fluid resuscitation of the head-injured patient include avoiding and treating hypotension, replenishing intravascular volume, and maintaining serum osmolality to prevent cerebral edema and worsening intracranial hypertension. Glucose-free isotonic crystalloids should be administered to achieve these goals.
- Elective anesthetics should be avoided in patients with recent concussions. When anesthesia cannot be avoided in these patients, utmost care must be taken to prevent secondary neurologic injury.

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Anesthesia for Traumatic Spine Injury

16

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16.1 Introduction

Anesthesia management of traumatic spinal cord injury (SCI) is associated with potential risks, depending on the location and severity of injury. Challenges with airway stabilization and hemodynamic disruptions also complicate acute management. SCI and its secondary sequelae make preoperative evaluation prior to general anesthesia induction important. There is not a specific general anesthetic technique during surgery which is most suitable and effective for traumatic spinal cord surgery per se. However, the use of intraoperative spinal cord monitoring may dictate the anesthetic agents that can be employed without negatively impacting such monitoring. The main concern is providing general anesthesia to SCI patients with hemodynamic perturbations. Intraoperative vasopressor and inotrope usage should be considered to maintain injured spinal cord perfusion and oxygenation. This chapter summarizes the specific noteworthy points through the perioperative period in SCI management.

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16.2 Preoperative Evaluation: Airway Problems

Following traumatic SCI, airway management and maneuvers for laryngoscopy are more challenging prior to anesthesia induction because of restrictions related to stabilization of the cervical region from a cervical collar. A thin-section computed tomographic assessment of the spine from the occiput to the first thoracic vertebra is crucial for deciding the location of injury and its relationship with airway manipulations [1]. Goals

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for difficult airway and anesthesia management of cervical SCI include avoiding excessive flexion or extension of the cervical spine to prevent spinal cord traction and secondary neurological injury. Maintaining a neutral spine positions facilitates stabilizing the airway for adequate ventilation [2]. The skull base and atlas support 15–20% of cervical extension and 5% of flexion, while the atlas and second cervical vertebra supports approximately 10% of both cervical flexion and extension. Sixty-five percent of flexion and extension is provided by third to seventh cervical vertebras [3]. Direct laryngoscopy causes extension of cervical vertebrae, particularly in the occipito-atlantoaxial region.

A cadaveric study of a destabilized third cervical vertebrae demonstrated that placement of a face mask, orotracheal intubation with a laryngoscope, and placement of both esophageal tracheal Combitube™ and laryngeal mask airway device clearly affects the stabilization of the third cervical vertebrae. Fiber-optic nasal intubation did not have any destabilizing effects [4]. Cervical spine movement is affected during laryngoscopy and tracheal intubation more than during face mask placement. Orotracheal intubation with an illuminating intubating stylet or with GlideScope™ video laryngoscopy is more effective means to reduce cervical spine movement compared to the use of the Macintosh blade [5]. This study found GlideScope™ reduced movement of C2–C5 segments but did not alter the motion at the occiput-C1 junction or C1–C2 junction during the orotracheal intubation. Novel devices for difficult intubation have been discussed in the literature; nevertheless, fiber-optic intubation prior to anesthesia is currently the optimal technique for intubation following traumatic cervical SCI in patients whose condition allows such an approach. Anesthesiologists must understand the risk for airway complications between termination of anesthesia and recovery, as they can affect weaning strategies and require reintubation or tracheostomy. The main reasons for airway complications after cervical spine surgery include laryngopharyngeal edema, hematoma formation, paravertebral soft tissue edema, and cerebrospinal fluid leak. Prolonged surgery time and extensive spinal surgery also contribute to airway complications [6].

16.3 Anesthetic Considerations

Anesthesia induction is a critical step during the perioperative management of traumatic SCI, particularly when a high spinal cord segment is involved or when the injury is severe. Following intravenous or inhalational anesthesia induction, attention should be given to maintenance of adequate spinal cord perfusion by preventing systemic hypotension. Spinal cord hypoperfusion following anesthesia induction can lead to an acute decline in systemic vascular resistance, preload, and myocardial contractility. In addition to cardiovascular impairment, high spinal cord lesions can lead to significant reductions in vital capacity and inspiratory capacity. Respiratory compromise escalates the vulnerability to spinal cord ischemia at the time of anesthesia induction. Preventing cardiac and respiratory complications reduces the risk for secondary neurological complications [7].

Preserving mean arterial pressure (MAP) between 85 and 90 mmHg in the first week following SCI improves spinal perfusion and neurologic outcome. To achieve this target range, vasopressors such as phenylephrine or ephedrine and inotropic agents such as dopamine, norepinephrine, or epinephrine can be used safely during anesthesia maintenance. A study compared propofol and sevoflurane induction in patients undergoing fiber-optic nasal intubation for cervical spine surgery in patients with cervical myelopathy. Echocardiogram results indicated ejection fraction, end-diastolic diameter, and end-systolic diameter of the left ventricle were not affected by these induction techniques. Mean arterial pressure, fractional shortening, and left ventricular end-systolic quotient were significantly reduced after anesthesia induction and prior to intubation. The authors explained the hemodynamic reductions were a result of propofol depressing myocardial contractility and causing systemic vasodilation [8]. Bradycardia, supraventricular arrhythmias, and cardiac asystole are possible consequences of autonomic nervous system deterioration.

Anesthesiologists must be aware of the risk for systemic hypotension following induction with propofol, benzodiazepines, or barbiturates,

specifically in patients with hypovolemia or cardiac impairment. Additionally, no technique is more neuroprotective once hemodynamic stability, normocapnia, and normoglycemia are accomplished. The essential goal with all techniques and treatment options is to reduce the duration of hypotension during surgery [9, 10].

Though there is no satisfactory data in the literature to use one general anesthetic agent or regime over another to improve hemodynamic stability and safety, there are several factors that may improve clinical outcomes following SCI. Careful monitoring of somatosensory- and motor-evoked potentials might serve to eliminate complications resulting from patient positioning, systemic hypotension, and hypothermia during anesthesia management. A technique that uses total intravenous anesthesia without neuromuscular blockers is preferred when these monitoring modalities are employed. Inhalation agents and neuromuscular blockers narrow the strength of transcranial motor-evoked potential monitoring and increase the amount of false-positive readings during spinal surgery. Opioids do not have a serious impact on evoked potentials [11]. Animal studies reported weakening of cortical electroencephalography activity following complete transection of the spinal cord as well as reductions in anesthesia demand, but no direct clinical consequences were reported [12]. Anesthesia management following SCI is complex and dynamic, requiring careful consideration of neurological, respiratory, and cardiovascular complications that can present during acute SCI management.

16.4 Hemodynamic Management: Autoregulation and Spinal Shock

Loss of descending input from supraspinal structures leads to neurogenic shock following severe SCI, and immediate management is required to achieve hemodynamic stabilization. This includes the use of vasopressors to augment MAP and improve spinal cord perfusion to maintain cellular requirements [13]. As previously mentioned, current recommendations advise that systolic blood pressure remain above 90 mmHg and MAP be maintained between 85 and 90 mmHg for at least 7 days following SCI. Hypotension and bradycardia are common complications in patients with complete SCI due to neurogenic, spinal, and hemorrhagic shock (Fig. 16.1). These complications are often seen with concomitant injuries [14]. Addressing hemodynamic variables is crucial in medical stabilization following SCI.

The Consortium for Spinal Cord Medicine bases the choice of vasopressor on the level of SCI. Injuries above T6 require a vasopressor such as dopamine (Fig. 16.1), with inotropic, chronotropic, and vasoconstrictive properties, and low thoracic and lumbar injuries with hypotension are the results of peripheral vasodilation and require a pure vasoconstrictor such as phenylephrine [15]. Complications from the use of vasopressors include ventricular tachycardia, elevated troponin levels, atrial fibrillation, and extremely high (>130) or low (<50) heart rate (Fig. 16.1). Risk factors for these include the use of dopamine and phenylephrine, age >60, and complete SCI [16]. The use of vasopressors is more significant in complete cervical cord injuries because of the likelihood of more severe hypotension compared to incomplete or lower-level spinal cord injuries [17]. Considering this, a recent retrospective study found dopamine to be associated with more complications in individuals with complete penetrating SCI. They determined that the use of vasopressors to prevent hypotension did not help avoid permanent injury or prevent progressive cell death, suggesting the benefits did not outweigh the risks in this specific cohort of SCI [13]. While physicians are often hesitant to use aggressive vasopressor therapy in complete SCI, a study found that higher blood pressures correlated with improved outcome in patients with initially complete motor and sensory injuries (AIS A). Thirty-three percent of patients with AIS A improved by at least one grade on neurological exam at time of discharge, and 24% improved by even more with the use of aggressive vasopressor therapy [18]. Management following SCI needs to consider the type of injury, level of injury, and independent risk factors to aid in determining the use and type of vasopressor.

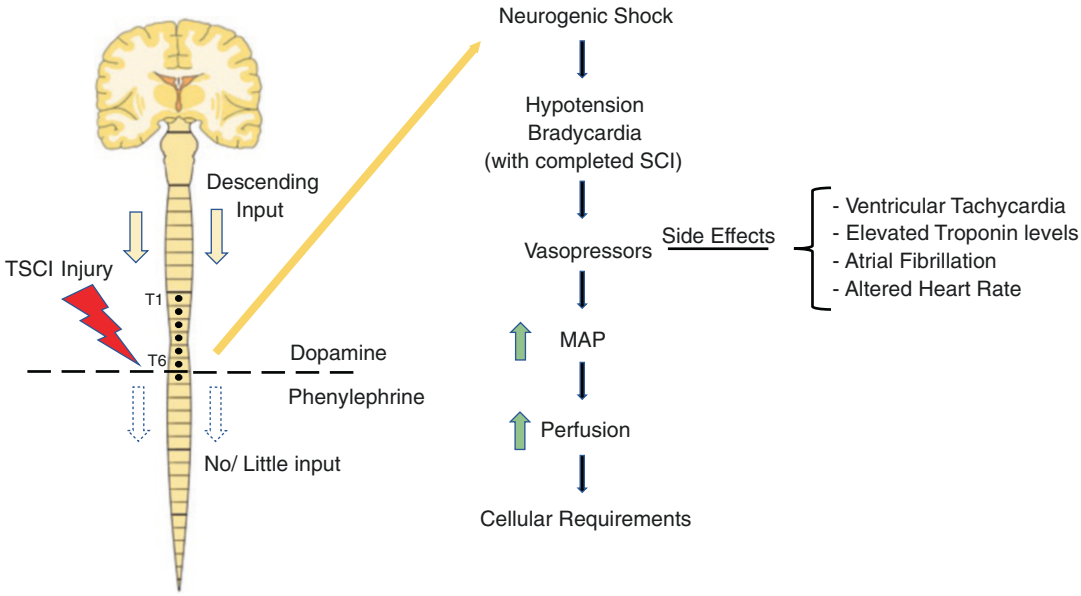

Fig. 16.1 This figure demonstrates the descending input being interrupted by a traumatic spinal cord injury (TSCI). After TSCI neurogenic shock occurs, leading to hypotension and bradycardia. Vasopressors will be used to increase mean arterial pressure (MAP) and increase perfusion to meet cellular requirements. Injuries above T6 require a vasopressor such as dopamine, and in cases of hypotension with low thoracic and lumbar injuries, a pure vasoconstrictor such as phenylephrine is required

Individuals who suffer traumatic brain injury often receive intracranial pressure (ICP) and MAP monitoring, but outcomes of patients whose medical treatment was guided by clinical examination and imaging are comparable to those receiving ICP monitoring [19]. In the case of SCI, using imaging is difficult due to spinal instrumentation, and using clinical examination is challenging when the patient is sedated or intubated. Due to these challenges, a study aimed to develop a technique to monitor intraspinal pressure (ISP) at the injury site following traumatic SCI to help determine if elevated ISP had the same detrimental effects as elevated ICP following traumatic brain injury. The authors were able to successfully monitor ISP for 1 week following SCI without complications and proposed that the combination of decreased CSF and spinal cord swelling causes a rapid and local rise in ISP, leading to loss of autoregulation. Impaired autoregulation can lead to hypo- or hyperperfusion of the spinal cord and increases the risk for secondary damage. Mannitol and sevoflurane had little effect on ISP or perfusion pressure, but inotropes raised MAP, which in turn increased perfusion pressure and ISP. Surgical laminectomy did not reduce intraspinal pressure effectively because the spinal cord remains swollen and compressed by the dural sac [20]. Adequate spinal cord perfusion is required to prevent neurological compromise, and continued clinical research on the use of ISP monitoring will help elucidate whether this procedure should be incorporated in standard guidelines for SCI treatment.

Initial bradycardia occurs in all patients with cervical SCI and spinal shock, and typically recovers back to baseline within 1 week, or when spinal shock resolves, but some go on to have cardiac asystole or persistent bradycardia. Positioning and endotracheal suctioning are significantly associated with bradycardia and asystole in cervical SCI. Parasympathetic dominance and a weakened cough reflex in these individuals lead to increased bronchial secretions and infections, with pneumonia being a major risk factor for developing bradycardia or asystole. The normal tachycardia response to hypoxia from atelectasis is reduced due to loss of sympathetic outflow [21]. Ipratropium bromide

to treat bronchial secretions and airway hyperresponsiveness may help decrease the incidence of bradycardia [22]. Careful monitoring and recognition of an individual's risk for hemodynamic compromise due to impaired autoregulation and spinal shock are critical to facilitate recovery and minimize secondary complications.

16.5 Fluid Therapy

Molecular pathophysiology of SCI not only determines how clinicians manage hemodynamics but also how to properly manage fluid balance. Immediately following SCI, microhemorrhages form and erythrocytes leak into the perivascular area, causing breakdown of the blood spinal cord barrier and damage to the spinal subarachnoid space. Subsequently, spinal cord edema occurs starting 30 s after injury and lasting for up to 15 days. Furthermore, perfusion impairment after SCI results in ischemia that is most apparent 3–24 h after injury [23]. Hypotension after traumatic SCI is caused by suspension of supraspinal sympathetic drive to the peripheral vascular system and a decrease in systemic vascular resistance. Fluid management after traumatic SCI requires finding the balance between fluid overload from worsening spinal cord edema and hypovolemia resulting from spinal cord ischemia and acute loss of sympathetic outflow.

Maintaining intravascular volume using fluid therapy decreases tissue hypoperfusion and increases oxygen delivery. However, aggressive fluid administration during spinal surgery or critical care management can result in cardiac dysfunction, abnormal electrolyte distribution, dilutional coagulopathy, and peripheral edema. Hypotonic crystalloids can worsen spinal cord edema because their contribution to effective intravascular volume is less than normal saline or lactated Ringer's solution. Previously it was shown that colloids can induce a more effective intravascular volume expansion than crystalloids. There are recent controversial results from studies using trauma patients regarding no colloid superiority in correcting tissue perfusion or critical care outcomes. Coagulopathy and the risk of acute kidney injury have been described with hydroxyethyl starch solution administration to critical care patients [24]. Following traumatic SCI, there are no clear recommendations or results in the literature regarding the use of a specific fluid therapy being more advantageous in preserving perfusion pressure. However, the use of invasive or noninvasive intraoperative hemodynamic monitoring might be beneficial. Furthermore, early vasopressor support can maintain spinal cord perfusion pressure above 50 mmHg and helps avoid volume overload. Preserving spinal cord perfusion pressures above 50 mmHg has prognostic importance for neurologic recovery [25].

16.6 Postoperative Pain Management

Pain after traumatic SCI is the consequence of nociceptive and neuropathic pathway stimulation. Nociceptive pain dominates after major spinal surgery, and neuropathic pain is the primary source of pain following the acute surgical phase. Neuropathic pain can develop into intractable pain that decreases patients' quality of life and functional capacity and commonly persists long after the initial trauma. The International Spinal Cord Injury Pain Classification (ISCIP) chart assists clinicians during evaluation and classification of pain after SCI [26]. According to the literature, molecular mechanisms underlying this neuropathic pain include inflammation, neuronal membrane excitation, loss of inhibitory control, glutamate receptor activation, synaptic plasticity, dendritic spine remodeling, astrocytic reorganization, and microglial activation [27–29]. To target these reported molecular processes, pregabalin, gabapentin, amitriptyline, tramadol, and lamotrigine are the first-choice pharmacologic agents to reduce the severity of neuropathic pain following SCI [30]. Multimodal pain management is strongly recommended because different mechanisms are responsible for the neuropathic pain, and individual variations to the treatment response commonly occur [31].

16.7 Conclusion

Anesthetic management following acute SCI requires careful consideration, particularly in patients with high-level cord injuries. When choosing an intubation technique, it is important to consider options that prevent excessive cervical spinal flexion and extension to avoid causing secondary injury to the spinal cord. It is important to maintain and closely monitor MAP following anesthesia induction, as hypoperfusion is a major complication and can lead to secondary neurological injury. Following careful intubation, decisions regarding choice of anesthetic agents should primarily focus on reducing the risk for hypotension during surgery and the need for neurophysiologic monitoring. Damage to the blood spinal cord barrier along with loss of sympathetic nervous system input leads to challenges in both fluid maintenance and proper hemodynamic stabilization. The use of vasopressors is not only an important adjunct therapy in maintaining appropriate spinal perfusion during anesthesia induction but is important to prevent secondary complications from spinal shock and impaired autoregulation. It is important to consider monitoring techniques to avoid changes in intraspinal pressure that could compromise the spinal cord. Lastly, pain management is an important aspect of treatment, and should be addressed both postoperatively and long term, as neuropathic pain can lead to further debilitation following surgical recovery.

Key Points

- Goals for airway management after cervical SCI include avoiding excessive flexion or extension of the cervical spine to prevent spinal cord traction and secondary neurological injury.
- Fiber-optic intubation prior to anesthesia is currently the optimal technique for intubation before anesthesia.
- Anesthesiologists must be aware of the risk for systemic hypotension and bradycardia following anesthesia induction especially when the severity and level of spinal cord injury is higher. Vasopressors and inotropic agents can be used safely during general anesthesia.
- Because of disruption in spinal cord autoregulation and potential spinal shock, maintaining the mean arterial pressure between 85 and 90 mmHg during the perioperative period improves spinal cord perfusion and neurologic outcome.
- Invasive intraoperative hemodynamic monitoring for intraoperative fluid therapy might be beneficial for preserving intravascular volume. Hypotonic crystalloid usage should be avoided.

Conflict of Interest Authors declare no conflict of interest.

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Part IV

Co-existing Problems

17 Co-Existing Hypertension in Neurosurgery

Ramamani Mariappan and Rajasekar Arumugam

17.1 Introduction

Hypertension is a common medical problem which afflicts 25% of the general population [1]. The World Health Organization has predicted that by 2025, one-third of the world's population will be hypertensive, and this will be responsible for over 7.1 million deaths per year [2]. High blood pressure can arise from a variety of physiological abnormalities which affects the central nervous, cardiovascular, and renal system [3]. Among which the brain is the major target organ for the adverse effects of untreated hypertension [4] followed by the cardiovascular and renal system [1, 3]. Moreover, hypertension is a major risk factor for stroke and its related morbidity and, also, is one of the powerful risk factors for cognitive decline, dementia, and Alzheimer's disease (AD) [4, 5].

In the neurosurgical population, perioperative hypertension is a common event due to the interaction between the heart and brain [6, 7]. Direct stimulation of certain regions of the brain termed as CNS trigger zones (hypothalamus, brain stem, cervical spinal cord nuclei) by surgical handling or the presence of blood, (ICH, IVH) thrombus (stroke), infection (meningitis, encephalitis, abscess), or inflammation (TBI) can cause profound sympathetic stimulation which can lead to severe hypertension, neurogenic pulmonary edema, arrhythmias, and myocardial and respiratory failure [6, 8]. Furthermore, pre-existing hypertension in neurosurgical patients is one of the major risk factors for postoperative cerebrovascular and the cardiovascular morbidity [9, 10].

17.2 Classification of Hypertension

According to the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC VIII), hypertension is diagnosed if the systolic blood pressure (SBP) is >140 mmHg and the diastolic blood pressure (DBP) is > 90 mmHg on at least two occasions measured 1–2 weeks apart. It is further classified depending on the value of SBP and the DBP, as given in Table 17.1. The recent 2014 JNC VIII report recommends the desired BP target while treating the hypertensive patients with and without diabetes and chronic kidney disease (CKD) [11]. For instance, patients above 60 years, the goal is to target less than 150/90 mmHg, whereas the target should be reduced to 140/90 mmHg while treating less than 60 years old and in patients with diabetes and chronic kidney disease. Additionally, patients with prehypertension are very prone to

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Table 17.1 Classification of hypertension based on SBP and DBP

Blood pressure classification	SBP (mmHg)	DBP (mmHg)
Normal	<120	<80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	≥160	or ≥100
Hypertensive urgency (high BP with no end-organ damage)	≥180	≥110
Hypertensive emergency (high BP with end-organ damage involving the brain, heart, kidney, eye)	≥180	≥110

develop hypertension, but at this stage, medication is not needed to normalize the BP, instead such patients have to adopt lifestyle modification to control the BP within the normal limit. Lifestyle modification includes physical activity, smoking cessation, reduced alcohol consumption, control of blood sugar and the cholesterol, weight reduction, and diet modification (i.e., dried fruits and vegetables, whole grains, low-fat dairy products), and restrict sodium intake to 2.4 g/day.

17.3 Hypertensive Crisis

Acute elevation of systolic blood pressure (SBP) more than 180 mmHg and diastolic blood pressure (DBP) more than 110 mmHg is defined as hypertensive crisis, which in turn can be classified into hypertensive emergency and hypertensive urgency, with and without evidence of end-organ injury, respectively [12]. Hypertensive emergencies occur in up to 2% of patients with systemic hypertension [13]. Patients with hypertension frequently have coexisting diabetes, atherosclerosis, hypercholesterolemia, and ischemic heart disease and can present with hypertensive crisis which could lead to numerous adverse complications such as postoperative hematoma, cerebral hemorrhage, cardiac failure, cardiac arrhythmia, pulmonary edema, unstable angina, and myocardial ischemia. The incidence of hypertensive crisis is common during neurosurgery due to the stress and sympathetic activity associated with major neurosurgeries. Patients with limited cardiac reserve are more prone to cardiac complications during the neurosurgical procedure, and long-standing untreated hypertension can cause end-organ damage.

17.4 Classification of Hypertension Based on the Etiology

Hypertension is classified as primary or essential and secondary hypertension. When the cause of the hypertension is unknown, it is termed as primary hypertension which accounts for about 95% of cases of persistently raised BP. However, genetic factors in combination with environmental factors might play a role in the development of primary hypertension. For example, high sodium intake, physical inactivity, chronic high alcohol, tobacco intake, psychological stress, and low potassium and calcium intake are some of the environmental factors responsible for the development of primary hypertension [1]. Recent animal and cadaveric studies have shown that the brain stem hypoperfusion due to natural variations in vertebral arterial system anatomy could be responsible for a significant number of cases of idiopathic or essential hypertension [14–16]. Warnert et al. in their retrospective study using magnetic resonance imaging (MRI) showed a high incidence of vertebral artery hypoplasia (53%) and incomplete circle of Willis (64%) in hypertensive subjects as compared to 27% and 36% respectively in normotensive subjects, While treating hypertension, if the target BP cannot be attained with a diuretic-containing triple drug therapy at a maximum dose, it is termed as resistant hypertension. Before labeling as resistant hypertension, one should rule out the patient's compliance with medication and all the secondary causes of hypertension. Recently studies have shown an association between posterior circulation hypoperfusion

due to congenital variation in the circle of Willis and vertebral artery diameters and the development of essential hypertension [15, 16]. Sandell et al. have shown that pulsatile vertebral artery and the cranial nerve compression on the brain stem can cause hypertension which is often termed as neurogenic hypertension [17].

17.5 Pathophysiology of Neurogenic Hypertension

The rostral ventrolateral medulla (RVLM) located in the brain stem is the center of the neuronal regulation of BP and heart rate. The sympathoexcitatory C1 neurons are located beneath the surface of the brain stem in the RVLM, so stimulation of this area can cause sympathetic activation [17]. On the other hand, a depressor region in caudal medulla can reduce the sympathetic activity by direct inhibition of the RVLM and by stimulation of medullary parasympathetic centre. Various studies have shown that the neurovascular pulsatile compression (NVPC) of the RVLM by the posterior inferior cerebellar artery or the left vertebral artery was responsible for neurogenic hypertension, with gradual normalisation of BP after neurovascular decompression [18]. Furthermore, pulsatile compression of RVLM and C1 neuron can stimulate the SNS and activates angiotensin II (AngII) production causes vasoconstriction and endothelial dysfunction, which inturn causes overexpression of neural factor leading to vascular inflammation and remodeling. Additionally, an increased expression of ET-1 and NADPH oxidase-derived reactive oxygen species (ROS) results in neurogenic hypertension which is explained in detail in the section on cerebrovascular remodeling.

17.6 Secondary Hypertension

High blood pressure can arise from a variety of physiological abnormalities affecting the central and autonomic nervous systems and cardiovascular, endocrine, neurohumoral, and renal disturbances. Approximately 5% of hypertensive patients have secondary hypertension and its management depends upon the underlying cause [1].

Box 17.1 Key Points

Neurological causes of hypertension

- Traumatic brain injury, spinal cord injury
- Intracranial tumors
- GH secreting pituitary adenoma—acromegaly
- ACTH secreting pituitary adenoma—Cushing's diseases
- Infection—encephalitis, meningitis, cerebral abscess
- Brainstem lesion
- Trigeminal neuralgia
- Intramedullary spinal cord lesion
- Sinus venous thrombosis
- Dysautonomia—Guillain-Barre syndrome

17.7 Hypertension and Cerebrovascular Remodeling

Hypertension induces several adaptive changes in the cerebrovascular system among which the most important adaptive changes are hypertrophic or eutrophic remodeling and vascular stiffening. In hypertrophic remodeling, smooth muscle cells undergo hypertrophy or hyperplasia and grow inward encroaching into the lumen and reduce the luminal diameter of the artery increasing the wall thickness [4]. In eutrophic remodeling, the smooth muscle cells undergo a rearrangement that leads to a reduction of the vessel lumen without changes in total vascular mass or wall thickness [4, 19].Vascular stiffening is a process in where the collagen content increases together with the rigidity of the vessel wall [19].

Many factors are responsible for cerebrovascular remodeling such as sympathetic overactivity, reduced bioavailability of nitric oxide and endothelial dysfunction. Recently, angiotensin II

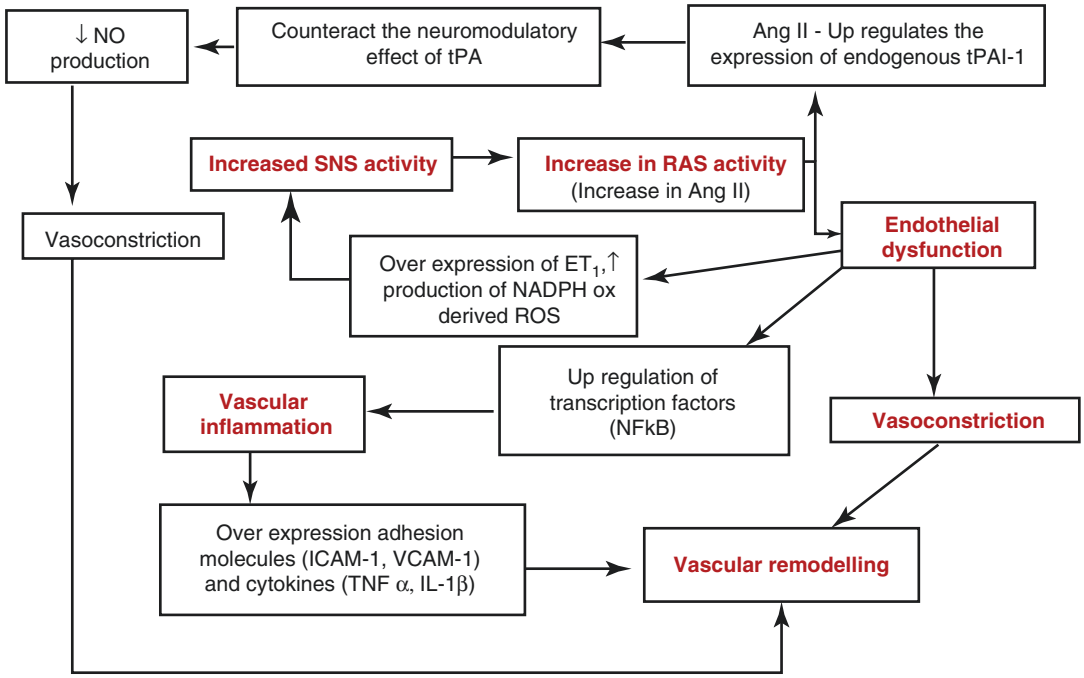

Fig. 17.1 Pathophysiology of cerebrovascular remodeling in hypertension

(AngII) has emerged as a key factor in the mechanisms of cerebrovascular remodeling [4, 20]. Although such adaptive responses reduce the stress on the vessel wall and protect the downstream microvessels from the effect of increased intravascular pressure [19, 20], it increases vascular resistance resulting in vascular insufficiency. Therefore, the duration and magnitude of the blood pressure elevation, as well as the size of blood vessels are important determinants of hypertension-induced alterations in the vascular wall. Hypertension also promotes atherosclerosis and lipohyalinosis leading to vascular occlusion. Brain activity-induced increase in CBF (functional hyperemia) is attenuated in patients with chronic hypertension by altering the endothelium-dependent relaxation of cerebral blood vessels [4, 21]. In addition, hypertension induces oxidative stress in cerebral blood vessels which leads to increased production of reactive oxygen species (ROS) [4, 20]. NADPH oxidase is a multiunit enzyme found in abundance in cerebral blood vessels and has emerged as a major source of the ROS mediated cerebrovascular dysfunction and has been implicated in the cerebrovascular dysfunction induced by angiotensin II (AngII). Another pathway through which AngII could induce vascular dysfunction involves the tissue plasminogen activator (tPA), which contributes to functional hyperemia by regulating the coupling between NMDA receptor activity and neuronal NO production. AngII counteracts the biological effect of tPA by upregulating the expression of its endogenous inhibitor plasminogen activator inhibitor-1 (PAI-1) [22] as explained in Fig. 17.1.

17.8 Effect of Hypertension on Cerebral Autoregulation

With chronic hypertension, the baroreceptor function is blunted, the autoregulatory range is higher with a rightward shift of the curve, as opposed to normotensives as shown in Fig. 17.2 [23]. Such effects are more pronounced in chronic untreated hypertensive patients, which increases the cerebral oxygen extraction fraction by up to 80%. Therefore, targeting the generally acceptable mean arterial pressure (MAP) of 65 mmHg might

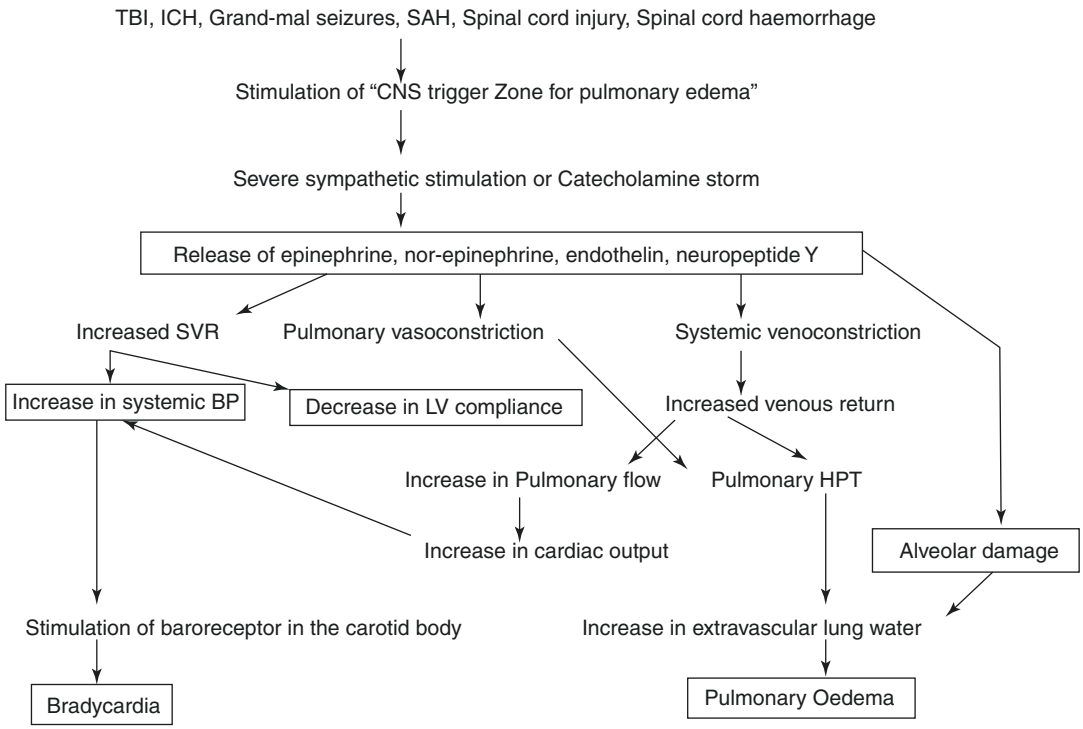

Fig. 17.2 Pathophysiology of neurogenic pulmonary edema

result in under perfusion of the brain in such patients. Hypertensives are more prone for ischemia around the periventricular white matter area since it is located at the boundary between two arterial territories such as superficial and the deep arteries. The severity of periventricular white matter injury or leukoaraiosis correlates with the magnitude of autoregulatory dysfunction [24]. The rightward shift of autoregulation indicates that they will tolerate hypertension better as compared to normotensives as presented in Fig. 17.3. However, such impaired autoregulatory response not only leads to more severe ischemia after arterial occlusion but also causes cerebral hyperperfusion during acute severe rise in blood pressure (>180 mmHg) which overwhelms the regulatory capacity disrupting the blood-brain barrier, in turn leading to cerebral edema (hypertensive encephalopathy) and intracerebral hemorrhage (ICH) [19]. Chronic untreated hypertension can cause the development of microaneurysms in small perforating arteries which are <0.9 mm in diameter, and the rupture or leak from this aneurysm could lead

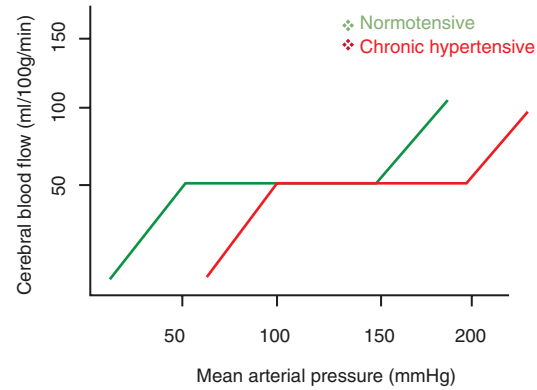

Fig. 17.3 Cerebral autoregulation curve in normotensive and hypertensive patients

to ICH commonly in basal ganglia, thalamus, pons, and cerebellum. Manifestations of hypertension can be observed as end-organ damage in almost every organ system, but more profound effects of untreated hypertension are noted in cerebrovascular system, cardiovascular system, and renal system. In the brain, extraparenchymal arteries and arterioles account for 2/3 of the vascular

resistance, while intracerebral arterioles and capillaries account for the remaining 1/3, therefore, vessels residing outside the brain have the greatest impact on parenchymal blood flow. Hypertension potentiates atherosclerosis which in turn potentiates constrictor responses of large cerebral arteries to serotonin and thromboxane contributing to vasospasm and transient ischemic attacks.

Box 17.2 Key Points

Hypertension induced end organ damage

Cardiovascular system
- Coronary artery disease
- Left ventricular hypertrophy
- Diastolic dysfunction
- Cardiac failure
- Peripheral vascular disease
- Atherosclerosis

Neurological
- Cerebrovascular accident
- Hypertensive encephalopathy

Renal
- Glomerulosclerosis
- Renal tubular ischemia
- End stage renal disease

Eye
- Hypertensive retinopathy

17.9 Pathophysiology of Neurogenic Pulmonary Edema

Neurogenic pulmonary edema (NPE) is a dreadful complication that occurs following various intracranial injuries such as intracranial and subarachnoid hemorrhage, traumatic brain injury, spinal cord injury, and refractory status epilepticus [25–30]. This clinical condition usually presents with tachypnea, tachycardia, hypertension, and bilateral basal pulmonary crepitation and even hemoptysis [29, 31]. It is often called as "death rattle" [31] due to its presentation of severe respiratory distress, pulmonary edema with normal jugular venous pressure, and severe hypoxemia [29]. The appearance of bilateral diffuse infiltrates on the chest X-ray within minutes to hours after the CNS injury is the most pathognomonic finding for the diagnosis [29]. The precise mechanism underlying this condition is incompletely understood; however, dissociation of the pulmonary autonomic system from the central vasomotor center and overstimulation of the CNS trigger zone that has been associated with excessive sympathetic discharge are the two commonly proposed mechanisms [32]. Studies have shown that the NPE does not initiate any systemic inflammatory response, as demonstrated by the lack of damage to organs other than lungs, and it is treated with adequate positive end expiratory pressure [32]. The pathophysiology of development of NPE is explained in Fig. 17.2.

17.10 Brain-Heart Interaction and Hypertension

Modern neuroimaging data, including positron emission tomography and functional magnetic resonance imaging, shows a complex set of neural interactions between the heart and brain, termed the neuro-cardiac axis [7, 33, 34]. The insular cortex, the anterior cingulate cortex, the prefrontal cortex, the amygdala, and the hippocampus are the areas connected to regions involved in autonomic control causing changes in BP and HR.

17.10.1 Role of Insular Cortex on Hemodynamic Alteration

The insular cortex controls the balance between the parasympathetic and sympathetic tone, and the right insula predominantly regulates sympathetic tone, while the left insula controls parasympathetic tone [35, 36]. During the intraoperative period, stimulation of the rostral posterior insula causes tachycardia, whereas

stimulation of the caudal posterior insula causes bradycardia. Also, intraoperative bradycardia or a depressant effect of BP especially diastolic arterial pressure is more frequent with stimulation of the left insular cortex, whereas tachycardia or a pressor effect was elicited while stimulating the right insula. In the setting of cerebrovascular accidents (CVA), involving the left insula can shift the cardiac autonomic balance toward sympathetic predominance, while CVA involving the right insula shifts toward vagal predominance.

17.10.2 Role of Brainstem on Hemodynamic Changes

It is widely recognized that regulation of cardiac function is dependent on the nucleus of the solitary tract (NST) and the rostral ventrolateral medulla (RVLM) of medulla. The NST receives signals from baroreceptors and vagus nerve. while the RVLM controls the excitatory neurons that are responsible for generation of sympathetic response. Thus stimulation of the RVLM causes sympathetic overactivity, while stimulation of NST can cause parasympathetic overactivity [7, 17].

17.10.3 Role of Prefrontal Cortex on Hemodynamics

Patients with lesions in the frontal prefrontal cortex or ischemia of the frontal lobe can present with parasympathetic features such as bradycardia and hypotension due to sympathetic activity blockade [7].

17.10.4 Role of Hippocampus on Hemodynamics

Large hemispheric brain infarcts involving hippocampus insults can result in seizures and are associated with sudden unexpected death due to the intense sympathetic dysfunction resulting in acute MI or heart failure [32].

17.10.5 Role of Hypothalamus on Hemodynamics

It has been known for a long time that stimulation of the hypothalamus could lead to cardiovascular autonomic disturbances, thus intraoperative stimulation of the lateral hypothalamus produces hypertension and/or rhythm abnrmalities. For instance, stimulation of the anterior hypothalamus produces bradycardia, while stimulation of the posterior hypothalamus results in tachycardia and sympathetic overactivity [7].

17.11 Effect of Hypertension on the Cardiovascular System

Long-standing hypertension leads to loss of arterial elasticity and compliance in both smaller arterioles and the large conduit arteries resulting in increased myocardial afterload. In order to minimize the wall stress, the cardiac myocytes undergo hypertrophy which leads to left ventricular hypertrophy (Laplace's law). Such hypertrophy of the cardiac myocytes not only increases the myocardial oxygen demand but also reduces the myocardial compliance resulting in diastolic dysfunction. Furthermore, it also accelerates atherosclerosis which further increases the demand and decreases the supply resulting in subendocardial ischemia and myocardial infarction. A subset of patients with diastolic dysfunction may progress to isolated diastolic heart failure with preserved left ventricular ejection fraction which is often undiagnosed and increases the risk for adverse cardiovascular events during high-risk procedures [37].

17.12 Hypertension and Alzheimer's Disease

The Alzheimer's Disease (AD) is a neurodegenerative condition caused by accumulation of amyloid plaques and neuronal cytoskeletal abnormalities [38]. Studies have shown that mid-life hypertension can promote AD by increasing the production of the amyloid-β

peptide. The cerebral autoregulation is impaired by amyloid-β deposition, so hypotension is likely to cause cerebral hypoperfusion, as hypertension can lead to ICH [38].

17.13 Hypertension in Neurosurgical Emergencies and Its Management

17.13.1 Acute Ischemic Stroke

Large intracranial vessel occlusion compromises the blood flow to significant portion of the brain, and it is extremely crucial to maintain adequate perfusion to the potentially salvageable penumbric regions surrounding the infarcted tissue [39]. Moreover, the normal protective homeostatic mechanisms are often impaired, and therefore, it is essential to maintain an adequate pressure in the collateral vessels to limit the infarct size. In acute ischemic stroke patients who are eligible for thrombolysis, it is crucial to bring down the BP to 180/105 mmHg before administration of intravenous rtPA and to be maintained it for the first 24 h after rtPA administration to avoid ICH. On the other hand, BP management in patients not undergoing reperfusion strategies remains a challenge, and many patients have spontaneous decline in blood pressure during the first 24 h after onset of stroke. Moreover, the recommendations available in the literature are conflicting and inconclusive. Even in the 2013 ASA/AHA guidelines for the early management of patients with acute ischemic stroke, the benefit of treating arterial hypertension in the setting of acute ischemic stroke is not well established (Class IIb; Level of Evidence C) [40]. However, aggressive reduction of blood pressure is indicated in patients with malignant hypertension associated with other medical emergencies such as MI, aortic dissection, and heart failure to avoid cardiac morbidity and mortality. While in patients, who are not eligible for tPA, the MAP should be reduced only by 15% over a period of 1–2 h while keeping a close watch on neurological status to limit the infarct size.

17.13.2 Acute Hemorrhagic Stroke

Elevated systolic blood pressure of >140 mmHg is found in almost 75–80% of patients with intracerebral hemorrhage (ICH), as the incidence of secondary hematoma is as high as 30% in the first 24 h which is associated with worse outcomes [39]. At the same time, the associated intracranial hypertension compromises perfusion to normal areas of the brain, and thus while controlling the BP, it is essential to prevent development of cerebral ischemia or re-expansion of cerebral hematoma. According to the recent 2015 ASA/AHA guidelines, in a patient with ICH who presents with the SBP between 150–220 mmHg, acute lowering of SBP to 140 mmHg is considered safe unless there is any other contraindication to acute reduction in SBP (Class I; Level of Evidence A) and can be effective for improving functional outcome (Class Ia; Level of Evidence B), whereas, for ICH with SBP >220 mmHg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion with frequent BP and neurological monitoring (Class IIb; Level of Evidence C) [41].

17.13.3 Aneurysmal Subarachnoid Hemorrhage (aSAH)

Subarachnoid hemorrhage (SAH) is a devastating complication associated with hypertensive crisis, often following rupture of an aneurysm which in turn raises ICP and decreases the CPP resulting in medullary ischemia, subsequently resulting in severe sympathetic activation and catecholamine surge. Therefore managing SAH is a challenging task since it is associated with several intracranial and systemic adverse effects which could lead to significant neurological morbidity and mortality (50%). Also patients with a recent aneurysmal SAH are more prone to rebleed (6.9%). So, it is important to optimise cerebral perfusion pressure. maintaining the balance between rebleeding and ischemia. The magnitude of blood pressure control to reduce the risk of rebleeding has not

been established. According to 2012 ASA/AHA guidelines for management of a patient with aSAH, a decrease in systolic blood pressure to <160 mmHg is reasonable to prevent rebleeding before securing the aneurysm by clipping or coiling [42].

Cerebral vasospasm and delayed cerebral ischemia (DCI) are the two devastating complications associated with aSAH. Vasospasm occurs due to a combination of cerebral hypoperfusion and autoregulatory dysfunction, which usually peaks between 3 and 14 days following SAH. Also patients with symptomatic vasospasm had been shown to benefit from induced hypertension with use of vasopressors in order to achieve a target increase in blood pressure by 10–15% from the baseline after securing the aneurysm by coiling or clipping. It is reasonable to elevate the systolic blood pressure to 180–220 mmHg while managing the symptomatic vasospasm if there is no contraindication for this acute elevation. (Class II evidence)

17.13.4 Paroxysmal Sympathetic Hyperactivity (PSH) in Severe Traumatic Brain Injury

The injured brain is at an increased risk of developing secondary damage during episodes of inadequate perfusion, and has been associated with an unfavorable outcome [43, 44]. Also, the injured brain is extremely vulnerable to both global cerebral ischemia and hyperperfusion because of impaired vascular reactivity and autoregulation [45]. So it is very important to maintain an optimal BP to balance the risk between ischemia and hyperperfusion. The recent 2016 Brain Trauma Foundation guidelines for the management of severe traumatic brain injury, could not provide a level I or II recommendation regarding the optimal management of BP [46]. However, it is suggested to maintain the SBP at ≥100 mmHg for patients of 50–69 years old and at ≥110 mmHg for patients 15–49 or over 70 years old to decrease mortality (level III evidence).

Paroxysmal sympathetic hyperactivity (PSH) or central dysautonomia is a clinical condition observed in patients with severe TBI, especially among young males [47, 48]. Episodes of tachycardia, tachypnea, hypertension, and hyperthermia and dystonic postures are common manifestations of this syndrome. Its incidence varies from 7.7 to 33% following TBI, and the available data regarding the management of PSH is limited. The use of alpha-2 agonist clonidine, beta-blockers, bromocriptine, intravenous morphine, midazolam, and intrathecal baclofen all has been tried to treat this condition [47].

17.14 Perioperative Hypertension

Perioperative hypertension is characterized by an increase in BP by 20% compared to baseline BP. Sympathetic stimulation, activation of the renin-angiotensin-aldosterone pathway, and the metabolic stress associated with cerebral activation, surgical handling of certain areas of the brain (hypothalamus, left insula, brain stem), and cranial nerve manipulation (trigeminal nerve stimulation) are the common causes of perioperative hypertension in neurosurgical patients [1, 9, 49–51]. Presence of preoperative hypertension is one of the risk factors for perioperative bradycardia, tachycardia, and hypertension and was found to be the second most common risk factor for surgical morbidity [9, 52]. Marked intraoperative fluctuations in blood pressure are common among hypertensive patients undergoing the neurosurgical procedure under general anesthesia that might result in adverse perioperative outcomes. Longterm hypertension is associated with constricted blood volume, the vasodilation secondary to anesthesia predisposes them to intraoperative hypotension. On the other hand, LVH-induced ventricular diastolic dysfunction can lead to fluid overload and heart failure during the perioperative period [37]. The various causes of perioperative hypertension and its management are listed in Table 17.2.

The most common postoperative complications after the neurosurgical procedure are high blood pressure (25%) and the cardiovascular events (7%). The incidence of acute postoperative

Table 17.2 Common causes of perioperative hypertension and their management

Perioperative causes of hypertension	Management
Preoperative factors	
Pre-existing essential hypertension	Antihypertensive therapy (see Table 17.7)
Pre-existing secondary hypertension	Antihypertensive therapy + treatment of the cause
Anxiety	Adequate reassurance and premedication with benzodiazepines; exert Caution: in patients with raised ICP
Pain	Analgesics. Caution: in presence of raised ICP, a non-opioid based analgesics has to be chosen
Raised ICP	Antiedema measures (osmotherapy, dexamethasone, hyperventilation, and head end elevation)
Intraoperative factors	
Laryngoscopy and intubation	Adequate anesthesia and analgesia using propofol and fentanyl, remifentanil, inhalational agents (except for patients with raised ICP), esmolol, metoprolol, lignocaine
Application of pins	Scalp block or local infiltration prior to skull pinning and analgesics
Local anesthetic with adrenaline infiltration	Avoid intravascular administration by repeated aspiration; avoid beta-blockers to treat this hypertension; it may cause unopposed α stimulation leading to hypertensive crisis. This hypertension can be treated with propofol bolus, labetalol. GTN in case of hypertensive emergency
Surgical stimulation (periosteal elevation and temporalis muscle dissection)	Adequate anesthesia and analgesia and short-acting beta-blockers for tachycardia
Intracranial hypertension due to anesthetic-induced increase in CBF	Hyperosmotic therapy, temporary hyperventilation, change from inhalational agents to TIVA
The inadequate plane of anesthesia	Increasing the depth of anesthesia
Hypercarbia	Increase the minute ventilation, adequate paralysis, treat hyperthermia, and rule out malignant hyperthermia
Hypervolemia	Restrict fluids Consider diuretics
Hyperthermia	Avoid external warming, administer cold intravenous fluids, rule out malignant hyperthermia
Withdrawal of antihypertensive	Increase the plane of anesthesia Reinstituting the regular drug if oral administration is not possible, use short-acting adrenergic receptor blockers, calcium channel blockers
Medication error	Immediate recognition and discontinuation of the offending drug
Full bladder	Catheterize the patient if not done already; ensure there is no occlusion by lignocaine jelly; or kink at the urinary catheter if the patient is catheterized
Intraoperative seizure	Cold saline irrigation at the surgical field A bolus dose of the regular anticonvulsant drug Midazolam, propofol bolus
Pin site extradural hematoma/subdural hematoma	Evacuation of hematoma [suspect pin site hematoma once all the above mentioned causes has been ruled out for the intra-operative brain bulge]
Intraoperative cranial nerve, brain stem handling while tumor removal	Inform surgeon so that traction on these vital structures are removed
Emergence hypertension	Lignocaine, labetalol, esmolol, nicardipine clevidipine, hydralazine, dexmedetomidine

Table 17.2 (continued)

Perioperative causes of hypertension	Management
Postoperative factors	
Pain, ETT intolerance in case of planned post-op elective ventilation	Adequate analgesia and sedation
Shivering	Treat hypothermia, administration of a small dose of pethidine, clonidine, ketanserin, ondansetron, tramadol, fentanyl, propofol
Raised ICP (postoperative edema, hematoma)	Reinstitute anti-edema measures, surgical evacuation of hematoma if needed
Postoperative delirium	Low dose dexmedetomidine
Full bladder	Empty the bladder by catheterization
Hypoxia Hypercarbia	Oxygen therapy Noninvasive CPAP ventilation if no contraindications, e.g., TNTS surgery
Withdrawal of antihypertensive	Reinstituting the regular drug Short-acting antihypertensive drugs
Postoperative myocardial infarction	Morphine, labetalol, esmolol, low dose nitroglycerin without causing a precipitous drop in BP

ICP intracranial pressure, *GTN* glyceryl trinitrate, *CBF* cerebral blood flow, *ETT* endotracheal tube, *TIVA* total intravenous anesthesia, *CPAP* continuous positive airway pressure, *TNTS* transnasal transsphenoidal, *BP* blood pressure
Note: Acute postoperative hypertension therapy should be individualized for the patient

hypertension following craniotomy is very high and varies from 54 to 91%, especially after carotid endarterectomy where it is about 9–65% [53]. Postoperative hypertension occurs during the first 20 min of the postoperative period, although their resolution can require up to 3 h, and if left untreated, postoperative hypertension increases the risk of postoperative hematoma and myocardial ischemia [1, 54, 55]. Basali et al., in their retro-spective study, found that the incidence of acute postoperative hypertension is about 57% and also have shown that there is a correlation between postoperative hypertension and the incidence of postoperative hematoma [55]. So, it is extremely important to control the blood pressure for such high-risk cases. The various risk factors for the development of postoperative hematoma are listed in Table 17.3.

Table 17.3 Various risk factors of post craniotomy hemorrhage

Pre-operative factors
Preoperative hypertension
Pre-op use of anticoagulants and antiplatelet drugs
Location of intracranial space-occupying lesions and their histological type
Vascularity of a tumor
Invasion of a tumor into the venous sinuses
Vascular surgeries—AVM surgery and carotid endarterectomy
Heavy alcohol consumption
Intraoperative factors
Intraoperative hypertension
The extent of tumor removal
Quality of surgical hemostasis
Coughing and bucking on ETT during surgery—increase in venous pressure and bleeding
Excessive intraoperative bleeding leading to coagulopathy
Postoperative factors
Postoperative hypertension
Use of cerebral vasodilator to control the postoperative hypertension
Coughing and bucking on the ETT during extubation or during elective ventilation
Uncorrected coagulopathy
Early institution of anticoagulants

ETT endotracheal tube, *AVM* arteriovenous malformation

17.15 Emergence Hypertension

Increased sympathetic activity and increased RAA activation during withdrawal of the anesthetics together with the extubation response during coughing and straining on ETT and hypercarbia

due to ventilatory insufficiency are the some of the causes for emergence hypertension in neurosurgery. Emergence hypertension may cause intracranial complications such as bleeding and cerebral edema. Postoperative bleeding can be a devastating complication after intracranial surgery, whose incidence varies from 0.9 to 3.5%. Also, emergence hypertension can increase the risk of myocardial ischemia due to an increase in myocardial oxygen demand in patients with high cardiac risk. Studies have shown that there is an association between high systolic BP (>160 mmHg) and intracranial bleeding. So, it is imperative to control the systolic blood pressure between 120 and 150 mmHg during emergence from anesthesia.

17.16 Perioperative Hypertension in Carotid Endarterectomy and Its Management

The majority of the patients undergoing carotid endarterectomy often have coexisting hypertension. Also, hemodynamic fluctuations are quite frequent during carotid surgeries due to manipulation of the carotid baroreceptors. Thus it is essential to maintain adequate blood flow by keeping the SBP above 180 mmHg during carotid cross-clamping in order to increase the collateral flow. Furthermore, it is extremely crucial to control postoperative hypertension to prevent cerebral hyperperfusion syndrome. Moreover, postoperative carotid sinus dysfunction could manifest as either hyper or hypotension which necessitates close monitoring neurological status with appropriate immediate treatment.

17.17 Preoperative Evaluation of Hypertensive Patients Coming for the Neurosurgical Procedure

The existing evidence doesn't show any benefit in postponing an elective surgery if diastolic pressure is <110 mmHg [52, 56, 57]. Similarly, it is not advisable to start a new antihypertensive drug to control BP in the immediate preoperative period, because such treatment could result in marked hemodynamic fluctuations in the intraoperative period. All neurosurgical procedures are considered to be a moderate to high-risk surgeries; therefore it is better to defer the surgery when the DBP is >110 mmHg. It is also recommended that high BP should be reduced slowly over a period of 6–8 weeks to ameliorate the myocardial and cerebrovascular changes related to severe hypertension. The decision to delay surgery for stabilization of BP or to proceed with the surgery after moderate reduction of BP by using antihypertensive drugs depends upon the urgency of the surgical procedure. The recommended target blood pressure in various neurosurgical cases is listed in Table 17.4.

17.18 Preoperative Evaluation of Hypertensive Patients Coming for Elective Surgery

While evaluating a patient with hypertension, it is essential to know the cause of hypertension (essential or secondary), duration of hypertension, the type of antihypertensive medications, adequacy of blood pressure control, the presence of hypertension-associated end-organ damage, and the presence of coexisting diseases such as diabetes and IHD. The factors that needs to be considered during the preoperative evaluation of neurosurgical patients with hypertension are given in Table 17.6.

17.19 Preoperative Investigation Needed in Patients with Longstanding Hypertension

Table 17.5 shows the necessary investigation indicated for patients with essential hypertension undergoing neurosurgical procedure, as the extent of the investigations depends on the presence of other comorbidities, end-organ damage, nature and extent of the surgical procedure. The routine preoperative investigation needed for secondary hypertension depends on the cause of secondary hypertension which is beyond the scope of this chapter.

Table 17.4 Blood pressure management of various neurosurgical cases

Type of neurosurgical cases	Hemodynamic target	Caution
Acute ischemic stroke with BP > 220/120 mmHg	*Patients eligible for i.v tPA* BP reduction to <180/105 mmHg *Patients not eligible for i.v tPA* 15% reduction in MAP over 1–2 h	Close neurological examination
Acute intracranial hemorrhage with systolic BP > 150–220 mmHg	A gradual reduction in systolic BP to <140 systolic, over 1–2 h	Close neurological examination
Hypertensive encephalopathy	25% reduction in MAP over 4–8 h	Avoid sodium nitroprusside
Subarachnoid hemorrhage	A gradual reduction in systolic BP to <160 mmHg over 1–2 h before clipping or coiling	Avoid sodium nitroprusside
Hypertension after craniotomy	Reduction in systolic BP to <160 mmHg and maintain the systolic blood pressure between 120–150 mmHg	Close neurological examination
In elective neurosurgery for tumors	Intraoperative MAP should be maintained within 10–15% of baseline BP	Cardiac and neurological monitoring
Carotid endarterectomy	During cross clamp SBP should be normal or *20% above* the baseline After surgery—SBP should be reduced <170 mmHg or *within 20% of baseline* to prevent cerebral hyper perfusion syndrome	Close neurological monitoring
Post AVM surgery	SBP should be maintained between 90 and 110 mmHg to prevent perfusion breakthrough hypertension	Close neurological monitoring

i.v tPA intravenous tissue plasminogen activator, *BP* blood pressure, *MAP* mean arterial pressure, *SBP* systolic blood pressure, *AVM* arteriovenous malformation, *MAP* mean arterial pressure

Table 17.5 Preoperative investigation for hypertensive patients

Preoperative investigation	Rationale
Blood investigations	
Hemoglobin/Hematocrit	Most neurosurgical procedures are associated with blood loss Patients with chronic hypertension-could have a contracted blood volume so might have spuriously high hematocrit
Fasting, postprandial blood glucose	To diagnose co-existing diabetes
Fasting lipid profile	Hypertension accelerates atherosclerosis in presence of altered lipid profile
Serum electrolytes (Na^+, K^+, HCO_3)	Diuretics can cause various electrolyte abnormalities. For example, loop diuretics-hypokalemia, ACE –i, or ARB—hyperkalemia
Serum urea and creatinine	Serum creatinine >2 mg/dL—increases the risk of perioperative renal failure
Urine examination	
Urine albumin or Protein Albumin/ Creatinine ratio (ACR) Protein/ Creatinine ratio (PCR)	In patients with coexisting diabetes and renal dysfunction, macroalbuminuria is considered when • >300 mg/day of albumin in urine • > 500 mg/day of protein in urine • ACR > 25 and 35 in male and female respectively • PCR > 40 and 60 for male and female
Other investigations	
Electrocardiogram (E.C.G)	LVH, ST depression, LVH with strain, Q waves, rhythm abnormalities
X- ray Chest	Optional; to look for cardiomegaly, in patients with coexisting COPD to compare in case of any postoperative pulmonary complications
Echocardiography	To look for systolic and diastolic dysfunction in patients with known structural heart disease, poor effort tolerance or if ET cannot be assessed
Carotid Doppler	In patients with h/o stroke or transient ischemic attacks
Renal artery Doppler	In patients with renovascular hypertension

COPD chronic obstructive lung disease, *LVH* left ventricular hypertrophy, *ET* effort tolerance

Table 17.6 Factors to be evaluated during the preanesthetic evaluation in hypertensives

Preanesthetic assessment	Implications
Type of hypertension	Primary or secondary
Duration of hypertension	Longer duration is associated with end-organ damage and contracted volume status
Type of antihypertensive	Each class of drug carries an unique implication under anesthesia
Adequacy of blood pressure control	Trends in blood pressure should be noted to check the adequacy of antihypertensive therapy instead of a single preoperative reading on the day before surgery
Presence of long-term complications	LVH with systolic and diastolic dysfunction, coronary artery disease Presence of renal dysfunction (creatinine >2.0 mg/dL) Increased risk of perioperative stroke due to impaired cerebral autoregulation Retinopathy—increased risk of perioperative blandness
Presence of other medical comorbidities	Coexisting diabetes mellitus, atherosclerosis, ischemic heart disease increase the perioperative morbidity and mortality

LVH left ventricular hypertrophy

17.20 Perioperative Oral Antihypertensive Drugs and Its Perioperative Implications

In general, both the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) guidelines for the management of patients with hypertension recommend continuing the routine antihypertensive drugs even on the day of surgery [56, 58] as sudden withdrawal of antihypertensive drugs could result in rebound hypertension during the peri-operative period. Moreover, it is reasonable to initiate betablockers prior to surgery in patients with a moderate to high RCRI risk score for major adverse cardiac events, provided it is started well in advance instead of starting immediately before the surgery (Class IIb). On the other hand, the peri-operative management of angiotensin receptor blockers (ARB) and angiotensinogen-converting enzyme inhibitor (ACEI) still remains uncertain, because of the concern of the potentially significant intraoperative hypotension. However, the recent 2017 ACC/AHA task force guidelines on perioperative cardiovascular evaluation suggests to continue them and also to restart in the postoperative period at the earliest possible [58].

17.21 Management of Perioperative Hypertension Using Parenteral Antihypertensive Drugs

The common causes for intraoperative as well as postoperative hypertension and its treatment are given in Table 17.2. Most of the intraoperative hypertensive episodes are short-lived, and treating these episodes with long-acting antihypertensive drugs can cause an unpredictable drop in BP when the stimulus is ceased and also can lead to wide fluctuation in BP throughout surgery that can increase the perioperative morbidity and mortality. It is better to treat these episodes with short-acting IV anesthetics, analgesics, and antihypertensive drugs, and various patient and surgery related implications should be considered while selecting these drugs. Commonly used parenteral antihypertensive drugs and the recommended doses and their side effects are provided in Table 17.7.

17.22 Conclusion

Perioperative hypertension is frequently encountered during neurosurgery, and is one of the major risk factors for perioperative cerebrovascular and cardiovascular morbidity. Therefore understanding the various implications of hypertension with proper preoperative evaluation, optimization of antihypertensive agents, meticulous administration of anesthetic and analgesic agents, avoidance of wide fluctuations in BP and strict control of BP during the perioperative period are the essential elements while managing a patient with hypertension.

Table 17.7 Commonly utilized parenteral antihypertensive agents and their recommended dose

Class	Drugs	Dose	Caution
Vasodilators	Hydralazine	Initial 10 mg slow IV infusion repeated every 4–6 hourly	Effects are unpredictable and relatively long acting
	Sodium nitroprusside	Initial 0.3–0.5 mcg/kg/min Maximum 10 mcg/kg/min but only for a limited period	Causes tachyphylaxis with prolonged use Cyanide toxicity can result in irreversible neurotoxicity
	Nitroglycerin	Initial 5 mcg/kg/min Maximum 10 mcg/kg/min	Avoid in hypovolemic patients
Selective $beta_1$ receptor blockers	Esmolol	Loading dose 500–1000 mcg/kg/min over 1 min, maintenance 50–200 mcg/kg/min	Caution in patient with heart block
Combined alpha and beta receptor blockers	Labetalol	Initial 0.3–1 mg/kg slow IV, maintenance 0.3–1 mg/kg/h	Contraindicated in chronic obstructive lung disease
Calcium channel blockers	Nicardipine	Initial 5 mg/h, maximum 15 mg/h	Contraindicated in aortic stenosis
	Clevidipine	Initial 1–2 mg/h, maximum dose 32 mg/h	Contraindicated in egg allergy
Alpha-adrenergic receptor blockers	Phentolamine	IV 5 mg bolus every 10 min	Useful in pheochromocytoma, cocaine toxicity, and clonidine withdrawal
Selective $dopamine_1$ receptor agonist	Fenoldopam	Initial 0.1–0.3 mcg/kg/min Maximum 1.6 mcg/kg/min	Contraindicated in patients with raised intracranial and intraocular pressures
Others: α2 receptor agonist	Dexmedetomidine	Bolus 0.5–1 μg/kg Infusion 0.2–0.7 μg/kg/h	Elderly, patients with heart block, severe ventricular dysfunction, hypovolemia

IV intravenous

Key Points

- Hypertension accelerates atherosclerosis which in turn potentiates the vasoconstrictor responses of large cerebral arteries to serotonin, and thromboxane and lead to several cerebrovascular morbidities, and it is a powerful risk factor for cognitive decline, dementia, and Alzheimer's disease.
- Perioperative hypertension and hypertensive crisis are common events in neurosurgical population due to the sympathetic stimulation, activation of the renin-angiotensin-aldosterone pathway and the metabolic stress associated with cerebral activation, surgical handling of certain areas of the brain, and cranial nerve manipulation.
- It would be prudent to defer the elective surgery when the DBP is >110 mmHg, and the high BP should be controlled gradually over a period of 6–8 weeks to ameliorate the myocardial and cerebrovascular changes related to severe hypertension.
- In patients in whom the surgery cannot be postponed, it is not advisable to start a new antihypertensive drug to control BP in the immediate preoperative period which can lead to severe hemodynamic instability.
- Most of the intraoperative hypertensive episodes are short-lived, and treating these episodes with long-acting antihypertensive drugs can cause wide fluctuation in BP throughout the surgery and an undesirable drop in BP when the stimulus is ceased and could add on to morbidity.

- High blood pressure and adverse cardiovascular events are more common after the neurosurgical procedure. Postoperative hypertension increases the risk of postoperative hematoma which inturn could worsen the postoperative outcome. Therefore, aggressive control of systolic blood pressure between 120 and 150 mmHg during emergence from anesthesia is necessary to reduce the postoperative morbidity.
- The shift of autoregulation curve to the right in hypertensive patients mandates that the blood pressure should not be dropped more than 15–20% of baseline to maintain the adequate cerebral perfusion pressure.

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Co-existing Diabetes Mellitus in Neurosurgical Patients

18

Manikandan Sethuraman

18.1 Introduction

After a brief primary acute insult to the brain like head trauma, ischemia as in stroke, bleed as in intracranial hemorrhage (ICH), or subarachnoid hemorrhage (SAH), patients can suffer from a variety of secondary insults which aggravates the primary brain injury leading to poor outcomes including mortality. In addition, these secondary insults prolong the intensive care unit (ICU) and hospital stay with added cost of treatment. High degree of vigilance for prevention and aggressive management of these secondary aggravating factors form a major part of the perioperative as well as critical care pathways to improve the outcomes. Hyperglycemia is one of such frequent secondary insults that occur in these patients that need to be diagnosed and managed aggressively. Writing Committee of American Diabetes Association has classified hyperglycemia seen in hospitalized patients of three types: patients with known diabetes mellitus (DM), newly diagnosed DM, and hospital-related hyperglycemia due to the illness and which reverts back after discharge from hospital [1]. Hyperglycemia is seen in both neurosurgical and neurological diseases especially in acute stages of the disease process. The incidence of hyperglycemia is very high varying from 30 to 50% in patients with acute stroke, 69% in subarachnoid hemorrhage, 40% in head injured, 47% in ICU, and 32% in non-ICU hospitalized patients [2–5]. This chapter will enumerate the various pathophysiological, diagnostic, and therapeutic aspects of hyperglycemia occurring in brain disease.

18.2 Hyperglycemia in Hospital Setting (ICU and Non-ICU)

18.2.1 Stress Hyperglycemia

In patients admitted in the medical and surgical ICU and in the perioperative period, transient hyperglycemia is seen, especially without history of DM. This is termed "stress hyperglycemia" (SH). Initially the condition was thought to be insignificant. However, such hyperglycemia was found to be associated with increased morbidity, and aggressive treatment of hyperglycemia has been advocated [6]. The mortality rates were found to be higher for critically ill patients with newly diagnosed hyperglycemia in the hospital compared to normoglycemia as well as hyperglycemia in known patients with DM [7, 8]. The mechanism of stress hyperglycemia is thought to be due to complex interplay of counter-regulatory hormones like catecholamines, growth hormone, ACTH, and

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cortisol along with insulin resistance. Stress caused by various types of brain injury leads to enhance production of various inflammatory mediators like cytokines. Tumor necrosis factor-alpha (TNF) increases the production of glucagon which enhances hepatic production of glucose [9].

The inflammation and cytokines also cause insulin resistance which prevent hepatic formation of glucose as well as inhibition of insulin receptors (GLUT4) in the peripheral tissues causing poor uptake of glucose and reduced production of muscle glycogen from glucose [10]. In addition, the hyperglycemia itself suppresses immune function and increases the inflammatory mediators release causing further hyperglycemia [11]. There is enhanced lipolysis in tissues causing impaired insulin sensitivity. Hence stress hyperglycemia is characterized by glucose toxicity, lipotoxicity, and enhanced inflammation leading to endothelial dysfunction and organ damage.

18.2.2 Hyperglycemia in Head Injury

Since many years it has been well recognized that hyperglycemia occurs frequently in patients with head injury irrespective whether preexisting diabetes mellitus is present or not. In majority, the condition occurs as hyperosmolar nonketotic hyperglycemia. Presence of hyperglycemia has been associated with poor Glasgow coma scale score (GCS) and poor survival. The degree of hyperglycemia was found to be independent of the magnitude of raise in intracranial pressure [12]. Severe hyperglycemia was seen within 12 h of head injury and reduced in 36–48 h; however, there was a tendency for persistent mild hyperglycemia in the early phase of head injury till 5–7 days. The systemic hyperglycemia was found to correlate with CSF hyperglycemia and lactate levels [13].

In pediatric patients with closed head injury, Parish et al. found that transient hyperglycemia was also seen in children; an older study showed that the hyperglycemia was not associated with poor prognosis as seen in adult population with head injuries [14]. However, a recent study has found that severe hyperglycemia (>200 mg%) was associated with poor outcome in pediatric patients compared to mild hyperglycemia [15]. Another recent study has shown that early hyperglycemia was associated with increased hospital mortality and reduced ventilator free days and hospital stay in moderate to severe head injured paediatric patients [16].

18.2.3 Hyperglycemia in Stroke

Acute stroke is one of the leading causes of morbidity in the world, and high incidence of hyperglycemia is seen at admission regardless of whether they are diabetic or not. Patients presenting with admission hyperglycemia have been found to have poor National Insitiute of Health Stroke scale (NIHSS) score indicating the severity of stroke [17]. A cutoff value of admission glucose level of more than 143 mg% has been shown to increase short-term mortality in their study [17]. The etiology of hyperglycemia is thought to be due to stress induced. Admission hyperglycemia has been found to be associated with poor functional outcome, inadequate recanalization, and risk for hemorrhagic transformation following intra-arterial thrombolysis [18]. In addition to admission hyperglycemia, Osei et al. have found that presence of impaired fasting glucose as well as prediabetic state has been associated with poor outcome in patients with acute stroke for IA thrombolysis [18]. The pathogenic mechanism of hyperglycemia causing poor outcome is due to multiple etiology. Excess glucose in the presence of ischemia causes the mitochondria in neurons to produce more lactic acidosis via anaerobic pathway leading to intracellular acidosis and cell death [19]. This is particularly seen in penumbral regions. Moreover, hyperglycemia causes disruption of blood capillary barrier and blood brain barrier leading to increased brain edema and hemorrhagic transformation [20]. Hyperglycemia has also been thought to alter the cerebrovascular reactivity leading to poor recanalization following intra-arterial thrombolytic therapy.

18.2.4 Hyperglycemia in SAH

Hyperglycemia is frequently seen at admission in patients with SAH. The hyperglycaemia occurrence is thought to be due to the effect of brain injury. Hyperglycemia at admission as well as higher blood glucose values that were seen in the first 14 days following SAH has been found to be associated with higher 1-year mortality [21]. Poorer grade SAH is associated with higher admission hyperglycemia compared to good grades (Hunt and Hess) [22]. In addition to immediate and delayed poor outcome, mean hyperglycemia in the ICU has been associated with increased incidence of vasospasm, delayed cerebral ischemia, and prolonged stay in ICU [23]. However, recently it was found that in patients with SAH, glucose value of <80 mg/dl is associated with cerebral infarction, vasospasm, and worse functional outcomes [24]. Hence both hyper- and hypoglycemia were found to be detrimental in patients with SAH.

18.2.5 Hyperglycemia of Endocrinopathies

Hyperglycemia can be seen in patients with excessive secretion of pituitary hormones notably growth hormone (GH) and adrenocortical-stimulating hormone (ACTH). Hyperglycemia that occurs in acromegaly patients is due to glucose intolerance or diabetes mellitus. The incidence is estimated to be 12–37%. The etiology is thought to be due to both excessive levels of circulating GH and insulin-like growth factor (IGF-1) concentrations both of which cause insulin resistance. There is decreased glucose utilization as well as increased production of glucose [25]. Hyperglycemia seen in these patients has been associated with increased mortality compared to general population [26]. Patients with Cushing's disease also present with increased blood glucose. Up to 40–45% of patients with Cushing's disease have been reported to develop DM, and 10–30% of patients have impaired glucose tolerance [27]. Similar to acromegaly, these patients also have insulin resistance as well as increased production of glucose by liver which is responsible for hyperglycemia.

18.2.6 Other Conditions

Hyperglycemia is also seen in acute phase of variety of other neurological conditions like intracranial bleeds due to various etiology, central nervous system infections like acute meningoencephalitis, spinal cord injuries, status epilepticus, sepsis, etc. Use of high dose of steroids and immunosuppressive therapies for the treatment of various neurological conditions are also associated with hyperglycemia in ICU and non-ICU hospitalized patients. A single dose of dexamethasone has been found to cause hyperglycemia in the perioperative period in neurosurgery [28]. It has been suggested to monitor the blood glucose concentration for 12–24 h in a nondiabetic patient who has been administered dexamethasone for craniotomy.

18.3 Effects of Hyperglycemia on Brain

Glucose is the main source of energy for the brain under normal conditions. Brain glucose concentration is approximately two thirds of plasma concentration, and it is shown to rise with hyperglycemia. The effects of hyperglycemia in injured brain are multifactorial. Hyperglycemia, hypoglycemia, and greater fluctuations in plasma glucose levels have been proven to aggravate brain injury. Increased plasma glucose occurring both in acute conditions like SH as well as chronically seen in DM affects produce both structural and functional brain abnormalities. In acute states, hyperglycemia produces intracellular increase in lactate (acidosis) leading to apoptosis. In addition, it was found that acute hyperglycemia causes microvascular changes, reduced BBB permeability, reduces cerebral blood flow, and worsens ischemia [29]. Clinically hyperglycemia is characterized by increase in infarct size and increased cerebral edema (both cytotoxic and

vasogenic) and hemorrhagic transformation in focal brain ischemia seizures [30].

18.3.1 Diagnostic Criteria for Hyperglycemia

The basic diagnostic criterion for hyperglycemia is elevation in the blood glucose level. However, the cutoff for diagnosis of hyperglycemia in the ICU and perioperative period is very much varied and complicated by various factors. This is due to the differences in the management strategies adapted by different institutions. Moreover, the diagnostic criteria of hyperglycemia are often confused values used for diagnosis of diabetes mellitus (DM), and the values are even extrapolated. Admission hyperglycemia or its complications like ketoacidosis may occur in acute neurological patients who are previously euglycemic or undiagnosed DM or patients with documented DM. Moreover, the criteria specific for use in pediatric patients is not established.

The normal fetal mean blood glucose is approximately 3 mmol/L, and immediately after birth there is transient neonatal hypoglycemia due to the limited capacity of newborns to produce endogenous glucose. It was found that by 72 h after birth, the capacity to generate endogenous glucose improves, and the blood glucose level reaches a higher level comparable to the children and adult level which is maintained within a narrow range of 3.5–5.5 mmol/L due to interactions of various hormones [31].

The recent guidelines issued by the American Diabetes Association (ADA) for diagnosis of DM are (1) fasting plasma glucose (FPG) > 126 mg% (7.0 mmol/L) or 2-h postprandial plasma glucose (PG) > 200 mg% (11.1 mmol/L) or glycosylated hemoglobin (A1C) of more than 6.5% or patients with classical symptoms of diabetes or diabetic ketoacidosis with random plasma glucose >200 mg%. A *prediabetic state (impaired glucose tolerance)* is also described and defined with FPG levels between 100 mg% (5.6 mmol/L) to 125 mg% (6.9 mmol/L) or 2-h PG 140–199 mg% (7.8–11 mmol/L) or A1C between 5.7 and 6.4% [32].

The diagnosis of hospital-related hyperglycemia is not clear. Dungan et al. have proposed for diagnosis of hospital-related hyperglycemia in patients without previous history of DM to be fasting glucose >6·9 mmol/L or random glucose >11·1 mmol/L without evidence of previous diabetes. In patients with preexisting poorly controlled diabetes, deterioration of pre-illness glycemic control with elevated plasma glucose (>30 mg% from preexisting values or >200 mg%) is usually considered for diagnosis of the condition. In a well-controlled diabetic patient with A1C < 7%, the above criteria used for nondiabetic patients would suffice [33].

In addition to hyperglycemia, it is important to understand the criteria for hypoglycemia as aggressive treatment of hyperglycemia can result in reduced plasma glucose [32]. Hypoglycemia is defined as three levels: (a) hypoglycemia alert (PG < 70 mg%, 3.9 mmol/L), (b) clinically significant hypoglycemia (PG <54 mg%, 3.0 mmol /L), and (c) severe hypoglycemia with cognitive decline needing external assistance (PG values undefined).

18.3.2 Management of Hyperglycemia in Hospitalized Patients

Hyperglycemia in acute illness cannot be preventable; however high degree of anticipation, early recognition, and management of the condition can help in improving patient's outcome and reduced hospital stay. In patients with neurological illness with preexisting DM, A1C levels will help in understanding the control of glucose. The targets for control as suggested by American Diabetes Association (ADA) would help in reducing the perioperative as well as ICU complications. The ADA recommends A1C of <7.0%, fasting plasma glucose of 80–130 mg%, and postprandial plasma glucose of <180 mg% as targets for glycemic control in nonpregnant adult diabetic patients [34]. In pediatric patients and young adults with known DM, the recommended targets for glycemic control are A1C <7.5%, fasting PG 90–130 mg%, and postprandial PG 90–150 mg% [35].

The treatment targets and strategies for hospitalized especially ICU patients presenting with hyperglycemia without history of DM are very challenging.

1. The hyperglycemia may be transient, usually seen at time of presentation in the emergency department or in the first 24 h of admission to ICU especially in acute cases after which the glucose levels return to baseline.
2. The difficulty in differentiating SH from patients who have impaired glucose tolerance or undiagnosed DM may interfere in the short-term vs long-term management of the metabolic problem. The levels of A1C may give a clue about the type of hyperglycemia. Patients with diabetes ketoacidosis and hyperosmolar coma may present clinically with acute neurological problems and needs to be managed as per the protocols existing for the treatment of the condition [36].
3. Perhaps the most important is the different type of protocol followed in the management of hyperglycemia. Three methods are available for management of the condition, namely, tight control, liberal control, and conventional method, with each of them having the advantages and disadvantages. Hence it is difficult to give a recommendation for hyperglycemia management.

   Since hyperglycemia was associated with increased mortality, *tight control* of plasma glucose was thought to reduce mortality and was advocated in many ICU settings. However, studies analyzing the effects of tight control on outcomes showed conflicting results. A large randomized study NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) evaluated tight control of sugar (80–120 mg%, 4.5–6 mmol/dL) using intense insulin therapy vs conventional regime where plasma glucose was targeted 180 mg% (10 mmol/dL) or less in patients admitted to critical care units. The study investigators found that tight control of glucose resulted in more mortality compared to conventional regime [37]. A subgroup analysis of patients with TBI in NICE-SUGAR study has shown that high incidence of moderate and severe hypoglycemia was seen in tight control group even though mortality was not different thereby questioning the practice of tight control of glucose [38]. The curve plotting mortality vs glucose level is found to be U-shaped with increased mortality seen if glucose level exceeds >200 mg% and if it falls below 80 mg%. Given the high risk of hypoglycemia between 80–110 mg%, it would be beneficial to maintain the glucose level between 110 and 180 mg% in patient admitted to critical care unit [39].
4. In a recent guideline issued by the American College of Physicians, a more liberal target glucose level of *140–200 mg%* (7.8–11.1 mmol/dL) has been advised in patients with hyperglycemia requiring insulin therapy regardless of presence of diabetes or not [40]. A large retrospective study analyzed different levels of plasma glucose (tight blood glucose (4.4 < 6.1 mmol/l), moderate (6.1 < 7.8 mmol/l), mild (7.8 < 10.0 mmol/l), and very mild (10.0 to <12.2 mmol/l) in over 17,996 patients on the mortality benefits [41]. The study found that mild glycemic control (7.8 to <10.0 mmol/l) achieved the best outcome in relation to all-cause mortality and hypoglycemia which was recommended by the ADA [42].
5. In patients with TBI, recent Brain Trauma Foundation (BTF) guidelines (fourth edition) mentions that "it is not clear whether aggressive therapy is better than conventional glucose control. For this reason, the evidence was rated as insufficient and no recommendation about glucose control can be made at this time" [43].

18.4 Perioperative Hyperglycemia Management

The perioperative management of patients with hyperglycemia is even more complex as the condition is caused or aggravated by multiple factors like stress; severity of disease; surgical and anesthetic techniques; use of drugs that interfere

with action of endogenous insulin like steroids, catecholamines, etc.; different intravenous fluids administered; and the nutritional management of patient. No specific targets for control are available in patients undergoing neurosurgery though it is well known that intraoperative hyperglycemia worsens outcome [44]. Perioperative hyperglycemia is associated with increased risk of infection, pneumonia, and acute renal failure in different studies [45, 46].

The recommendations for intraoperative blood glucose (BG) management are not very clear compared to ICU and non-ICU settings. The Society for Ambulatory Anesthesia (SAMBA) recommends intraoperative BG levels to be maintained less than 180 mg% (10 mmol/dL) and to start subcutaneous insulin if it exceeds 180 mg% [47]. Though literature exists on perioperative glucose management in general and cardiac surgical population, there are limited resources available for neurosurgical patients. A similar approach in management of hyperglycemia as in elective general surgery can be applied in neurosurgery population till appropriate literature is available. The perioperative management has significantly changed over the years due to different classes of drugs available currently.

18.4.1 Preoperative Period

A thorough preoperative evaluation of patient is needed before elective surgery to rule out SH from DM as well as presence or absence of macrovascular and microvascular complications of DM. The perioperative glucose management differs from type 1, type 2 DM, and stress hyperglycemia. In a known patient with DM, a thorough knowledge of preoperative medications, and adequacy of control based on preoperative A1C and blood glucose levels of DM, is needed. Elective surgeries can be postponed till adequate control of blood glucose levels is achieved. A preoperative diabetic enteric diet containing low-carbohydrate high monounsaturated fatty acid has been shown to reduce postprandial sugars by 18–29 mg%. Prolonged fasting must be avoided in diabetic patients. In patients on insulin, sensitivity must be established based on the formula; insulin sensitivity factor is equal to 1800/the patient's total daily dose (TDD) of insulin or 40 (in patients with oral agents or details not available). Patients requiring >80 IU per day, high body mass index, on large dose of prednisolone (>20 mg/day), are considered insulin resistant.

18.4.2 Management of Diabetics with Preexisting Drugs

Patients with type 1 diabetes must receive insulin subcutaneous injection which is 80% of their basal dose in the previous day evening and in morning on the day of surgery to avoid hyperglycemia. Prandial insulin must be omitted. Among the class of oral hypoglycemic drugs in type 2 diabetic patients, metformin, thiazolidinediones, DPP-4(dipeptidyl peptidase-4) inhibitors can be given in the preoperative period and on the day of surgery for short duration surgeries. If the surgery is long (>4 h) then these drugs must be withheld on the day of surgery. If patient is on sodium-glucose cotransporter 2 inhibitor therapy, the drugs may cause diabetic ketoacidosis and need to be stopped 24 h before surgery, and alternate drugs or insulin needs to be started for BG control. In type 2 diabetic patients on insulin, basal dose of insulin (glargine or detemir) must be reduced to 75% on the previous evening and morning on the day of surgery. Patients on neutral protamine Hagedorn (NPH) or intermediate and long-acting insulin dose must be reduced to 50–70% of usual dose on the previous day, and the morning dose must be preferably withheld on the day of surgery in prolonged surgeries. If BG is less than 120 mg% in the morning on the day of surgery, insulin and oral antidiabetic drugs can be omitted for the risk of hypoglycemia [48].

18.4.3 Intraoperative Management

Intraoperatively insulin can be administered either as continuous infusion or subcutaneous boluses. In minimally invasive surgeries, short

duration surgeries (<4 h), and patients with hemodynamic stability, subcutaneous insulin (short acting) can be administered. In other cases, intravenous continuous short-acting insulin is preferred. Subcutaneous insulin is equally effective and avoids the fluctuation in glucose levels and prevents hypoglycemia than bolus doses of insulin. Two hourly BG must be monitored in subcutaneous route, and hourly monitoring is needed if infusion is chosen for correction. However, the subcutaneous dose should not be repeated within 2 h to avoid overdose. The dose of subcutaneous insulin required can be calculated as (measured glucose—100/insulin sensitivity factor). A rough estimate would be to administer 2–3 IU of insulin if BG > 180–220 mg% and to increase the dose by 1–2 IU for every 40 mg% increase in BG above 220 mg% [49].

Intravenous infusion of rapidly acting insulin (half-life 15 min) can be started at rate determined (blood glucose/100 = IU/h) to target a BG of 140–180 mg%. The infusion can be maintained at same rate if target levels are achieved. For every 40 mg% increase, infusion can be stepped up by 1 IU/h. If it falls below 110 mg%, the infusion can be stopped and hourly BG must be monitored. The infusion can be continued in the postoperative period with same targets in ICU till patient is stabilized. In stable postoperative patients, subcutaneous insulin can be considered till the patients are given the adequate oral intake of calories after which they can be given usual preoperative regime they were on. Follow-up of patients with impaired glucose tolerance and stress hyperglycemia is required as 60% of them have been found to develop diabetes within a year [50].

18.4.4 Specific Considerations for Neurosurgery Patients

1. Patients with DM known to have high incidence of cardiovascular disease and autonomic dysfunction. Since neurosurgical procedures are conducted in different positions like head elevation, sitting, etc., risk of cardiovascular adverse events including collapse can occur during positioning as well as in the maintenance phase. Perioperative cardiovascular events can complicate the surgical procedure.
2. Glucose-containing fluids (5% Dextrose) are avoided in neurosurgery due to risk of hypotonicity and cerebral edema. Aggressive management of hyperglycemia with insulin in this situation can cause hypoglycemia.
3. Uncontrolled hyperglycemia can cause hyperosmolarity, diuresis, electrolyte imbalances, and reduced intravascular volume. DM can worsen the cerebral edema due to cytotoxicity and disrupted BBB causing intraoperative brain bulge. Use of aggressive hyperosmolar therapy for treating brain edema in such situation can rapidly increase the serum osmolarity and renal dysfunction.
4. Patients with DM may have altered renal function. Radiological investigative procedures like CT scan and angiography requiring contrast can worsen the renal dysfunction.
5. Patients with longstanding DM can have cognitive dysfunction and can interfere in perioperative anesthetic management and neurological assessment.
6. Regional anesthesia techniques and total intravenous anesthesia have been shown to provide better glucose control compared to general anesthesia. Use of volatile agents inhibits insulin secretion and increases hepatic glucose production and worsens hyperglycemia [51]. Capillary blood samples are unreliable in the ICU and should never be used.

18.4.5 Hyperglycemia Management in Acromegaly and Cushing's Disease

Management of hyperglycemia is very challenging in patients with hypersecreting hormones like acromegaly and Cushing's disease due to the fact that the condition is caused by endogenous resistance to insulin secreted by pancreas rather than deficiency of insulin per se. In many of these patients, it may not be possible to achieve a good glucose control in preoperative period before surgery. The hyperglycemic state may revert to

normal after removal of hypersecreting tumor if the patient did not develop overt DM. Since corticosteroids antagonize insulin action, fasting BG may be normal, but postprandial BG may be more than 200 mg%.

Recently the Italian Society for the Study of Diabetes (SID)/Italian Endocrinological Society (SIE) had issued guidelines for the management of hyperglycemia in these subsets of patients [52]. Patients with acromegaly can be treated with medical management, radiotherapy, or surgery. Patients can present to surgery with preoperative medications for the treatment of the condition and may have implications. Medical management of patients with acromegaly includes dopaminergic agonist (bromocriptine, cabergoline), somatostatin agonist (SSA) (octreotide, pasireotide, lanreotide), and pegvisomant, a genetically engineered GH receptor antagonist. Among these agents, treatment with SSA has been shown to worsen the hyperglycemia, whereas other agents tend to improve the glycemic status. No literature exists on the type of drugs that can be used to control hyperglycemia in acromegaly. Treatment with metformin alone or in combination with other drugs like pioglitazone tends to improve sensitivity to insulin and can be effective. If it fails, insulin can be used to control the blood glucose.

In patients with Cushing's syndrome, drugs used in medical management like ketoconazole, metyrapone, and mifepristone have been found to improve glucose levels. In corticosteroid-induced hyperglycemia, the steroid drugs must be given at the lowest required doses. Insulin sensitivity can be improved by oral antidiabetic drugs like metformin, sulphonyl urea, glinides, glitazones, and gliptins. In patients not controlled by the above agents, insulin can be considered. The insulin can be given as bolus or basal-bolus technique. Since the hyperglycemia is postprandial type, bolus of short-acting insulin can be given subcutaneously in the prandial period. The main disadvantage of only bolus is fluctuation in glucose levels. If bolus doses do not achieve adequate control, a basal dose of intermediate-acting insulin subcutaneous route along with postprandial short-acting insulin will provide a good control.

Perioperative hyperglycemia can be managed as per institutional protocol as well as guidelines based on elective surgical patients. It must be remembered that following successful surgery, there can be risk of steep fall in blood sugar with risk of hypoglycemia due to fall in hormonal levels, especially if the patient is on long-acting oral antidiabetic drugs or insulin. Hourly or 2-hourly sugar level monitoring is essential in the postoperative period for immediate identification of its onset.

18.5 Conclusion

Hyperglycemia has been shown to be one of the important causes of secondary brain damage and poor outcome in patients with neurological and neurosurgical conditions. Appropriate management of the condition has shown to have favorable outcomes in terms of infections, mortality, and reduced hospital stay. A protocol-based management with specific targets based on available literature and guidelines, as well as team approach, will facilitate achieving the goals of treatment. Follow-up of patients is required for incidental detected hyperglycemia to identify overt DM development, to provide antidiabetic therapy and prevent late complications.

Key Points

- Hyperglycemia is very common in various neurological and neurosurgical conditions with incidence ranging from 30 to 70%.
- Hyperglycemia worsens the outcome in various neurological diseases.
- Diagnostic criteria for perioperative hyperglycemia are not well established; criteria used by the American Diabetes Associations for the diagnosis of diabetes mellitus are often used.
- A more liberal target glucose levels of 140–200 mg% (7.8–11.1 mmol/dL) have been advised in patients with hyperglycemia requiring insulin therapy regardless of presence of diabetes or not.

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Part V

Special Considerations

Pregnancy and Neuroanesthesia

19

Monica S. Tandon and Aastha Dhingra

19.1 Introduction

Given the "nurturing effect" of "maternal physiological changes of pregnancy" on the growth rate of several intracranial pathologies, it is not surprising that these lesions tend to manifest earlier in pregnant patients as compared with the general population and often necessitate a neurosurgical intervention during the pregnancy itself. Needless to say, perioperative management of these patients poses unique challenges for the neuroanesthetist. Besides the standard neuroanesthesia concerns, the delicate feto-maternal homeostasis needs to be maintained, so that a good maternal outcome is achieved without compromising fetal safety. Moreover, the physiological adaptations of pregnancy necessitate several modifications in the conventional neuroanesthesia technique and, often, a need to skillfully balance, competing or even contradictory clinical goals. Optimal perioperative management in these circumstances mandates an integrated understanding not only of neurosurgical anesthesia but also of the maternal physiological changes during pregnancy and their implications on feto-maternal homeostasis, intracranial pathology, and the neuroanesthesia technique, along with the pertinent perioperative fetal concerns and the effect of anesthetic drugs on feto-maternal physiology and cerebral homeostasis. The initial sections of this chapter provide an overview of these basic concepts; the latter sections delve into principles of anesthetic management when these patients present for a cranial surgery, a combined cesarean section (CS) and neurosurgical intervention, spinal surgery, and neuroendovascular procedure or with a traumatic brain injury (TBI) or spinal cord injury (SCI). Since the anesthetic management of these procedures/conditions is discussed in detail elsewhere in the book, this chapter primarily focuses on the impact of pregnancy on the neuroanesthetic management of these patients.

19.2 Maternal Physiological Adaptations of Pregnancy and Their Implications for Neuroanesthesia

Significant changes occur in the maternal anatomy and physiology during pregnancy, which allow the pregnant woman to adapt to the requirements of growing fetus and placenta. While adaptations in the earlier stages are hormonally influenced, those in later stages of pregnancy

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usually occur due to mechanical effects of the enlarging uterus, increased fetal metabolic requirements, and a low-resistance uteroplacental circulation. The following sections describe the pertinent physiological changes that can influence the perioperative course of pregnant patients and, hence, often necessitate alterations in the conventional neuroanesthesia technique (Table 19.1).

19.2.1 Cardiovascular and Hematological Changes

19.2.1.1 Central Hemodynamics

The maternal cardiac output (CO) increases progressively and peaks during the third trimester (50%), secondary to an increase in the stroke volume (20–30%) and heart rate (HR; 15–25%) [1]. The systemic vascular resistance (SVR) and blood

Table 19.1 Maternal physiological changes during pregnancy

Maternal physiological change	Anesthetic implication	Prophylactic measures
Cardiovascular system		
Central hemodynamics		
Cardiac output: +50% Heart rate: +15–25% Stroke volume: +20–30% BP, systemic vascular resistance ↓ during midpregnancy, return to baseline by term Suppression of arterial baroreceptor reflexes Downregulation of adrenergic receptors	Hypovolemia difficult to assess; significant blood loss may occur before signs of shock present Impaired ability to compensate for blood loss Higher doses of vasopressors required for treatment of hypotension	Invasive BP monitoring recommended Central venous pressure monitoring recommended if significant intraoperative blood loss is anticipated, e.g., meningioma surgery Maintain BP within 20% of baseline and MAP >70 mmHg with fluids (isotonic, glucose-free solutions); vasoactive drugs (ephedrine, phenylephrine, norepinephrine, dobutamine)
Aortocaval compression	Supine hypotension syndrome	Maintain left lateral uterine displacement with a pelvic wedge/roll or a mechanical displacer or lateral tilt of operating table, in patients who have >20 gestational weeks
ECG changes		
Atrial and ventricular ectopics, Q wave (small) and inverted T wave in lead III, ST segment depression and T wave inversion in the inferior and lateral leads, left-axis shift of QRS	ECG may mimic myocardial disease	
Uterine blood flow		
↑ to 700–900 mL/min (prepregnancy value: 50–100 mL/min) Uteroplacental circulation: limited autoregulatory ability, pressure-passive perfusion	Maternal hypotension results in a parallel decrease in blood supply to fetus	Avoid maternal hypotension
Hematological changes		
Blood volume: +30–45% Plasma volume: +55% Red blood cell mass: +30% Hemoglobin: −20% ↓ Albumin and colloid osmotic pressure ↑ In coagulation factors (Factors I, VII, VIII, IX, X, XII) ↓ In protein S levels Inhibition of fibrinolysis Prothrombin time: shortened 20% Platelet counts: 80,000–150,000/mm^3 (in third trimester)	Hemorrhage may be misinterpreted as physiological anemia of pregnancy Pedal edema, decreased protein binding of drugs Risk of deep vein thrombosis and thromboembolism Benign gestational thrombocytopenia, usually not associated with platelet dysfunction or increased bleeding risk	

Table 19.1 (continued)

Maternal physiological change	Anesthetic implication	Prophylactic measures
Respiratory system		
Airway		
Increased hyperemia, edema, friability, distortion of upper airway mucosa	Increased risk of difficult airway, failed intubation with traditional laryngoscopy, bleeding during nasal instrumentation	Provisional difficult airway management plan should be formulated preoperatively Smaller endotracheal tube required (6.5 or 7.0 mm) Gentle laryngoscopy and suctioning
↑ Anteroposterior chest wall diameter Upward displacement of diaphragm Minute ventilation: +45% Alveolar ventilation: +45% Tidal volume: +45% Respiratory rate: +15% Expiratory reserve volume: −25% Residual volume: −15% Functional residual capacity: −20% Closing capacity: no change ↑ Oxygen consumption, carbon dioxide production ↑ Ventilation/perfusion mismatch	↑ Potential for hypoxemia in supine, Trendelenburg position Increased rate of oxygen desaturation during apnea	Preoxygenation
Acid base and blood gases		
Arterial pH 7.39–7.45 (prepregnant value: 7.36–7.42) ↑ PaO2 (103–107 mmHg) (prepregnant value: 90–100 mmHg) ↓ PaCO2 (30–32 mmHg) (prepregnant value: 36–44 mmHg) ↓ Serum bicarbonate (20 meq/L) (prepregnant value: 24 meq/L)	Mild, compensated respiratory alkalosis Decreased maternal buffering capacity	Maintain the "physiologically altered" values Avoid ↓ PaCO2 levels to below 25 mmHg to acutely ↓ ICP
Gastrointestinal system		
↓ Esophageal barrier pressure: ↑ Intragastric pressure (upward displacement and rotation of stomach; ↑ Volume and acidity of gastric secretions) ↓ Gastroesophageal sphincter f unction	↑ Risk of regurgitation, aspiration, and pulmonary injury	Aspiration prophylaxis with nonparticulate antacid, histamine receptor antagonist, and a prokinetic agent for pregnant patients with more than 14 weeks of gestation
Renal system		
Renal plasma flow: + 75% Glomerular filtration rate: +50% ↓ Reabsorptive capacity ↓ Serum creatinine (0.8 mg/dL) ↓ Blood urea nitrogen (8–9 mg/dL) Activation of renin-angiotensin-aldosterone system: increased sodium and water retention	Glycosuria, proteinuria slight ↑ in serum creatinine, blood urea nitrogen may be pathological Worsening of peritumoral edema and intracranial pressure Mild ↓ in serum sodium: 135–138 meq/L ↓ In serum osmolarity: 280 mOsm/L	

BP blood pressure

pressure (BP) fall during midpregnancy (hormonally induced vasodilation) and return toward baseline, by term. Perioperatively, these changes (decreased SVR, BP; increased CO, HR) often confound the assessment of intravascular volume and blood loss; typical signs of shock may not be reflected in the hemodynamic parameters, till significant blood loss has occurred. Additionally, inadequate peripheral vasoconstriction due to hormonally mediated suppression of arterial baroreceptor reflexes, impairs the ability to compensate for hypovolemia and further increases the risk of intraoperative hypotension [2].

Pregnancy results in an increase in the blood volume (BV, 30–45%), plasma volume (PV, 55%), red blood cell (RBC) mass (30%) and extravascular fluid volume [1]. A "physiological dilutional anemia" occurs because the rise in PV is disproportionately greater than the increase in RBC mass. Hemoglobin and hematocrit decrease to approximately 11.6 g/dL and 35%, respectively; a preexisting anemia in these circumstances increases the susceptibility to perioperative hypotension, particularly during neurosurgeries that involve significant blood loss, e.g., resection of meningioma and arteriovenous malformation (AVM).

19.2.1.2 Electrocardiographic (ECG) Changes

The heart gets displaced upward and to the left as pregnancy advances, because of pushing up of the diaphragm by the enlarging uterus. Normal findings on ECG in pregnancy that may partly relate to changes in the position of the heart include (a) atrial and ventricular ectopics, (b) Q wave (small) and inverted T wave in lead III, (c) ST segment depression and T wave inversion in the inferior and lateral leads, and (d) left-axis shift of QRS [3].

19.2.1.3 Uterine Blood Flow (UBF) and Uteroplacental Circulation

UBF progressively rises from a prepregnancy value of 50–100 mL/min (5% of CO) to 700–900 mL/min at term (12% of CO) [1]. The uteroplacental circulation is a highly vasodilated, low-resistance system, with a limited autoregulatory ability and a pressure-passive perfusion; the uterine perfusion pressure (UPP) is linearly related to the maternal mean arterial pressure (MAP); hence, any episode of maternal hypotension results in a parallel decrease in the blood supply to the fetus.

19.2.1.4 Aortocaval Compression

When a pregnant woman with more than 20 weeks of gestation lies in the supine position, compression of the inferior vena cava (IVC) between the enlarging gravid uterus and lumbar vertebrae can lead to a significant decrease in the venous return, preload, and CO and, hence, a reduction in the maternal BP and the UBF. Up to 15% women with term pregnancy manifest severe hypotension and bradycardia in the supine position (supine hypotension syndrome), because the compensatory sympathetic responses are unable to compensate for this reduced venous return. In addition, the obstructed uterine venous drainage [increase in uterine venous pressure (UVP)], partial aortic obstruction (decrease in distal aortic pressure), and diversion of blood away from the uterus because of compensatory sympathetic vasoconstriction, further jeopardize the uteroplacental blood flow. Importantly, abolition or attenuation of the compensatory sympathetic mechanisms during general anesthesia (GA) may further aggravate these adverse hemodynamic changes in anesthetized patients. Hence, the supine position is avoided and a "lateral uterine displacement" (LUD) is maintained in all anesthetized pregnant patients, after 20 weeks of gestation. Traditionally, use of a pelvic wedge/roll or a mechanical displacer or a lateral tilt of the operating table (15°, 30°, or full lateral tilt) is advocated; however there is limited evidence to support or refute the efficacy of these maneuvers. According to a Cochrane review on optimal perioperative maternal positioning, a left lateral pelvic tilt may be preferable to a right lateral tilt; and manual displacers may be better than a left lateral tilt of the table, for attenuating the perioperative hypotensive effects of aortocaval compression [4].

19.2.1.5 Coagulation System

A state of hypercoagulability occurs during pregnancy, consequent to an increase in the concentration of coagulation factors (Factors I, VII, VIII, IX, X, XII), along with a decrease in protein S levels and an inhibition of fibrinolysis; occurrence of phlebitis and pedal edema due to partial caval obstruction in the third trimester can further increase the risk of deep vein thrombosis (DVT) and thromboembolism.

19.2.2 Airway and Respiratory Changes

19.2.2.1 Airway

Pregnant women have an eightfold higher incidence of failed tracheal intubation (TI) as compared with the general population [5]. The increased hyperemia, edema, and friability of the upper airway mucosa (due to elevated estrogen, increased BV) predispose to an increased difficulty in bag-mask ventilation (BMV); greater propensity for mucosal bleeding and airway edema during airway manipulation; distortion of the upper airway structures, with difficulty in insertion of the tracheal tubes into the glottis; and a higher likelihood of a difficult tracheal extubation. The Mallampati score tends to worsen as pregnancy progresses, because the reduced pharyngolaryngeal space and the increased difficulty in elevation of the hyoid bone prevent proper visualization of the oropharyngeal structures [5]. Enlarged breasts, redundant soft tissue of the neck and chest, increased chest circumference, and the greater resistance to chest expansion by abdominal contents further increase the likelihood of a difficult BMV and laryngoscopy. The risk of a difficult airway is greater in preeclamptic patients (more severe airway edema because of greater fluid accumulation in the laryngopharynx).

19.2.2.2 Respiratory Changes

Pregnancy results in an increase in the tidal volume (45%), respiratory rate (15%), and minute ventilation (45%), consequent to an increase in the feto-maternal metabolic requirements and the associated rise in oxygen consumption and carbon dioxide (CO_2) production (40–60% above prepregnancy values) [1]. Hence, the arterial partial pressure of CO_2 ($PaCO_2$) is maintained between 30 and 32 mmHg (despite an increase in CO_2 production), and the arterial partial pressure of oxygen (PaO_2) rises to 103–107 mmHg [1]. As the renal excretion of sodium bicarbonate increases (to compensate for the hypocapnia), the serum bicarbonate levels decrease from 24 meq/L to 18–21 meq/L [1]. The resulting mild, compensated respiratory alkalosis (arterial pH 7.39–7.45) and the slight rightward shift of oxygen-hemoglobin dissociation curve facilitate uteroplacental oxygen transfer to the fetus.

The fall in the maternal $PaCO_2$ also creates a fetal-maternal $PaCO_2$ gradient, which allows free uteroplacental diffusion of CO_2 and its elimination through the maternal lungs. These "physiologically altered" values must be maintained during the perioperative period; in particular, any attempt to markedly reduce the $PaCO_2$ levels (below 25 mmHg) to acutely decrease the ICP should be avoided.

While maternal and fetal oxygen requirements increase, the residual volume, expiratory reserve volume, and functional residual capacity (FRC) decrease due to elevation of the diaphragm by the gravid uterus; the closing capacity (CC) remains unaltered. The FRC/CC ratio decreases; this fall is more pronounced in the supine position, when the CC exceeds FRC, and early closure of the small airways predisposes to atelectasis [6]. Because of these changes, pregnant patients, especially those who have obesity and/or preeclampsia, are prone to early and rapid oxygen desaturation, following even a brief period of apnea; an apnea of 1 min lowers the PaO_2 twice as rapidly in term pregnant versus nonpregnant women (139 versus 58 mmHg/min) [7].

19.2.3 Gastrointestinal System Changes

By end of the first trimester, the enlarging uterus tends to cause an upward displacement and rotation of the stomach and a potential shift of the

intra-abdominal esophagus into the thorax; consequently, the intragastric pressure rises. Ectopic gastrin production leads to an increase in the volume and acidity of gastric secretions. Moreover, the lower esophageal sphincter (LES) can become incompetent (obliteration of "pinchcock" mechanism at esophagogastric junction; hormonally influenced reduced LES tone). The reduced esophageal barrier pressure [LES pressure – intragastric pressure] markedly increases the risk of regurgitation during pregnancy; if aspiration occurs, the pulmonary injury is likely to be very severe [8]. Hence it is prudent to presume a "full stomach" and take adequate precautions to protect the airway in patients undergoing GA beyond 14–16 weeks of gestation and up to 48 h postpartum [8–10].

19.2.4 Renal and Hepatic Changes

There is a marked increase in the renal blood flow (75%) and glomerular filtration rate (GFR, 50%) and an associated decrease in the serum creatinine, blood urea nitrogen (BUN), and uric acid values; hence, a slight elevation in these parameters (serum creatinine >0.8 mg/dL; BUN levels >8–9 mg mL-I) may be a cause for concern [1]. The increased GFR reduces the proximal tubular reabsorption of glucose; hence, glycosuria can occur despite normal blood glucose levels. Despite altered normal values, drug responses appear to be unchanged by altered renal function.

Activation of renin-angiotensin-aldosterone system leads to increased retention of sodium and water, which can worsen the peritumoral edema and the intracranial pressure (ICP) in patients with intracranial pathologies. This dilutional effect also results in a mild decrease in the serum sodium concentration (135–138 meq/L) as well as in the serum osmolarity (280 mOsm/L).

Serum alkaline phosphatase levels increase by two to four times above nonpregnant values (placental, fetal production) and are not very useful for assessment of liver function in pregnant patients; serum bilirubin and transaminase levels remain unchanged.

19.2.5 Altered Responses to Anesthetic Drugs (Table 19.2)

The serum albumin concentration and colloid oncotic pressure decrease during pregnancy (due to expanded PV); however, the elevated total protein stores (due to increased BV) provide additional sites for drug binding; hence, response to anesthetic drugs is largely unaltered. The clearance of drugs is reduced secondary to the increased volume of distribution (VD) associated with the increase in blood volume (BV). Thiopental requirements decline by 17–18% after the first trimester; additionally, its VD and elimination half-life are prolonged [1]. However, the pharmacokinetics of propofol is not greatly altered by pregnancy [1].

The minimum alveolar concentration (MAC) for volatile anesthetics decreases by 25–40%, possibly due to elevated endorphins and progesterone levels [1, 8, 9]. The rate of rise of alveolar versus inspired anesthetic concentration and thus the speed of inhalational induction also increase during pregnancy [1].

Plasma pseudocholinesterase levels decline mildly (24–33%), but the duration of apneic response to succinylcholine is rarely affected in genotypically normal women [1]. Vecuronium and rocuronium have a more rapid onset and prolonged duration of blockade (due to altered hepatic blood flow) [1].

Downregulation of adrenergic receptors leads to a higher dose requirement of vasopressors (e.g., phenylephrine) for treatment of hypotension; chronotropic response to isoproterenol and epinephrine is also reduced in pregnancy, because of downregulation of beta-adrenergic receptors.

Neuraxial anesthetic drug requirement decreases by 30–40% during pregnancy (reduced volume of epidural and intrathecal spaces due to engorgement of epidural veins secondary to IVC compression by gravid uterus, biochemical or hormonally mediated increased neuronal sensitivity to drugs).

Table 19.2 Anesthetic drugs: important implications in pregnant patients

Drug	Anesthetic implications
Intravenous anesthetics	
Thiopentone Propofol	Rapid placental transfer Thiopentone: induction dose decreased (18–35% ↓), elimination half-life prolonged (26 v/s 11.5 h in nonpregnant women) Propofol: induction dose decreased (10% ↓), elimination half-life unaltered Maternal hypotension (negative inotrope, vasodilator) and ↓ in UBF, transient depression of fetal/neonatal cardiorespiratory and central nervous systems
Etomidate	Minimal effects on cardiorespiratory function, useful in hemodynamically unstable patients Intravenous injection may cause pain and involuntary muscle movements in unpremedicated patients, nausea and vomiting Potential activation of seizures in patients with an epileptogenic foci Impaired glucocorticoid response to stress Transient (<6 h) reduction in neonatal cortisol production
Ketamine	Sympathomimetic, increase in BP may occur, useful in hypotensive patients Emergence delirium, hallucinations, increased secretions; to be used in conjunction with midazolam/thiopentone and glycopyrrolate No neonatal depression at 1 mg/kg. At higher doses, low Apgar scores, neonatal respiratory depression
Inhalational agents	
Volatile agents	Minimum alveolar concentration (MAC) decreased (25–40%) Faster inhalational induction Maternal hypotension (vasodilation) and ↓ in UBF Decrease in uterine tone Depression of fetal cardiovascular and central nervous system
Nitrous oxide	Avoided in neurosurgery Potential fetal effects Prolonged exposure may inhibit DNA synthesis, risk of structural abnormality and fetal loss, diffusion hypoxia in neonate
Opioids	
Fentanyl Remifentanil Morphine	Neonatal respiratory depression, chest wall rigidity Prolonged use: symptoms of withdrawal, intrauterine growth restriction
Neuromuscular blocking drugs	
Depolarizing/ nondepolarizing	Minimal uteroplacental transfer Highly ionized at physiological pH, poor lipid solubility No fetal effects
Succinylcholine	Duration of blockade unaltered
Rocuronium	Increased sensitivity to aminosteroid muscle relaxants vecuronium and rocuronium: Increased clearance and a shortened elimination half-life
Local anesthesia agents	
Lignocaine	Less lipid soluble, low protein binding Accumulate in fetus due to “ion trapping” may lead to fetal acidosis
Bupivacaine/ Ropivacaine	High lipid solubility, high protein binding Higher safety margin than lignocaine
Anticholinergics	
Atropine	Lipid soluble, crosses the placenta Large doses: fetal tachycardia, loss of FHR variability
Glycopyrrolate	Highly ionized quaternary ammonium compound; does not cross the placenta

(continued)

Table 19.2 (continued)

Drug	Anesthetic implications
Reversal drugs	
Neostigmine	Low molecular weight, highly ionized quaternary ammonium compound; limited uteroplacantal transfer May cause fetal bradycardia when used with glycopyrrolate
Benzodiazepines	Accumulate in fetal tissues (limited fetal metabolizing capacity) Neonatal depression, floppy infant syndrome (reduced muscle tone, hyporeflexia, suckling difficulty) Cleft lip and palate. cardiac anomalies reported in animal studies Uteroplacental transfer: midazolam < diazepam; long-term use avoided (risk of neonatal withdrawal), single dose not harmful

UBF uterine blood flow, *FHR* fetal heart rate

19.3 Fetal Concerns During Neuroanesthesia (Table 19.3)

The fetus is highly dependent on an adequate uteroplacental circulation and an optimal maternal homeostasis for its growth and metabolic requirements. Hence, any perioperative adverse event that compromises the uteroplacental perfusion, maternal physiology, and/or fetal gas exchange can be detrimental for fetal well-being. Additionally, maternally administered drugs or radiation exposure during neuroimaging can also adversely affect the fetus. The following section reviews the potential factors that may jeopardize fetal safety in the perioperative period.

19.3.1 Uteroplacental Blood Flow

UBF = UPP/uterine vascular resistance (UVR)

Since UPP = uterine arterial pressure (UAP) − UVP, hence

UBF = UAP − UVP/UVR

Therefore an alteration in any of these parameters can result in a decrease in the UBF (Table 19.3); maternal hypotension is by far the most important cause of decreased UBF (UPP is linearly related to maternal MAP) and may occur due to hypovolemia, hemorrhage, aortocaval compression, anesthetic drugs, sympathetic blockade, or vasodilators.

19.3.2 Feto-maternal Gas Exchange

In maternal hypoxemia (severe or prolonged), reduced PaO_2 levels in the uteroplacental circulation, hypoxemia-induced vasoconstriction, and the reduced UBF can lead to profound fetal hypoxemia, metabolic acidosis, and, ultimately, fetal death [8, 9]. Similarly, severe maternal hypercapnia, as well as hypocapnia, cause uterine artery vasoconstriction; maternal hypercarbia, by limiting the feto-maternal CO_2 diffusion gradient, directly results in fetal respiratory acidosis (maternal and fetal $PaCO_2$ are linearly related) and may even cause fetal myocardial depression. Maternal hypocapnia causes a leftward shift in the maternal oxyhemoglobin dissociation curve and impairs the release of oxygen to the fetus [8].

19.3.3 Influence of Maternally Administered Drugs on the Fetus

Drugs administered to the mother can cross the placenta and directly harm the fetus by their teratogenic and/or toxic effects; those that do not cross the placenta may still compromise fetal safety, by adversely affecting the maternal physiology, UBF, or the uterine tone.

19.3.3.1 Drug Teratogenicity

All drugs, when administered in large quantities and for a prolonged duration, are potentially teratogenic. The risks vary from death of the embryo (embryogenesis, first 2 weeks of gestation) to congenital abnormalities (organogenesis, 2 weeks to 2 months of gestation) and to growth retardation of normally formed fetal organs (period beyond 2 months of gestation and until birth) [8, 9]. The risk of a major structural

Table 19.3 Factors affecting fetal safety in the perioperative period

I. Decreased uterine perfusion pressure	
A. Decreased uterine arterial pressure	*Increased uterine venous pressure*
Hypotension	Inferior vena caval compression
Hemorrhage	Uterine hypertonia
Hypovolemia	Oxytocin overstimulation
Anesthetic drug induced vasodilation	Alpha-adrenergic stimulation
Sympathetic blockade, e.g., neuraxial anesthesia	Uterine contractions
Aortocaval compression	Skeletal muscle hypertonia
	Seizures
	Valsalva maneuver
Increased uterine vascular resistance	
Uterine artery vasoconstriction due to	
Endogenous vasoconstrictors:	
Catecholamine release in response to stress, pain, noxious stimuli, e.g., skin incision, laryngoscopy	
Vasopressin release in response to hypovolemia	
Exogenous vasoconstriction:	
Adrenaline	
Vasopressors (phenylepinephrine, ephedrine)	
Local anesthetics in high concentrations	
Chronic hypertension	
Pregnancy-induced hypertensive disorders, e.g., preeclampsia	
II. Impaired feto-maternal gas exchange	
Maternal hypoxemia	
Maternal hypocarbia/hypercarbia	
Metabolic/respiratory acidosis	
III. Maternally administered drugs	
Direct toxic effects (by drugs that cross the placenta)	
Teratogenicity: severity depends on timing, duration, and level of exposure to drug	
Adverse effect on fetal organ systems especially cardiovascular and central nervous system	
Indirect toxic effects:	
Adverse effect on maternal physiology, UBF, and uterine tone	
IV. Onset of preterm labor	

anomaly, covert embryopathy with a possible manifestation later in life, or an increased risk of childhood cancer (fetal exposure to radioactive iodine or contrast) is highest during the period of organogenesis.

19.3.3.2 Anesthetic Agents and Fetal Toxicity (Table 19.2)

Uteroplacental Transfer

Almost all anesthetic drugs, including intravenous sedative-hypnotic drugs (thiopentone, propofol), inhalational agents (sevoflurane, isoflurane, desflurane), opioids (fentanyl, remifentanil), and local anesthetics, are lipophilic, have low molecular weights (<500 Daltons), and are minimally ionized; hence, they can readily cross the placenta by passive diffusion across a concentration gradient [10]. The only exceptions are nondepolarizing muscle relaxants (NDMR; vecuronium, atracurium, rocuronium), depolarizing muscle relaxant (succinylcholine), and reversal agents (neostigmine, glycopyrrolate); these drugs have negligible uteroplacental transfer, because of their high ionization and/or low lipid solubility [9].

Teratogenicity

Though there are concerns regarding the teratogenicity of some anesthetic drugs, such as nitrous oxide (N_2O), ketamine, and benzodiazepines, in some animal species under certain conditions, no anesthetic agent is a proven teratogen in humans, when used in standard concentrations, at any gestational age and when normal maternal physiology and UPP are maintained [8–11]. Though a small increase in the risk for preterm delivery, miscarriage, growth restriction, and low birth weight has

been reported, it is unclear whether these adverse fetal effects are a consequence of anesthetic drugs, surgery, or an underlying maternal disease [10].

Furthermore, though some animal and epidemiological studies report about neurodevelopmental delay in infants following an in utero exposure to GA, however, more data is needed to provide conclusive advice regarding avoidance of specific drugs in the perioperative period [8].

Direct Toxic Effects

Sedative-hypnotics (e.g., propofol, thiopentone), inhalational agents (isoflurane, sevoflurane, desflurane), opioids (fentanyl, remifentanil), and benzodiazepines (midazolam, diazepam) can cause depression of fetal cardiorespiratory and central nervous systems (CNS). Benzodiazepines accumulate in fetal tissues (limited fetal metabolizing capacity); hence their long-term use is usually avoided (risk of neonatal withdrawal), though a single dose is usually not harmful [9]. These direct effects can cause concern during a combined CS and neurosurgical procedure.

Indirect Toxic Effects

Propofol, thiopentone, and volatile inhalational agents can reduce the maternal BP and UBF, because of their negative inotropic and vasodilatory effects. Atropine in large doses causes fetal tachycardia and loss of fetal heart rate (FHR) variability [12].

Inhalational agents cause a dose-dependent decrease in both spontaneous (at >0.5MAC) and oxytocin-induced uterine contractions (at >1–1.5MAC) and consequently increase the risk of blood loss after a CS; isoflurane has the least effect on uterine tone [13]. Ketamine increases the uterine tone and should be avoided in the first two trimesters; this effect is not seen in the third trimester.

19.3.3.3 Adverse Effects of Commonly Used Medical Drugs During the Perioperative Period

Mannitol, an osmotic diuretic used for ICP reduction, can decrease the maternal BP and UBF. Moreover, it accumulates in the fetus and can cause fetal dehydration by forcing free water from the amniotic fluid and fetus to the maternal circulation; administration of higher doses is associated with volume contraction, reduced urinary blood flow, decreased lung fluid production, cyanosis, and bradycardia in the fetus. Lower doses of mannitol (0.25–0.5 mg/kg) are reported to be safe [8, 12].

Prolonged use of corticosteroids (to decrease peritumor edema in intracranial lesions, to accelerate fetal lung maturity) is associated with a risk of hypoadrenalism and oro-palatal-mandibular clefts in the fetus; they should preferably be avoided in the first trimester.

Anticonvulsants, especially valproate, are implicated in various fetal anomalies, including neural tube defects [14]. Levetiracetam and lamotrigine are reported to have the least teratogenic risk among all antiepileptics [10].

The adverse fetal effects of other commonly used drugs, e.g., antihypertensives, vasoactive drugs, and anticoagulants, are listed in Table 19.4. Among antihypertensives, labetalol is considered to be relatively safe; esmolol should be used with caution. Heparin and antiemetic drugs, e.g., metoclopramide and droperidol, are also safe in pregnant patients (no uteroplacental transfer). Angiotensin-converting enzyme inhibitors, warfarin, and cyclooxygenase inhibitors are contraindicated during pregnancy, because of their teratogenic potential [15].

19.3.4 Radiation Teratogenicity

There is a definite, albeit small, risk of fetal exposure to ionizing radiation during diagnostic neuroimaging; hence guidelines by the American College of Obstetricians and Gynecologists (ACOG) recommend prudence with their use during pregnancy [16]. Ultrasound and magnetic resonance imaging (MRI) are the techniques of choice; X-rays and computerized tomography (CT) can also be used, if they are absolutely necessary, or are more readily available. Use of gadolinium contrast with MRI is justified only if it significantly improves the diagnostic performance (uteroplacental transfer; recirculates in fetal circulation because of its presence in amniotic fluid) [16].

Table 19.4 Fetal adverse effects of commonly administered medical drugs

Nonsteroidal anti-inflammatory drugs	Avoided after 28 gestational weeks: risk of premature ductus arteriosus closure, fetal renal failure and necrotizing enterocolitis, inhibition of platelet aggregation
Anticoagulants	
Warfarin	Teratogenic, crosses the placenta, contraindicated in pregnancy
Heparin	Does not cross the placenta, safe in pregnancy
Anticonvulsants	
Phenytoin, carbamazepine, sodium valproate	Fetal neural tube defects
Levetiracetam	Safe in pregnancy
Magnesium sulfate	Maternal effects: decrease in maternal BP and uterine tone, muscle weakness, prolongs action of neuromuscular blocking agents Neonatal effects: reduced muscle tone, respiratory failure, pulmonary edema
Antihypertensives	
ACE inhibitors	Contraindicated during pregnancy Intrauterine growth restriction, oligohydramnios, renal impairment
B-blockers	Intrauterine growth restriction High doses: neonatal hypoglycemia, fetal bradycardia Labetalol relatively safe, esmolol to be used with caution
Hydralazine, SNP, nitroglycerin	Uteroplacental transfer +, SNP: risk of fetal cyanide toxicity
Thiazides	Neonatal thrombocytopenia
Vasoactive drugs	
Epinephrine Norepinephrine Ephedrine Phenylepinephrine	Decrease in UPP
Dobutamine	No decrease in UPP
Tocolytics	
Beta-2 agonists: ritodrine, terbutaline, salbutamol	Tachyarrhythmias, pulmonary edema, hypokalemia, hyperglycemia
Oxytocin receptor antagonists: atosiban	Nausea, vomiting, fewer side effects than beta-2 agonists
Calcium channel blockers: nifedipine	Hypotension, fewer side effects than beta-2 agonists

Angiotensin-converting enzyme (ACE) inhibitors, *BP* blood pressure, *UPP* uterine perfusion pressure, *SNP* sodium nitroprusside

19.3.5 Intraoperative Fetal Monitoring and Prevention of Preterm Labor

Fetal cardiotocography (CTG) monitors the FHR and uterine contractions. It can be used for perioperative assessment of fetal well-being (FHR monitoring, 18–22 weeks onward; FHR variability, 25 weeks onward) and may be valuable for early detection of aortocaval compression and cardiovascular insufficiency due to poor maternal positioning; importantly, it may also influence the decision to deliver the fetus [11]. Alternatively, a transesophageal echo probe of an ultrasound machine has also been successfully used for this purpose; being flexible, it can be easily attached to mother's lower abdomen and also allows a hands-free operation [17].

There is a slight controversy regarding the usefulness of intraoperative FHR monitoring (insufficient data to evaluate its efficacy, unnecessary CS due to misinterpretation of data, reports of successful patient management without monitoring). Hence, the ACOG guidelines recommend that this decision should be individualized following a multidisciplinary consensus based on the following factors: gestational age of fetus, complexity of the neurosurgery (e.g., surgeries with potential for severe blood loss and/or hemodynamic instability), clinical status of the mother (presence of significant comorbidities), and availability of appropriate

technical expertise and facilities (neonatal services, qualified persons to reliably interpret FHR variability, fully equipped operating room, and a qualified obstetrics team to safely perform the emergency CS, with the parturient's consent) [11]. These guidelines state that in a viable fetus (approximately 24 gestational weeks) CTG analysis should at least be performed immediately prior to and after the neurosurgery. Continuous intraoperative FHR monitoring may be appropriate if the neurosurgical center has adequate logistics. In a pre-viable fetus, Doppler confirmation of FHR prior to and immediately after the neurosurgery usually suffices; continuous intraoperative fetal monitoring may be considered in selected cases, e.g., to optimize placental blood flow in cases of fetal bradycardia [11].

19.3.5.1 Interpretation of FHR

A decrease in the baseline FHR [normal, 110–160 beats per minute (bpm)] and beat to beat variability (normal variability 5–25 bpm) is often observed during anesthesia and may reflect the normal effects on anesthetics on the fetal autonomic nervous system. However, non-reassuring signs such as bradycardia (<100 min), reduced or increased variability or sinusoidal pattern, deceleration >5 min, and repetitive late or prolonged decelerations for >30 min (or >20 min if reduced variability) indicate a high probability of fetal hypoxia/acidosis [18]. These signs should prompt an immediate search and treatment of potentially reversible causes, e.g., maternal hypoperfusion, maternal hypoxia, hypercarbia, acidosis, umbilical cord compression due to improper positioning, and anesthesia-induced depression of fetal cardiovascular system. Occurrence of prolonged deceleration or bradycardia with <80 bpm for 2 min despite corrective measures might be an indication for an emergency CS.

19.3.5.2 Tocolytic Therapy

The risk of preterm labor is higher during intra-abdominal surgeries, e.g., ventriculoperitoneal shunt (VP shunt). Prophylactic tocolytic therapy (e.g., calcium channel blockers, beta-2 antagonists) is not advisable, because of its unproven efficacy during non-obstetric surgery, and also due to its associated side effects (Table 19.4) [9, 10]. It may be used cautiously if uterine contractions are detected on intraoperative CTG monitoring. Drugs which can increase uterine tone (e.g., ketamine) should be avoided.

19.4 Common Intracranial Lesions During Pregnancy

Common pathologies that may necessitate a neurosurgical intervention during pregnancy are tumors, cerebrovascular lesions (aneurysms, AVM), TBI or SCI, obstructive hydrocephalus, and spontaneous spinal epidural hematoma (SSEH) [19, 20]. Besides the standard perioperative concerns, other pertinent dilemmas that arise during the neurosurgical, obstetric, and neuroanesthetic management of patients with these lesions include decisions regarding the optimal timing of surgery, continuation or termination of pregnancy, optimal timing and mode of delivery, and possibility of a combined CS and neurosurgery in patients with near-term pregnancy. In absence of well-defined recommendations, it is very important that an individualized, multidisciplinary approach is used to guide the management of these patients; the multidisciplinary team should comprise of a neurosurgeon, obstetrician, anesthetist, and a neonatologist [12, 19, 20]. Several factors influence these decisions, such as type of the neurosurgical pathology (location, size, morphology, invasiveness), patient's neurological condition (clinically stable or unstable), urgency of the neurosurgery (emergent, elective, nonurgent but essential), gestational age of the fetus (first trimester, 1–12 weeks; second trimester, 12–28 weeks; third trimester, 29–40 weeks; viable fetus, 24 weeks), and the patient's wishes.

Broad principles of management are as follows:

- Neurosurgical considerations usually take precedence over obstetric considerations.
- Emergency neurosurgery is performed irrespective of the stage of pregnancy [11].

- Elective surgery should be postponed until after delivery [11].
- If possible, nonurgent essential surgery should be performed in the second trimester, when the risk of fetal anomalies, preterm contractions, and spontaneous abortion is the lowest [11].
- If feasible, pregnancy should be allowed to continue, till at least 32 weeks of gestation (risk of preterm delivery becomes proportionately lesser than risks to the fetus from maternal therapies, e.g., osmotic diuresis and mechanical hyperventilation) [11].
- In clinically stable patients, the choice of route of delivery (vaginal/CS) is made solely on basis of obstetric criteria (no proven advantage of CS over vaginal delivery in protecting against increased ICP); however, a CS is preferred in clinically unstable patients.

19.4.1 Cerebrovascular Pathologies

Intracranial hemorrhage (ICH) from a cerebrovascular pathology is a leading cause of indirect maternal mortality during pregnancy [21, 22]. It usually occurs due to an aneurysmal rupture (aneurysmal subarachnoid hemorrhage [aSAH]) or an AVM-related intracerebral bleed; hypertensive disorders of pregnancy, peripartum cortical venous/arterial sinus thrombosis, and, rarely, vertebral artery dissection or moyamoya disease may also cause ICH. Independent risk factors that increase the susceptibility to pregnancy-related aSAH include increasing age (>35 years), hypertension, coagulopathy, African-American or Hispanic ethnicities, and drug abuse. Aneurysmal SAH typically has a higher maternal mortality than non-aneurysmal SAH [21].

19.4.1.1 Ruptured AVM and aSAH

Pregnancy per se does not increase the risk of AVM-related hemorrhage; however, it definitely increases the risk of rebleeding (25% versus 3–6% in nonpregnant patients) [12]. On the other hand, the risk of aSAH increases during pregnancy; it rises markedly at 30–34 weeks' gestation (8%, 11%, 78% in first, second, and third trimesters, respectively), possibly due to the increased BV and hormonally influenced weakening of the aneurysmal sac in late pregnancy, and peaks during labor, presumably, because of the hypertensive nature of childbirth [23–25]. Hypertensive patients have seven times higher risk of SAH as compared with normotensive patients; large aneurysms (>6 cm) are also twice more likely to bleed than smaller aneurysms (<6 cm) [23].

Patients usually present with sudden onset of severe headache, vomiting, and photophobia; loss of consciousness and neurological deterioration can occur rapidly, secondary to raised ICP and acute vasospasm. Rebleeding, vasospasm-induced cerebral ischemia, hydrocephalus, cardiopulmonary dysfunction, and electrolyte disturbances can further complicate the clinical course of these patients. The prognosis is rather grim; patients with an impaired level of consciousness on admission, advanced age, and a large volume of blood on initial CT scan have a high likelihood of death or a major disability.

Management

These patients require emergent neurosurgical (craniotomy with aneurysmal clipping/obliteration of AVM) or neuroendovascular management (coiling of aneurysm/embolization of AVM), irrespective of the stage of the pregnancy [19–24].

Though in principle there is no neurosurgical contraindication to vaginal delivery after an aneurysmal obliteration, however CS might be preferable in the following circumstances: incomplete coiling of the aneurysm; clinically unstable patient (coma, brainstem damage); if the interval between treatment of the aneurysm and labour is likely to be less than 8 days; or if the aSAH has occurred beyond 34 weeks of pregnancy [23].

Furthermore, patients who develop aSAH close to term pregnancy may undergo a combined procedure in which the cesarean delivery usually precedes the neurosurgery (minimizes fetal anesthetic exposure and also provides optimal operating conditions for the neurosurgeon without harming the fetus) [23].

Neuroendovascular techniques are increasingly being used for management of these lesions (ruptured or unruptured) in pregnant patients. These techniques are minimally invasive, have shorter anesthesia timings (lesser anesthetic exposure to the fetus), and have lower complication rate than craniotomies. However, the risk of bleeding complications is increased because of systemic heparinization; risk of fetal exposure to ionizing radiation, especially during first trimester interventions, is another important concern [23].

19.4.1.2 Unruptured Aneurysms and AVM

Patients with smaller (<6 mm), asymptomatic, stable aneurysms or unruptured AVMs are often managed conservatively (under vigilant monitoring); pregnancy can be allowed to continue till term and is followed by an elective intervention in the postpartum phase [23]. However, an intervention is indicated for unruptured aneurysms that are either large (>6 mm), symptomatic, or show signs of instability.

19.4.1.3 Neoplasms

All types of intracranial neoplasms have been reported during pregnancy; glioma, meningioma, pituitary adenoma, and acoustic neuroma are relatively more frequent; gliomas can vary in their degree of invasiveness, ranging from slow-growing pilocytic astrocytoma to the highly malignant glioblastoma multiforme (GBM) [19, 20, 26–28]. Pregnancy, per se, doesn't increase the incidence of these lesions; however, the associated physiological changes tend to exacerbate their natural course and may even unmask a previously undetected lesion [27, 28]. The rise in maternal BV, as well as increased sodium and water retention during pregnancy, can aggravate the tumor vascularity and peritumoral edema and, consequently, worsen the ICP [27, 28]. Elevated progesterone levels during pregnancy can accelerate the growth of benign, slow-growing meningiomas (progesterone receptors identified in meningiomas) [10]. Prolactinomas especially macroprolactinomas tend to enlarge as pregnancy advances (stimulatory effects of elevated estrogens, prolactin on pituitary tissue); acromegalic patients are reported to have an exacerbation of their symptoms during pregnancy [26]. Furthermore, increased estrogen and human chorionic gonadotropin concentrations can lower the seizure thresholds in pregnant patients.

Patients can present with features of raised ICP (headache, vomiting, and nausea), seizures, focal neurological deficits, and/or an alteration in the mental status. Symptoms such as headache and vomiting may be mistaken as pregnancy-related complaints, but their persistence beyond second trimester, exacerbation with cough or Valsalva maneuver (indicates raised ICP), and presence of accompanying neurological signs should raise the suspicion of an intracranial pathology. Patients with pituitary adenomas usually have headache, features of endocrinopathy, and/or visual problems (compression of optic pathways). Patients with growth hormone (GH)-secreting adenomas are at greater risk for hyperglycemia (carbohydrate intolerance/diabetes mellitus due to antagonism of effect of insulin by GH). Sudden headaches, vomiting, and rapid deterioration of vision or ocular motility may be a sign of pituitary apoplexy, a rare complication, in which a sudden hemorrhage or ischemic/hemorrhagic infarction of the pituitary adenoma results in a rapid increase in intrasellar pressures.

Management

Neurosurgical options include craniotomy and tumor resection, stereotactic tumor biopsy, transsphenoidal resection (for pituitary adenomas), VP shunt/endoscopic third ventriculostomy (ETV) for an associated obstructive hydrocephalus, and decompressive craniectomy [19, 20]. Sometimes, patients also undergo adjuvant treatment with radiotherapy or chemotherapy, after the neurosurgery.

Elective neurosurgery may be considered in neurologically stable patients with benign, slow-growing tumors and negligible mass effect, e.g., pilocytic astrocytoma, meningioma, pituitary adenoma, and acoustic schwannoma [10, 29, 30]. The pregnancy is allowed to proceed to term, with

conservative management and vigilant feto-maternal monitoring; obstetric criteria determine the mode of delivery. The neurosurgery is subsequently performed, as an elective procedure, preferably after 6 weeks postpartum (to allow resolution of physiological changes) [9, 10, 30].

Emergency neurosurgery may be necessary in some circumstances, in order to save the life of the mother, irrespective of the gestational age of the fetus e.g. in patients with aggressive malignant tumors (e.g., GBM), or if patients develop sudden or severe neurological deterioration. Pertinent considerations during these emergency procedures, are as follows [9]:

(a) First trimester/early second trimester: risks of fetal loss and congenital malformations in the newborn, (especially if adjuvant chemotherapy/radiotherapy is advised) should be explained, and an option of termination of pregnancy should be given to the patients.
(b) Late second/early third trimester: normal gestational advancement is permitted after the neurosurgery; route of delivery is determined by obstetric criteria.
(c) Neurosurgery in near-term pregnancy: CS under GA followed by neurosurgery.

Nonurgent but essential neurosurgery may be performed, on a "as soon as possible" basis, in neurologically stable patients, who do not harbor malignant tumors but have a large tumor, progressive symptoms of a raised ICP, or evidence of disease progression on neuroimaging [9, 10, 19, 20, 27, 30].

(a) First/early second trimesters**:** it is acceptable to allow pregnancy to proceed beyond the first trimester and perform the neurosurgery in early second trimester; radiotherapy, radiosurgery, and image-guided surgery are also feasible at this time.
(b) Late second and third trimesters: gestational advancement can be permitted, with close observation of the mother and fetus; vaginal or cesarean delivery can occur after 32 weeks of gestation, followed by the neurosurgery.

Osmotic diuretics, corticosteroids, and antiepileptics are useful adjuncts, while waiting for the pregnancy to advance, before the neurosurgery is undertaken. Patients with an obstructive hydrocephalus should undergo a VP shunt or an ETV.

19.4.2 Spinal Pathology

Lower back pain is one of the most common pregnancy-related complaints, but rarely, it may indicate a serious underlying spinal pathology, e.g., spinal neoplasm (vertebral hemangioma, meningioma, astrocytoma, schwannoma, metastasis), significant lumbar intervertebral disk herniation, cauda equina syndrome, or SSEH. Generally, associated features of spinal cord (SC) compression are also present [12, 31, 32]. Cauda equina syndrome usually presents with severe, unilateral, radicular pain, numbness in sacral region, decreased sensations and tone in lower limbs, areflexia, and bowel and bladder dysfunction [31, 32]. SSEH is caused by rupture of thin-walled vertebral veins; it accounts for 1% of all epidural compressive lesions and usually occurs in association with coagulopathy, spinal AVM, or anticoagulant therapy [33].

Benign SC lesions are managed conservatively; however, acute progressive neurologic deficits or cauda equina syndrome (due to symptomatic disk prolapse, spine tumor, hemorrhage from tumor, SSEH, or vertebral AVM) often necessitate an emergent neurosurgical intervention [12, 31–33].

19.4.3 Trauma

Trauma occurs in approximately 7% of pregnancies; TBI or SCI can complicate the course of some of these patients [12, 34]. Early and aggressive maternal resuscitation is the first priority; surgical intervention may involve evacuation of the hematoma (cranial or spinal), decompressive craniectomy, decompression, and stabilization of the injured spine.

19.4.4 Hydrocephalus

Up to 58% of patients with VP shunts show signs of increased ICP during pregnancy, possibly due to the pregnancy-related, reduced ventricular compliance and increased intra-abdominal pressure; additionally, a previously compensated hydrocephalus may become symptomatic during pregnancy [20, 35, 36]. Symptoms range from transient headache, nausea, vomiting, and visual disturbances to severe persistent neurological deficits or miscarriage [35, 36]. These patients require an ETV or a shunt revision surgery (VP shunt till second trimester, ventriculoatrial shunt in third trimester). During VP shunt placement, the distal catheter should be inserted gently into the abdomen, to avoid the risk of uterine trauma and/or premature labor.

19.5 Anesthetic Management of Pregnant Patients for Neurosurgery

19.5.1 General Considerations

There are no well-established recommendations regarding the perioperative management of pregnant patients with a neurosurgical pathology. Hence anesthesia strategy for these patients is generally formulated on the basis of our knowledge of the fundamentals of pregnancy and neuroanesthesia, supplemented by the clinical experience and data reported in the literature; a well-planned, individualized, and multidisciplinary approach is vital for a favorable maternal and fetal outcome. The primary aim of the anesthesia strategy is to use a technique that maintains the normal maternal physiology, especially the cardiorespiratory parameters and CPP, provides optimal operating conditions, is safe for the fetus, and also facilitates an early neurological recovery. Pertinent concerns that need to be considered when formulating this strategy are:

- Pregnancy increases the risk of supine hypotension syndrome, aspiration, difficult airway, more rapid oxygen desaturation, and ICP increase during induction (especially if cerebral autoregulation is impaired).
- Occurrence of maternal hypoxemia, acidosis, and/or extreme hypercarbia/hypocarbia poses a severe and acute risk to the fetus.
- Neuroprotective interventions that benefit the mother may be harmful for the fetus, e.g., hyperventilation and mannitol provide brain relaxation, but may decrease UBF and induce fetal dehydration, respectively.
- Furthermore, conventional anesthesia technique for pregnant patients may adversely influence the intracranial homeostasis, e.g., a rapid sequence induction to decrease the aspiration risk, may elevate maternal CO_2, BP, and hence the ICP.

19.5.2 Preoperative Evaluation and Preparation

The preoperative evaluation includes an assessment of the patient's neurological, obstetric, surgical, anesthetic and medical history; details of the neurosurgical pathology (diagnosis, site, size, morphology, invasiveness); pertinent aspects of the proposed neurosurgical procedure (intended surgical procedure, surgical approach, patient's position, potential peri-operative complications, anticipated surgical duration; blood loss, need for intraoperative neuro-physiological monitoring); a focussed clinical examination; and a review of the investigations, medical records, allergies and current medications.

During the evaluation, special attention should be given to the gestational age of fetus, patient's airway (possible difficulty during BMV, tracheal intubation, supraglottic airway [SGA] insertion, front-of-neck access for a surgical airway) and neurological status, cardiac evaluation (especially in patients with GH-secreting adenomas), presence of coexisting medical and/or gestational morbidities (e.g., hypertensive disorders of pregnancy, gestational diabetes), hormonal profile in patients with pituitary adenomas, and blood glucose levels, especially in patients with GH-secreting adenomas.

On the basis of this evaluation, the neuroanesthetist can effectively analyze the critical perioperative concerns; seek specialist advice if indicated (e.g., cardiology consultation, echocardiography, in patients with elevated GH levels); discuss pertinent issues with the caring obstetric, neonatal, and neurosurgical teams; implement appropriate measures to optimize the patient's clinical condition; and also, formulate an optimal anesthesia plan.

Potential risks of miscarriage, teratogenicity, and preterm labor, albeit low, should be explained; and the option of a therapeutic abortion (for first trimester neurointerventions) should be discussed with the patient. Fetal well-being should be confirmed preoperatively by CTG.

Given the high incidence of a failed airway in these patients, a provisional difficult airway management plan should be formulated preoperatively; critical decisions, e.g., whether to awaken the patient or proceed, in case of a failed TI, and when to consider a surgical airway access, should be taken in consensus with the neurosurgical and obstetric teams [5].

19.5.3 Anesthetic Choices

Most cranial surgeries are performed under GA; the choice of anesthetic drugs is largely determined by their effect on the maternal cardiovascular and cerebral physiology, uterine tone and uteroplacental blood flow, fetal toxicity, gestational age at which the surgery is planned, and whether a simultaneous CS neurosurgery is contemplated. As discussed in the previous sections, most anesthetic agents have a good feto-maternal safety record (avoid ketamine in first and second trimesters); their effect on the maternal cerebrovascular physiology is as follows:

19.5.3.1 Intravenous Agents

Thiopentone, propofol, and etomidate have a favorable cerebral profile: cerebral vasoconstriction; decrease in cerebral blood flow (CBF), cerebral blood volume (CBV), ICP, and cerebral metabolic rate of oxygen ($CMRO_2$); preservation of cerebral autoregulation and CO_2 reactivity; attenuation of hypertensive response and ICP increase during laryngoscopy and intubation (airway reflexes better suppressed with propofol); and rapid awakening from anesthesia, to allow an early evaluation of the postoperative neurological status. Thiopentone and propofol are most frequently used but may cause hypotension due to their negative inotropic and vasodilatory effects [9, 12, 37]. Etomidate and ketamine provide hemodynamic stability and are good alternatives in hypotensive patients; however, etomidate can cause adrenal suppression. Traditionally, ketamine has been relatively contraindicated in neurosurgery, because of its unfavorable dose-dependent effect on CBF and ICP; however, this premise has been challenged in recent literature; it is used in combination with a benzodiazepine (to decrease the incidence of associated psychomimetic effects) and glycopyrrolate.

19.5.3.2 Inhalational Agents

Volatile inhalational agents (isoflurane, sevoflurane, desflurane) cause cerebral vasodilation, increase in CBF, and decrease in $CMRO_2$, with preservation of cerebral autoregulation and minimal disruption of cerebral flow metabolism coupling at clinically relevant doses; sevoflurane has the most favorable cerebral profile. These agents are used for maintenance of anesthesia at a 1.0 or lower MAC concentrations; at these concentrations, they have a very minimal effect on maternal BP and uterine tone and bleeding.

N_2O should be avoided because it causes cerebral vasodilation; increases the CBF, $CMRO_2$, and ICP; impairs autoregulation; expands air bubbles; and may contribute to postoperative nausea and vomiting.

Opioids and NDMR have minimal direct effects on cerebrovascular physiology and ICP. Opioids provide excellent hemodynamic stability; remifentanil has the advantage of a very short duration of action. A carefully titrated single dose of a benzodiazepine may be useful for premedication and/or as an adjunct to other agents, during induction or maintenance of anesthesia.

19.5.4 Anesthesia for Cranial Neurosurgery During Pregnancy

19.5.4.1 Preoperative Preparation

Aspiration Prophylaxis and Fasting Guidelines

A combination of a nonparticulate antacid (e.g., sodium citrate), histamine (H2) receptor antagonists (e.g., ranitidine, cimetidine), and a prokinetic agent (e.g., metoclopramide) is administered to pregnant patients with more than 14 weeks of gestation. H2 blockers decrease basal gastric acid secretion and volume; antacids help to maintain the gastric ph at >2.5; metoclopramide, a dopamine antagonist, increases LES tone, decreases volume of gastric secretions, and also has central antiemetic effects. Food is withheld for 6 h, and clear fluids may be given up to 2 h prior to elective neurosurgery [5].

Premedication

Sedative premedication is best avoided but if deemed necessary (e.g., in highly anxious patients) should be administered under close monitoring in the preoperative holding area, to minimize the chances of aspiration and hypoventilation. Anticonvulsant medication (if prescribed) should be continued perioperatively, and neurological reference should be sought to confirm adequacy of therapy. Antibiotic prophylaxis is administered according to institutional protocol and keeping in view its safety profile in pregnancy.

Monitoring

HR, ECG, arterial oxygen saturation (SaO_2), end-tidal carbon dioxide (Et CO_2), invasive arterial BP (IABP) temperature, fluid intake, urine output, arterial blood gases (ABG), serum electrolytes, and glucose levels are routinely monitored during a craniotomy or a major spine surgery; IABP monitoring should be established before induction (early detection and prompt management of hemodynamic instability). Monitoring of depth of anesthesia (e.g., bispectral index, patient state index) and neuromuscular blockade, if available and feasible (electrode placement doesn't interfere with surgical site), enables precise titration of anesthetic drug dosages and facilitates an early postoperative recovery. A central venous line is highly recommended if significant intraoperative blood loss is anticipated, e.g., meningioma surgery (monitoring of central venous pressure [CVP], mixed venous oxygen saturation, administration of vasoactive drugs and fluids), and/or if there is a risk of venous air embolism, e.g., sitting position surgery (for aspiration of entrained air). Fetal CTG, if available, can be useful for assessment of FHR and uterine contractions.

19.5.4.2 Patient Positioning

Optimal patient positioning markedly increases the likelihood of a successful tracheal intubation. Recent guidelines recommend a "supine with a 20–30° head up" position, for intubation in pregnant patients; this position increases FRC, aids insertion of a laryngoscope in patients with large breasts, improves the view at laryngoscopy, and may reduce risk of aspiration by reducing reflux [5]. The "ramped-up" position further facilitates intubation in obese patients and is achieved by elevating the shoulders (by placing pillows beneath them) so that the external auditory meatus aligns with the suprasternal notch, and the face is parallel to the ceiling. LUD is maintained after 20 weeks of gestation, by placing a wedge/roll under the patients right hip or by lateral tilting the operation table (15–30° to left) [5].

19.5.4.3 Preoxygenation

Preoxygenation increases the pulmonary oxygen reserves and is mandatory in pregnant patients, owing to their limited oxygen reserve and the exaggerated fetal response to maternal hypoxia [5]. Effective preoxygenation is achieved by administering 100% oxygen (fresh gas flow rate $\geq$10 $L.min^{-1}$) for 2–3 min, with a tight mask-to-face seal, prior to induction of anesthesia; its efficacy is assessed by an end-tidal oxygen fraction

of >0.9, (assessed by breath-by-breath oxygen monitoring) [5]. In addition, continued passive oxygenation by bulk flow of oxygen (preoxygenation, oxygen insufflation by nasal cannulae at the rate of 5 $L.min^{-1}$) during induction also helps to increase the time to desaturation [5].

19.5.4.4 Pre-induction

Equipment for management of a difficult airway should be kept ready prior to induction. It may be prudent to consider an awake fiber-optic intubation, in patients with a known difficult airway.

19.5.4.5 Induction of Anesthesia

A "modified rapid sequence anesthetic induction technique" is preferable after the first trimester; this is a trade-off between the conventional slow induction technique used in neurosurgical patients (increased aspiration risk) and the "rapid sequence apneic induction" used in pregnant patients (risk of hypoxia, hypercapnia, and rise in ICP). It is achieved by administration of a sedative-hypnotics, e.g., propofol (2–2.5 mg/kg) or thiopentone (4–5 mg/kg) (ketamine [1–1.5 mg/kg] or etomidate [0.3 mg/kg] in hemodynamically instable patients) and a muscle relaxant (succinyl choline [1–1.5 mg/kg] or rocuronium [0.9–1.2 mg/kg]); pressor response to laryngoscopy can be blunted with a short-acting opioid (e.g., fentanyl [2–3 μg/kg] or remifentanil [1 μg/kg]), lignocaine (1–1.5 mg/kg), and/or beta-blockers (esmolol, labetalol); magnesium sulfate (30–60 mg/kg IV bolus) is preferred in patients with eclampsia or SAH [5, 12]. Precurarization with a defasciculating dose of a NDMR to prevent succinylcholine-induced fasciculations is not recommended.

After loss of consciousness, cricoid pressure (10 N–30 N) is applied (direction of the pressure should account for lateral tilt of the operation table) and maintained till tracheal intubation is confirmed by capnography. Gentle BMV is performed using low peak ventilatory pressures (<20 cmH2O); this technique reduces oxygen desaturation and also allows an assessment of adequacy of BMV should it be required in the event of a difficult/failed airway. A short-handled Macintosh laryngoscope and smaller-sized endotracheal tubes (6.0–6.5 mm internal diameter) are used for TI; nasal instrumentation is preferably avoided (mucosal trauma). Video laryngoscopes provide better view of glottis and have been suggested by recent studies as first-line device for all tracheal intubations [38].

19.5.4.6 Management of an Unexpected Difficult Airway

If TI is initially unsuccessful, additional efforts are made to improve the laryngoscopic view by decreasing or removing cricoid pressure, external laryngeal manipulation, repositioning of the patient's head and neck, use of a different laryngoscope blade and/or laryngoscope, use of tracheal tube introducer (bougie or stylet), and, if possible, a further attempt by an experienced colleague.

When TI has failed, ventilation with oral airway-face mask and cricoid pressure or with a SGA is attempted. If ventilation is successful (cannot intubate, can ventilate), the next decision is whether to continue anesthesia or to wake the patient (usually depends on the neurosurgical urgency). However, if is not possible to either ventilate (cannot intubate, cannot oxygenate) or awaken the patient, then an emergency surgical access, e.g., cricothyrotomy, tracheostomy, or transtracheal jet ventilation, needs to be immediately established, to prevent maternal and fetal hypoxemia.

Guidelines published by the Obstetric Anaesthetists' Association and Difficult Airway Society emphasize planning and multidisciplinary communication, continued oxygenation immediately after induction, limiting intubation attempts to two, early release of cricoid pressure if there is difficulty in glottic visualization, early shift to a SGA (preferably second generation) if appropriate (after declaring failed TI with clear decision points), and management of the "can't intubate, can't oxygenate" situation with an emergency front-of-neck airway access [5].

19.5.4.7 Maintenance of Anesthesia

Total intravenous anesthesia (TIVA) (e.g., propofol, opioid infusion), inhalational anesthesia (e.g. sevoflurane, opioids), as well as, balanced GA technique (e.g. sevoflurane, propofol and opioids) have been successfully used in combination with a NDMR (e.g. vecuronium, atracurium) for maintenance of anesthesia, without any difference in the maternal or fetal outcome. Several drug combinations are feasible, provided they maintain the maternal cerebral perfusion, UBF, and fetal oxygenation. TIVA may be preferred in patients with a marked intracranial hypertension and/or if neuromonitoring will be performed (inhalational agents may decrease the amplitude and increase the latency of electric signals). An adequate anesthetic depth should be maintained to prevent maternal catecholamine release and consequent reduced uteroplacental perfusion.

19.5.4.8 Intraoperative Management

The intraoperative aim is to maintain the "physiologically altered values" to optimize the feto-maternal homeostasis; hence, mechanical ventilation is adjusted to maintain a maternal $PaCO_2$ of around 30–32 mmHg and a mild respiratory alkalosis. Normothermia is maintained; episodes of hypotension, hypoxemia, extreme hypercarbia/hypocarbia, and acidosis are avoided and/or aggressively managed.

IV Fluid Therapy, Brain Relaxation

Isotonic, glucose-free solutions (e.g., 0.9% isotonic saline) are used to reduce the risk of cerebral edema and hyperglycemia. Elevation of the patient's head by 20–30°, restrained use of diuresis (low dose of mannitol [0.25–0.5 mg/kg] or loop diuretic), and, if required, a brief period of maternal hyperventilation ($PaCO_2$: 25–30 mmHg) can help to decrease the cerebral volume and facilitate the surgical exposure.

Hemodynamic Considerations

BP should be maintained within 20% of the baseline levels and the MAP should not be less than 70 mmHg (approximately 140/90 mmHg in patients with a concomitant preeclampsia [8]). A systolic BP <150 mmHg is recommended for normotensive patients with an unsecured cerebral aneurysm [12]. Normotension is maintained with administration of fluids; vasopressors may be required during surgeries associated with significant blood loss, e.g., meningioma and AVM resection. Contrary to past recommendations, both ephedrine and phenylephrine are considered safe and effective vasopressors during pregnancy. Recent literature also supports the use of norepinephrine as a vasopressor [9].

Controlled hypotension can compromise uteroplacental perfusion and may increase the risk of delayed neurological deficit in the mother; therefore, its use is on the decline. However, if deemed necessary, BP may be lowered to a level not detrimental to maternal well-being, for a very brief duration, and preferably with fetal monitoring to alert anesthesiologist to fetal distress [8]. Propofol infusion and sevoflurane, in combination with a beta-blocker, may be used to provide hypotension; use of sodium nitroprusside should be restricted, because of the potential risk of cyanide toxicity in the fetus [8].

19.5.4.9 Emergence from Anesthesia

Upon completion of neurosurgery, depth of anesthesia should be maintained till pins are removed and dressing is secured; this prevents coughing and straining on tube which can cause increased ICP and rebleed. Coughing and straining on the tracheal tube can be prevented by administration of a bolus of lidocaine (75–100 μg) or fentanyl (25–50 μg). Emergence hypertension can be managed with carefully titrated doses of labetalol or esmolol. Tracheal extubation should be performed with the patient fully awake, with intact airway reflexes, and, preferably, in the lateral position [9]. Patients with a poor preoperative neurological status or a complicated intraoperative course may require postoperative

mechanical ventilation with sedation in the intensive care unit till their neurological condition improves.

19.5.4.10 Postoperative Management

Analgesia

Adequate analgesia, besides providing maternal comfort and mobility, reduces undesirable hemodynamic and fetal disturbances, especially pain-induced catecholamine release, which can potentially compromise the uteroplacental perfusion. A multimodal approach combining a local anesthetic infiltration/scalp block, paracetamol, and opioids may be the best analgesic technique. Opioid agents should not be withheld, but close monitoring to prevent maternal and fetal hypoxia is necessary. Patient-controlled analgesia (e.g., fentanyl) is another option.

Cyclooxygenase 1 inhibitors are generally avoided because of the risk of bleeding after intracranial surgery (inhibition of platelet function) and their potential fetal adverse effects; cyclooxygenase 2 inhibitors have no platelet effects but have not been evaluated during pregnancy.

Risk of Preterm Labor

Preterm labor should be suspected if the patient complains of abdominal pain. Analgesia may mask the signs of early preterm labor; hence, postoperative TCG monitoring may be useful for early detection of uterine contractions and prompt administration of tocolytic therapy. Generally, if a pregnancy continues beyond the first postoperative week, then the incidence of premature labor is almost similar to nonsurgical pregnant patients. Postoperative prophylactic tocolysis is generally indicated only if the risk of fetal loss is high.

DVT Prophylaxis

Postoperative venous stasis and hypercoagulability of pregnancy increase the risk of thromboembolic events; hence, nonpharmacological prophylaxis (calf compression devices or antithromboembolic stockings) should be started perioperatively; early mobilization and maintenance of adequate hydration should be encouraged. The risk-benefit of initiating pharmacological prophylaxis (e.g., subcutaneous low-molecular-weight heparin) should be discussed with the neurosurgeon.

19.5.4.11 Cardiac Arrest and Cardiopulmonary Resuscitation

A critical event due to an acute perioperative neurosurgical/anesthetic complication, or a preexisting pregnancy-related disorder, renders both the mother and fetus at a markedly high risk for morbidity and mortality. An unstable patient is placed in full lateral decubitus position to relieve aortocaval compression, oxygen is administered with face mask at 15 L/min, and intravenous access is established above diaphragm to prevent obstruction by gravid uterus.

In case of a cardiac arrest, a minimum of four staff members should respond for basic resuscitation of the pregnant patient. Recommendations for chest compression and airway management are same as current basic life support (BLS) guideline [39]. Manual LUD should be maintained throughout resuscitation effort by cupping and lifting up the uterus leftward off the maternal vessels while standing on the left side of the patient to prevent aortocaval compression [39]. A universal code should activate an adult resuscitation team, neonatology team, anesthesia, and obstetrics care providers. Throughout resuscitation, the mother should remain the primary focus.

Defibrillation is safe in all stages of pregnancy and should be administered promptly when indicated. The energy requirements are same as in nonpregnant state. Adhesive shock electrodes are preferred over traditional paddles to allow consistent electrode placement with lateral pad placed under the breast tissue.

Due to limited oxygen reserve, hypoxemia should always be considered as a cause of cardiac arrest and treated early. Peri-mortem

cesarean delivery should be performed in patients with fundus height at or above the umbilicus and in whom spontaneous circulation has not returned at 4 min after usual resuscitation efforts. Medications for advanced cardiac life support do not require alteration secondary to physiological changes of pregnancy; however, vasopressin can induce uterine contractions, and hence epinephrine is the preferred agent of the two [39].

19.5.5 Anesthesia for Combined Cesarean Section and Intracranial Neurosurgery

Besides the standard management principles discussed in the previous sections, pertinent concerns that need to be addressed are, risk of neonatal depression due to administration of opioids, fetal bradycardia due to administration of beta-blockers, and postpartum hemorrhage (PPH) due to uterine atony. A neonatologist should be present during these procedures, to provide neonatal resuscitation and support respiration, if the need arises. A slow oxytocin infusion is started after placental extraction (10 IU oxytocin in 500 cc of 0.9% normal saline) to reduce the risk of PPH (side effects: transient hypotension, tachycardia). Ergometrine, if required, should be used only after consultation with the neurosurgeon; though it causes venoconstriction, reduces the intracranial BV, and is also a part of Lund approach for treatment of intracranial hypertension, however, it also induces a hypertensive response that may further worsen the ICP in patients with a disrupted blood-brain barrier and an impaired autoregulation. Because of concerns that volatile anesthetics decrease the uterine tone, some anesthetists tend to shift from a volatile-based anesthetic for cesarean delivery to TIVA technique for the subsequent neurosurgery; others have uneventfully used a volatile anesthetic for both procedures [12, 40]. In addition, though there are some reports of reduced neonatal neurobehavioral performance with use of TIVA with propofol as compared with a volatile anesthetic maintenance, these effects are probably of arguable clinical significance [12, 41].

19.5.6 Anesthesia for Interventional Neuroradiology

The interventional neuroradiology suite is a difficult and "remote" environment, in which provision of obstetric anesthesia can be rather difficult. Besides the standard concerns, other pertinent factors that merit attention are the risks of bleeding complications due to systemic heparinization and of fetal teratogenicity due to exposure to ionizing radiation.

Heparinization is of particular concern when spontaneous labor or sudden fetal distress commences during or soon after embolization and necessitates an expeditious delivery or an emergency CS, respectively. In this situation the neurointervention may need to be halted until delivery of the baby; the intracranial catheters are withdrawn, femoral artery sheath is left in situ, and residual effect of heparin is reversed by administration of protamine.

The potential risks of ionizing radiation-induced fetal abnormalities, growth restriction, or abortion are highly dependent on the fetal age at time of exposure (maximum susceptibility between 8 and 25 weeks of gestation) and the dose absorbed (>5 rads (radiation absorbed dose)) [16]. Adequate precautions, such as anterior and posterior abdominal shielding; and avoidance of fluoroscopy caudad to the aortic arch, can limit radiation exposure to the mother and the fetus [23]. The expected radiation exposure of the fetus during endovascular procedures is expected to be approximately 0.49 rads, which is considerably lower than the teratogenic dose [24, 42].

19.5.7 Anesthesia for Spine Surgery

Apart from a few discernible concerns which are discussed below, the principles of anesthetic management for intracranial neurosurgery are also applicable to spinal pathologies.

19.5.7.1 Airway

Difficulty in securing an airway may be enhanced in patients with cervical spine pathologies. A neutral position of the head and cervical spine should be maintained during airway control, or an awake fiber-optic intubation should be considered to minimize risk of spinal cord compression.

19.5.7.2 Patient Positioning

Spine surgery can be performed in the prone or the left lateral position, as both these positions provide relief from aortocaval compression; in contrast, the right lateral decubitus may increase IVC compression [31, 43]. The prone position provides better surgical access but is also associated with a higher risk of precipitating preterm labor if excessive compression of the gravid uterus occurs inadvertently. On the other hand, the lateral position allows better vigilance regarding abdominal compression; moreover, it also makes it easier to expose the patient's abdomen after sterile draping, monitor the FHS, and convert to the supine position in case a need for an emergency CS arises. Generally, cervical surgeries are performed in the prone/sitting position. For lumbar and lower thoracic spine surgeries, the prone position can be used during first and early second trimesters; left lateral decubitus position is preferred from second trimester onward [43, 44]. Among the various tables used for prone positioning, Jackson table, Relton-Hall frame, and Wilson frame have been reported to be safe from the perspective of abdominal and IVC compression. Irrespective of position or operating table chosen, meticulous care during positioning to ensure free abdominal movement and maintenance of an optimal SC cord perfusion is (MAP > 75–80 mmHg) of paramount importance.

19.5.7.3 General or Regional Anesthesia

Lumbar spine surgeries may be performed under general or epidural anesthesia. While the latter provides the advantage of allowing women to comfortably position themselves in the prone/lateral position on the table/frame, after receiving the regional block, there is no evidence to suggest that either of these techniques offers significant benefits to the mother or the fetus.

19.5.8 Anesthesia for Head and Spine Trauma

Principles of management of TBI and SCI injury are almost similar for pregnant and nonpregnant patients; the primary management goal is optimal maternal resuscitation and early fetal assessment [45]. Maternal resuscitation follows the general guidelines for trauma management (avoidance of hypoxia, hypercarbia, hypotension [systolic BP <90 mmHg]; maintenance of normoglycemia [140–180 mg/dL, adequate CPP {50–70 mmHg}]) with appreciation of the physiological and pharmacological issues specific to pregnancy. Fetal well-being is assessed during or immediately after maternal resuscitation and stabilization; CTG monitoring (in a viable fetus) should be performed for at least 2–6 h after the injury [13].

In TBI with suspected CSI, awake fiber-optic intubation is preferred over direct laryngoscopy. Therapies to control intracranial hypertension include deep sedation, pain control, brief hyperventilation, hyperosmolar agents, vasopressors, and decompressive craniotomy. Since most of these treatments can lead to adverse fetal outcome, decompressive craniotomy is possibly the only treatment which allows continuation of pregnancy [46].

A full LUD may be required in patients with a SCI. Management of these patients depends upon the site, extent, and duration of SCI. A lesion above C4 vertebral level may lead to bradycardia and decreased CO secondary to sympathetic

autonomic blockade. CVP-guided fluid therapy should be initiated as signs of hypovolemia are not clinically apparent. Dobutamine may be started to maintain cardiac output and UPP; it is not known to cause fetal teratogenicity.

Key Points

- Intracranial hemorrhage due to rupture of an aneurysm or arteriovenous malformation is a leading cause of indirect maternal mortality and is frequently associated with hypertensive disorders.
- The incidence of intracranial tumors does not increase; however, they can grow more rapidly during pregnancy, due to the associated hormonal changes and increased maternal blood volume; glioma, meningioma, pituitary adenoma, and acoustic neuroma are relatively more common in these patients.
- Pregnant women have an increased cardiac output and blood volume, increased oxygen demand with higher minute ventilation, lower functional residual capacity and faster oxygen desaturation during apnea, reduced lower esophageal sphincter tone with greater aspiration risk, reduced responsiveness to vasopressors, and greater risk of supine hypotension syndrome and failed tracheal intubation as compared with nonpregnant women.
- Uteroplacental circulation has a pressure-passive perfusion; hence, maternal hypotension results in a parallel decrease in blood supply to the fetus; perioperative catastrophes that result in hypoxemia, acidosis, and/or extreme hypercarbia/hypocarbia are also highly detrimental for fetal well-being.
- Almost all anesthetic drugs (except reversal agents, depolarizing and nondepolarizing muscle relaxants) readily cross the placenta. None of them is a proven teratogen in humans, when used in standard concentrations.
- Mannitol accumulates in the fetus. Administration of higher doses is associated with fetal dehydration, cyanosis, and bradycardia; lower doses (0.25–0.5 mg/kg) are reported to be safe.
- Neurosurgical considerations take precedence over obstetric considerations; while emergency neurosurgery is performed irrespective of the stage of pregnancy, elective surgery should be postponed until after delivery.
- A "modified rapid sequence anesthetic induction technique" is preferable after the first trimester.

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Pediatric Neuroanesthesia

20

Jue T. Wang and Craig McClain

20.1 Introduction

Children and infants undergoing neurosurgical procedures present unique challenges for the anesthesiologist. The anesthetic plan must take into consideration the various stages of organ development as well as changes in both the structural and physiological parameters between neonates, infants, and children. The goal of this chapter is to elucidate the age-dependent complexities of the management of pediatric patients undergoing neurosurgical procedures.

20.2 Development

The central nervous system (CNS) undergoes significant growth and development with accompanying changes in physiology and hemodynamics throughout development from neonate to adulthood. Neonates have open cranial sutures and fontanelles. Subtle and slow changes in intracranial pressure (ICP) are often not recognized until late in the disease process as the open cranial sutures are able to expand in response to rising ICP. However, acute changes in ICP in the neonate can cause herniation just like in adults. The posterior fontanelle closes at 2 months of age, and the anterior fontanelle is closed in most infants by 2 years of age. After the fontanelles close, children have the same intracranial compliance as adults.

20.2.1 Intracranial Compartments

The Monro-Kellie hypothesis states the rigid cranial vault causes all intracranial volumes to be constant. The intracranial space is occupied by the brain and its interstitial fluid (80%), cerebrospinal fluid (CSF, 10%), and blood (10%). An increase in one compartment will cause a proportional decrease in another compartment. Any disease process that involves space-occupying lesions (tumors, hematoma, abscess, edema, etc.) will alter the above proportions and potentially cause increases in ICP. When the ICP increases, cerebral perfusion pressure (CPP) and consequently cerebral blood flow (CBF) can decrease causing brain ischemia.

20.2.2 Intracranial Pressure

Normal ICP in a term neonate is 2–6 mmHg and in a child is less than 15 mmHg. Preterm neonates likely have an ICP that is even lower than that of term neonates. Children have a greater percentage

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of brain water content, less CSF volume, and greater percentage of brain content to intracranial capacity which all decrease intracranial compliance [1]. Thus children have a higher risk of herniation compared to adults when both experience a proportional relative increase in ICP.

20.2.3 Herniation Syndromes

There are several types of herniation syndromes. The most common type is transtentorial herniation, during which the uncus of the temporal lobe is pushed down from the supratentorial to the infratentorial space. During this process the compression of the third cranial nerve and brainstem causes pupillary dilation, hemiparesis, and loss of consciousness and then progresses to apnea, bradycardia, and death. A second common type of herniation is cerebellar herniation in which the cerebellar tonsils herniate through the foramen magnum in the posterior fossa into the cervical spinal space. This causes obstruction of CSF flow and brainstem compression causing hydrocephalus as well as cardiac and respiratory failure, which if not promptly treated, will lead to death.

20.2.4 Intracranial Compliance

Absolute values for ICP are important for establishing norms and ruling out gross pathology; it is important to understand those values do not completely represent the degree or extent of compensatory mechanisms. Intracranial compliance, defined as the change in pressure relative to a change in volume, is a very important concept that unites changes in ICP as it relates to changes in the volume of a relatively fixed intracranial compartment. Acute and rapid changes in intracranial volume can surpass the compensatory mechanisms for compliance. In such instances the expansion in intracranial volume will translate into rapid increase in ICP. Conversely slow and subtle changes over time may allow time for the brain to adapt and compensate without any clinical signs of elevated ICP or decreased CPP.

20.2.5 Signs of Increased Intracranial Pressure

The classic signs of elevated ICP such as papilledema, pupillary dilation, hypertension, and bradycardia are often seen in children as well as adults, but children may not reliably display these signs [2, 3]. Chronic increases in ICP often manifest as irritability, headache, and vomiting (particularly in the morning). Somnolence and decreased response to painful stimuli are often late signs of elevated ICP and warrant rapid attention. Radiographic imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) results often show small or obliterated ventricles or basilar cisterns, hydrocephalus, and midline shift.

20.2.6 Monitoring Intracranial Pressure

Several techniques of monitoring ICP have been reliably used in children [4–6]. Ventricular catheters are generally accepted as the most accurate and reliable means of measuring ICP with the added benefit of the ability to remove CSF through the catheter for both diagnostic and therapeutic uses. Ventricular catheters can be difficult to insert into the exact locations where they are indicated, especially in situations where significant cerebral edema causes obliteration of the ventricles. The complication rate of these catheters is low, but risks include bleeding and infection, both of which can cause severe sequelae. Subarachnoid bolts are less invasive and easier to place when ventricles are compressed and have a lower risk of hemorrhage or infection. Bolts frequently underestimate ICP and are harder to stabilize than ventricular drains. Epidural monitors can be placed outside the dura and thus can avoid the risk of significant bleeding or infection. These monitoring systems generally given an accurate assessment of ICP, but once inserted they cannot be recalibrated [7, 8]. Other systems utilizing fiber-optic catheters can be placed in intraventricular, subarachnoid, and other intraparenchymal sites, but they also cannot be recalibrated after insertion.

20.3 Cerebral Spinal Fluid

CSF production is balanced by CSF absorption. In adults the rate of production is 0.35 mL/min or roughly 500 mL/day [9]. The average adult has between 100 and 150 mL of CSF distributed throughout the brain and subarachnoid space. The rate of CSF production in children is similar to that of adults, but there is a proportionally smaller volume of CSF in children [9, 10].

The production of CSF is relatively constant and is only minimally affected by changes in ICP or the presence of hydrocephalus. In rare cases choroid plexus papillomas can cause increased CSF production. Drugs such as acetazolamide, furosemide, and corticosteroids can transiently decrease CSF production [11–13]. There is an inverse relationship between serum osmolality and the rate of CSF production. As serum osmolality increases, either from physiologic changes or from medications, there is a drop in CSF production.

The arachnoid villi appear to be important for CSF absorption into the venous system for drainage. Other sites such as the spinal subarachnoid space, ependymal lining of the ventricles, and one-way valves between the subarachnoid space and sagittal sinus also take part in CSF absorption. Increased ICP also increases the rate of resorption of CSF. Pathological processes such as tumors and malformations, hemorrhage, and infections can obstruct CSF flow and decrease CSF resorption [2].

20.4 Cerebral Blood Volume, Blood Flow, and Perfusion Pressure

Cerebral blood volume (CBV) accounts for only 10% of the intracranial space, but dynamic changes in the blood volume occur in both pathological states as well as under anesthesia. In a normal adult cerebral blood flow (CBF) is 55 mL/100 g of brain tissue per minute [14–16]. Though estimates of CBF for neonates and children are less uniform, it is generally accepted to be 100 mL/100 g of brain tissue per minute in a healthy awake child and approaches the adult rate in the teenage years. CBF in neonates and preterm infants is approximately 40 mL/100 g brain tissue per minute [17, 18]. The head comprises a proportionally larger percentage of body surface area in neonates and children, and thus a larger percentage of cardiac output is directed to the brain. This means the developing brain of children is particularly susceptible to hemodynamic changes.

Cerebral blood flow is very tightly coupled to cerebral metabolic demand. The cerebral metabolic rate for oxygen consumption ($CMRo_2$) in a healthy adult is 3.5–4.5 mL O_2/100 g/min and is even greater in children [19]. Any reduction in $CMRo_2$ will cause a similar decrease in CBF and CBV. The coupling of CBF and $CMRo_2$ is likely mediated by the local effect of hydrogen ion concentration in cerebral blood vessel. Any condition that produces acidosis will cause dilation of the cerebral vasculature which, in turn, will increase both CBF and CBV. When cerebral autoregulation is disrupted, CBF is determined by other factors and can cause both hyperperfusion and hypoperfusion of the brain.

One way of assessing whether cerebral circulation is sufficient is to calculate the cerebral perfusion pressure (CPP). CPP is the pressure gradient across the brain and can be calculated by the following formula: CPP = MAP − CVP or ICP. This calculation gives the pressure difference across the systemic arterial pressure entering the brain and the venous pressure exiting the brain the CVP (or ICP if there is elevated ICP and it is higher than the measured CVP).

20.5 Cerebral Vascular Autoregulation

Blood Pressure Cerebral blood flow and metabolic demand are tightly coupled to ensure adequate oxygen delivery even when there are physiologic changes in MAP or ICP. In adults the CBF remains relatively constant at MAP range of 50–150 mmHg (see Table 20.1). In neonates the blood pressure autoregulatory range is narrower and lower between 20 and 60 mmHg. This is a result of both lower blood pressure as well as

Table 20.1 Anesthetic agents and effect on intracranial parameters

Agent	MAP	CBF	CPP	ICP	$CMRo_2$
Nitrous oxide	Slight decrease to none change	Increase	Slight decrease	Increase	Increase
Isoflurane	Decrease	Slight increase	Slight increase	Slight increase	Decrease
Sevoflurane	Decrease	slight increase	Slight increase	Slight increase	Decrease
Desflurane	Decrease	Slight increase	Slight increase	Slight increase	Slight decrease
Propofol	Decrease	Decrease	No change	Decrease	Decrease
Etomidate	Slight decrease to no effect	Decrease	Slight increase	Decrease	Decrease
Ketamine	Decrease	Increase	Slight decrease	Increase	Slight increase
Benzodiazepine	Decrease	Decrease	Slight increase	No change to slight decrease	Decrease
Opioids	Slight decrease to no effect	Slight decrease	Neutral	No change to slight decrease	Slight decrease

CBF Cerebral blood flow, *$CMRo_2$* cerebral metabolic rate for oxygen, *CPP* cerebral perfusion pressure, *ICP* intracranial pressure, *MAP* mean arterial pressure

lower cerebral metabolic requirements in neonates. The cerebral autoregulatory curve drops and rises significantly at the two extreme limits of the curve, thus making neonates extremely susceptible to cerebral ischemia and intraventricular hemorrhage.

Autoregulation is partially mediated by arteriolar resistance. When CPP decreases, cerebral vessels dilate to maintain adequate CBF and increasing CBV. When the CPP increased, cerebral vessels constrict, thereby reducing CBV but maintaining CBF. When both ICP and CVP are low, the MAP approximates the CPP. Beyond the BP ranges of autoregulation, the CBF becomes dependent on blood pressure and varies with changes in the blood pressure. Cerebral autoregulation can be impaired by acidosis, medications, space-occupying lesions such as tumors or vascular malformations, trauma, and cerebral edema.

Oxygen Cerebral blood flow is constant over a wide range of oxygen tensions. In healthy adults when the partial pressure of arterial oxygen (Pao_2) decreases below 50 mmHg, CBF increases dramatically. The increase in CBF increases CBV which also causes a rise in ICP. However, it is important to remember the most important measure is oxygen delivery rather than an absolute value of Pao_2. While hypoxia should be avoided, evidence have suggested hyperoxia can also cause a decrease in CBF [20, 21].

Carbon Dioxide There is a near linear relationship between CBF and arterial partial pressure of carbon dioxide ($Paco_2$). In adults increasing the $Paco_2$ by 1 mmHg will increase CBF by about 2 mL/100 g/min and will subsequently increase CBV [20]. Decreases in $Paco_2$ will likewise cause a similar decrease in CBF and CBV. This linear relationship is the basis for decreasing ICP via hyperventilation. There is no data to define the limits of the effects of changing $Paco_2$ on CBF. Moderate hyperventilation has been shown to decrease ICP acutely and can be used to decrease ICP in situations of impending herniation. However, there are reports that show hyperventilation also can worsen cerebral ischemia via decreasing CBF in susceptible areas of the brain in children with already compromised cerebral perfusion [22–24]. Cerebral autoregulation is already damaged in the setting of space-occupying lesions, trauma, and hemorrhage, so further decreases in CBF can be catastrophic in this patient population.

20.6 Management of Anesthesia

20.6.1 Preoperative Assessment

History and Physical Exam Children undergoing neurosurgical procedures present along a broad spectrum of disease states. Some children may have been completely healthy with only minimal symptoms on presentation to others with severe congenital anomalies that have been life-threatening or debilitating since birth. Each patient must be carefully assessed, and plans must be tailored to the individual patient.

A thorough past medical history as well as food and drug allergies should be obtained. Pediatric patients with congenital disorders such as myelomeningoceles should be treated with latex precautions. Anaphylaxis has occurred frequently in this patient population due to frequent exposure to latex-containing medical equipment [25]. Signs and symptoms of an allergic reaction to latex can include rash, hive, lip or tongue swelling, as well as wheezing and difficulty breathing after coming into contact with latex-containing substances such as exam gloves and rubber dams in dental offices. A patient with latex allergies may also have food allergies to strawberries, kiwi, bananas, and avocadoes.

The preoperative evaluation should include a detailed assessment of any symptoms caused by the neurologic disease process. Patients with intracranial tumors often have signs and symptoms of elevated ICP and may have nausea, vomiting, enuresis, and anorexia. Pituitary function may be impaired in some intracranial processes causing diabetes insipidus, thyroid hormone fluctuations, as well as adrenal insufficiency that may require perioperative stress-dose steroid supplementation.

A thorough physical exam should be performed to assess for bulbar symptoms that may affect swallowing necessitating a rapid sequence induction and intubation in order to prevent aspiration. Neuromuscular disorders and previous strokes with resulting muscle weakness may precipitate life-threatening hyperkalemia when succinylcholine is used for muscle relaxation during intubation. Detailed cranial nerve examination is necessary for any intervention for intracranial processes to establish a baseline in order to discern new and potentially concerning changes in the exam postoperatively.

Laboratory and Imaging Studies A complete blood count and coagulation studies should be ordered for any procedure where sudden or large volume blood loss is anticipated. Liver function tests should be performed in children with seizure disorders taking antiepileptic drugs as the medications can cause significant upregulation of liver function and potential liver damage. Chemistry profile including thyroid function tests should also be obtained to assess for electrolyte imbalances that may occur as a result of intracranial pathology. Diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, and central adrenal insufficiency are only a few syndromes related to intracranial diseases that will cause significant changes in sodium, potassium, and hormone regulation.

Radiographic studies have usually been obtained by the neurosurgical team as part of preoperative work-up. Generally, anesthesiologists should review radiographic studies as they can significantly change the type of anesthetic needed. Patients with significant hydrocephalus showing ventricular effacement may have significantly altered mental status preoperatively. The location of intracranial tumors may cause pituitary dysfunction, cranial nerve injury, spinal cord injury, central apnea, and a host of other pathological processes.

Premedication Children will present for neurosurgical procedures in a variety of condition. Patients with preexisting altered mental status should not be given more sedatives or opioids as those medications can significantly impair the respiratory drive. Likewise, patients who have significantly elevated intracranial pressure should also be given premedication only in a strictly monitored setting, and medications should be titrated slowly to effect as hypoventilation could cause further increases in ICP. Children who are relatively asymptomatic and are coming from home for their neurosurgical procedures will likely require a premedication in order to facilitate a smooth separation from parents. In patients with-

out an IV, midazolam given 0.1–1 mg/kg orally is effective but will take 10–20 min to reach full effect. IV midazolam given 0.05 mg/kg works rapidly and effectively in patients with an existing IV.

20.6.2 Intraoperative Management

Induction Induction of anesthesia should be tailored to each patient's disease process. Hemodynamic stability and maintenance of normocarbia, normoxia, and normothermia are universally important in all neurosurgical cases. Management of patients with intracranial hypertension is aimed at avoiding further increases in ICP. Most IV induction drugs decrease $CMRO_2$ and CBF which decreases ICP [26]. The most commonly used hypnotic medication is propofol which is given as a 2–4 mg/kg bolus to induce anesthesia. Administration of adjunctive agents such fentanyl, sufentanil, and lidocaine (1.5 mg/kg) before laryngoscopy has also been shown to attenuate increases in ICP [27]. Controlled hyperventilation on induction is also effective at decreasing ICP. Ketamine should be avoided as it has been shown to increase cerebral metabolism, cerebral blood flow, and also ICP [28, 29].

Sevoflurane is the most commonly used volatile anesthetic agent used for inhalation inductions in children. Sevoflurane offers a favorable hemodynamic profile and is a very rapid acting agent. Volatile anesthetic agents generally increase ICP by causing cerebral vasodilation (see Table 20.1). However, that effect can be offset by mild hyperventilation for both sevoflurane and isoflurane [30–32]. However, sevoflurane used in conjunction with hyperventilation can cause epileptiform activity on EEG [33].

Neuromuscular drugs are often used to optimize intubation conditions. Succinylcholine (1–2 mg/kg intravenous or 3–4 mg/kg intramuscular) is often used in children with a full stomach to facilitate rapid intubation. Atropine (0.01–0.02 mg/kg) is often given in conjunction to prevent bradycardia in children. If succinylcholine is contraindicated, rocuronium (1.2 mg/kg intravenous) can be used to facilitate rapid sequence induction and intubation [34].

Intubation and Airway Management Adequate depth of anesthesia must be obtained prior to intubation as to minimize increases in ICP. Maintaining hemodynamic stability and avoiding excessive hypercarbia as well as hypocarbia and hypoxemia will ensure adequate cerebral perfusion while maintaining a normal ICP. Muscle relaxation is often desired to optimize intubation condition as well as to avoid coughing and bucking which can also increase ICP.

Both nasal and oral intubations are acceptable and should be determined based on the case. Nasotracheal intubation may offer more stability in prone cases or in instances where postoperative intubation is expected. However, nasotracheal intubations are contraindicated in patients with choanal atresia, suspected basilar skull fractures, transsphenoidal surgeries, and concurrent sinusitis.

If a nasotracheal intubation is planned, it is always advised to check for patency of each nare before instrumentation. A lubricated soft non-latex nasal trumpet can be used to both assess for patency and dilate the nares before an endotracheal tube is inserted. Application of a vasoconstrictor such as topical phenylephrine or oxymetazoline prior to instrumentation of the nares may help minimize bleeding, but be careful when giving either drug so as to avoid overdoses in small children.

Regardless of intubation technique or location, the endotracheal tube must be secured tightly to avoid airway loss during surgery. Application of benzoin or mastisol liquid adhesive to the skin before applying tape will help the tape stick to the patient's skin better. Suturing the endotracheal tube to the nasal septum is a secure option in cases where the face needs to be sterile or is in the surgical field.

20.6.3 Positioning and Vascular Access

Position is exceptionally important in the pediatric patient. Mayfield head pins are used in most pediatric patients with exceptions made for neo-

nates and very small children due to their thin calvarium which makes pinning an unstable option. Once the patient is positioned, all pressure points and joints should be padded, because even small amounts of pressure or tension on tubing over the course of a lengthy neurosurgical procedure can cause significant pressure ulceration or other skin damage. Care should also be taken to ensure the anesthesiologist has appropriate access to the patient once the surgical drapes are placed. The anesthesiologist must have a clear line of view of the face and endotracheal tube to ensure it isn't kinked, disconnected, or pushed too far in as to cause mainstem intubation. All extremities should be in the neutral position and free from compression by surgical equipment. All intravenous, arterial, and central venous lines should be untangled and placed in easily accessible locations.

Prone Position The prone position is most commonly used for surgical procedures involving the posterior fossa and the spinal cord. The torso is usually elevated and supported by rolled-up blanket or silicone rolls placed in parallel on either side of the torso. This ensures minimal impact on ventilation and oxygenation from thoracic compression and less vena cava compression which will cause less epidural venous congestion and help minimize blood loss. In older children a third support roll may need to be placed under the pelvis to support the lower extremities, but care must be taken to avoid compressing the femoral vessels and the genitalia.

The position of the head should be kept as neutral as possible unless the surgery requires the head to be turned. The head is often placed in Mayfield pins or on a horseshoe face support. In cases of lower spinal surgery, the face may be turned lateral and placed in a gel or foam headrest. In all of the above situations, it is important to check the position of the eyes, ears, nose, and lips to make sure there is no direct compression which can lead to tissue ischemia. Dependent edema can develop in the face after long prone procedures. This can cause periorbital and perioral edema which may look concerning but will quickly improve over time. Airway edema can also develop and may be severe enough to prevent post-op extubation. It is always recommended to check for tongue and oral edema as well as a cuff leak in long prone cases before extubation to ensure the airway is patent. Loss of vision has been reported in prone surgical cases as well [35]. Maintaining hemodynamic stability, replacing blood loss, avoiding excessive crystalloid administration, limiting the length of the case, and prevention of external compression on facial structures should be performed in every prone case [36].

Sitting Position The sitting position is used much less frequently now, but may still be used for certain posterior fossa tumors or in morbidly obese children who cannot be placed in the prone position due to concerns with ventilation and oxygenation. In the sitting position precautions against hypotension and air embolism should be taken; a precordial Doppler may be helpful. During positioning care should be taken to avoid excessive flexion of the neck which can cause blockage of lymphatic and venous drainage of the head and neck as well as impair perfusion to the brain and spinal cord causing ischemia. The endotracheal tube might be kinked or pushed into the mainstem bronchi during changes in positioning. All extremities should be padded and supported to avoid pressure ulcers.

Vascular Access Adequate peripheral intravenous access should be obtained, and the potential for large volume blood loss should always be considered in any neurosurgical procedure. An arterial line should be placed for any open intracranial surgery or surgery involving the spinal cord to help guide ventilation and resuscitation as well as keep strict hemodynamic control throughout the perioperative and operative time period. Central venous access is not uniformly necessary, but can be used as additional vascular access for cases where peripheral IV access has been difficult to obtain. In select surgeries where venous air embolus risk is high, a central line can be useful for the purpose of aspirating air emboli.

20.6.4 Maintenance of Anesthesia

General anesthesia with controlled ventilation is performed for most neurosurgical procedures. This allows for a motionless procedural field as well as the ability to manipulate ventilation to control ICP. General anesthesia can be maintained by either inhalational anesthetics, intravenous anesthetics, or a combination of both. All anesthetic agents can alter ICP, CBF, and $CMRo_2$ (Table 20.1). Agents that maintain CPP while decreasing ICP and $CMRo_2$ are preferable. Commonly used inhalational anesthetic agents are cerebral vasodilators and increase CBF and ICP, but decreases $CMRo_2$. These effects can be offset by using low concentrations of inhalational agents while controlling ventilation to maintain normocarbia [30, 31, 37]. Isoflurane is the commonly used maintenance inhalational anesthetic agent because at two times the minimum alveolar concentration (MAC), isoflurane can induce isoelectric EEG while maintaining relative hemodynamic stability.

Apoptotic Neurodegeneration Recently there has been concern regarding studies that have demonstrated anesthetic agents accelerate apoptosis in CNS tissue of rodents and rhesus monkeys [38–40]. The lay press has extrapolated this data to anesthetizing young children [41]. The American Association of Pediatrics has also issued guidelines in response to the press coverage of this topic. The study findings are certainly concerning, but much more research study is needed to determine whether the findings in other mammals are applicable to humans. The animal and in vitro studies raise several areas of concern regarding the experimental model, drug dosage and concentration, as well as the duration of exposure (all given in doses that are much higher than any amount a human child would be exposed to). The further question of whether changes seen on the microlevel can necessarily translate onto the macroscale, i.e., cause clinically significant changes in IQ or other measurable performance outcomes, is still debatable. The PANDA study, using healthy twins after single exposure to anesthetic agents before age 36 months, showed no decrease in IQ later in life [42]. While it is absolutely necessary to limit the amount of exposure to anesthetic agents, further study needs to be done before any conclusions can be drawn about the effects of anesthetic agents on the developing brain.

20.6.5 Management of Fluids and Blood Loss

Blood loss can be difficult to assess during neurosurgical procedures for children because surgical drapes can obscure a significant amount of blood loss. Incision can cause significant amount of blood loss as the scalp and calvarium are both highly vascularized. Once inside the skull, large volume blood loss can occur if one of the major vessels in the brain is disrupted. A type and screen should be obtained before surgery for all craniotomies and large spinal surgeries. If large volume blood loss occurs, the anesthesia team should transfuse and resuscitate the patient according to the massive transfusion protocol at their hospital and maintain a 1:1:1 transfusion ratio of packed red blood cells, fresh frozen plasma, and platelets.

The blood-brain barrier is often compromised by the underlying pathological process, and cerebral edema may already be present. Excessive crystalloid administration may worsen the cerebral edema, so judicious amount of normal saline should be used to maintain adequate cerebral perfusion and intravascular volume. Lactated Ringer's solution is not commonly used because its osmolality is 273 mOsm/L (normal serum osm 285–290 mOsm/L). Normal saline is slightly hypertonic (306 mOsm/L) and is the crystalloid of choice to maintain serum osmolality. Administration of large amounts of normal saline has been associated with hyperchloremic nonanion gap metabolic acidosis [43]. The significance of this effect is not clear, but using lactated Ringer's solution to supplement large volume fluid resuscitation can help avoid hypernatremia and acidosis as well as hypoosmolality. In cases where cerebral edema is of particular concern, using osmotic and loop diuretics to induce dehy-

dration can decrease the edema acutely, but may cause hypotension and rebound edema in the longer term.

Children can maintain adequate blood glucose concentrations even after fasting and during relatively long surgical procedures. In fact during ischemia, hyperglycemia (blood glucose value above 250 mg/dL) has been associated with larger cerebral infarct size [44]. However, specific patient populations may require maintenance IV fluids with glucose. Preterm and term neonates, diabetic children, children on hyperalimentation, and severely malnourished children will all likely require glucose supplementation during long procedures. In these cases, glucose-containing fluids should be given at or slightly below maintenance levels, and a blood glucose level should be checked at least every hour to ensure blood glucose levels between 100 and 150 mg/dL.

Temperature Control Temperature control is a key component in the operative management of all children. Infants in particular have a larger body surface area to mass ratio, with the head accounting for an even larger proportion of the surface area compared to adults, which makes them particularly prone to rapid heat loss. Patients should be maintained with normothermia by warming the operating room and using warming lights and blankets. Care should also be taken to avoid hyperthermia as this can increase $CMRo_2$.

20.6.6 Venous Air Embolus

Venous air embolism (VAE) is a seriously and potentially life-threatening complication during intracranial procedures. Intracranial procedures have higher risks of VAE because intracranial venous sinuses have dural attachments that prevent them from collapsing. In procedures where the head is above the heart, which increases the pressure gradient between operative site and the heart, there is a higher risk of VAE. Hypovolemia either from excessive fluid restriction or from operative blood loss also increases the risks of VAE.

Venous air embolism (VAE) is a seriously and potentially life-threatening complication during intracranial procedures. When air enters the venous circulation, it eventually travels to the right atrium, through the tricuspid valve and then to the right ventricle. Air that is ejected through the right ventricluar outflow track into the pulmonary circulation can potentially create an air lock that that can 1) increase afterload for the right ventricle, 2) create a V/Q mismatch in the lungs, and 3) prevent blood flow to the left side creating a preload problem on the left side. Depending on the size of the bubble, this can significantly decrease cardiac output and even lead to complete cardiovascular collapse. Intracranial procedures have higher risks of VAE because intracranial venous sinuses have dural attachments that prevent them from collapsing. In procedures where the head is above the heart, which increases the pressure gradient between operative site and the heart, there is a higher risk of VAE [45]. Hypovolemia either from excessive fluid restriction or from operative blood loss also increases the risks of VAE. Procedures done in the sitting position pose the higher risk of VAE, but other positions are not free of risk.

Many techniques may be used to detect VAEs. The most sensitive method to the least sensitive methods is transvenous intracardiac echocardiography followed by transesophageal echocardiography, precordial Doppler probe, measurement of pulmonary artery pressure, end-tidal OC_2 tension, arterial O_2 tension, mean arterial pressure, and finally arterial CO_2 tension [46, 47]. The most frequently used method in pediatric patients is the precordial Doppler probe which is not invasive, inexpensive, easy to use, and relatively sensitive. Monitoring end-tidal oxygen and CO_2 tensions are also very useful tools for detecting VAE under anesthesia (Table 20.2). When a VAE occurs, the air blocks blood flow through the pulmonary circulation thus causing a ventilation/perfusion mismatch, which increases dead space ventilation and causes a sudden decrease in end-tidal CO_2 partial pressure. An increase in the end-tidal partial pressure of nitrogen is also indicative of a VAE. When used together these relatively noninvasive methods are very effective at detecting VAE.

Table 20.2 Relative sensitivities of different monitoring devices for detecting venous air embolus

Sensitivity of monitoring device	Method of detecting venous air embolus
Most sensitive	Echocardiogram and precordial Doppler
	End-tidal nitrogen
	End-tidal carbon dioxide
	Right atrial pressure
	Systemic blood Pressure
	Esophageal stethoscope
Least sensitive	ECG

Immediate preventive care and treatment must be administered once a VAE is suspected or diagnose. The surgeons should flood the surgical field with saline and apply bone wax to the exposed bone edges to prevent further entrainment of air. The anesthesiologist should discontinue nitrous oxide (which is rarely used in neurosurgical procedures) and then place the child in Trendelenburg position which increases the cerebral venous pressure, prevents further entrainment of air, and increases systemic blood pressure by increasing the peripheral venous return. Occlusion of the internal jugular veins is generally not recommended unless the case is sever as compression of the jugular veins can also result in compression and occlusion of the carotid artery which can restrict blood flow to the brain and lead to cerebral ischemia. IV fluid resuscitation should be administered to increase the circulating volume which helps prevent further entrainment of air. The patient should be supported with vasopressor therapy and chest compression, if necessary, to maintain cardiac output. If a central venous line is available or can be readily placed, aspiration of the entrained air may be attempted, though it is rarely successful unless massive amounts of air were entrained.

20.6.7 Emergence

Emergence and extubation after a neurosurgical procedure is an especially important time as this period can produce significant hemodynamic changes. The goal is to facilitate a smooth and controlled emergence and extubation period while also keeping the patient awake to obtain a good postoperative neurologic exam. Excessive bucking, coughing, vomiting, and agitation are frequent occurrences post neurosurgical procedures because blood in the CSF, location of the surgery, and opioid use can all be emetogenic. The patient's age and pre-op anxiety may predispose the patient to post-op emergence agitation.

Administration of opioids such a fentanyl and sufentanil as well as lidocaine (1–1.5 mg/kg) before extubation can attenuate coughing and straining on the endotracheal tube. Labetalol, given in incremental doses of 0.1–0.4 mg/kg, has been used to control hypertension during the emergence period. Occasionally esmolol is used to control hypertension with the benefit of being fast acting and short acting. When any beta-adrenergic blocking agent is used in children, care must be taken, because the cardiac output of children is heart rate dependent and giving b-blocking agents may cause severe hypotension.

Dexmedetomidine is a useful drug to facilitate smooth emergence while still allowing for a good neurologic exam after extubation. Craniotomies are not extremely procedures, but pain should be treated by giving judicious amounts of opioids after surgery which will help facilitate a smooth emergence and also prevent increases in ICP and blood pressure. Acetaminophen is a useful adjunct to treat pain, but ketorolac is generally avoided due to its effects on platelet function. All neuromuscular blockade should be reversed, and the patient should meet standard extubation criteria prior to extubation. If extubation is not possible, the patient should be sedated with an endotracheal tube secured and transported to the ICU for further management.

Post extubation neurosurgical patients have some specific complications that warrant special attention. Patients should be wide wake in order to obtain a neurologic exam, and if there are abnormal findings or altered mental status after extubation, a CT scan may be obtained to rule out acute intracranial bleeding or other pathological processes as the cause. Surgeries done near the hypothalamus and pituitary gland may cause diabetes insipidus or syndrome of inappropriate

antidiuretic hormone, so electrolytes, fluid status, and temperature regulation should be monitored closely. Patients are usually transported to the intensive care unit post neurosurgery for close monitoring and frequent neurological tests.

20.7 Special Situations

20.7.1 Hydrocephalus

CSF production and absorption are in equilibrium; however in disease processes that disrupt this balance, hydrocephalus can occur. The imbalance can result from either excessive production (choroid plexus papillomas), decreased absorption, or obstruction of flow of CSF. Causes may include neonatal intraventricular hemorrhage or subarachnoid hemorrhage, infection, aqueductal stenosis, or tumors. Hydrocephalus is classified either as nonobstructive/communicating or obstructive/noncommunicating based on the ability of CSF to flow normally through the ventricles and around the spinal cord.

The acuity with which hydrocephalus develops can determine the severity of symptoms. If hydrocephalus develops in a young neonate, in whom the fontanelles are still open, the skull will expand and result in craniomegaly along with permanent neurologic damage. If the cranial bones are fused or if the cranium is unable to expand fast enough to keep up with rate of expansion caused by the hydrocephalus, signs and symptoms of intracranial hypertension can develop rapidly. The usual signs of elevated ICP in children include lethargy, nausea and vomiting, cranial nerve deficits, and bradycardia, and in severe cases if left untreated, brain herniation and death can ensue.

The anesthetic plan for a child with hydrocephalus should be centered around controlling ICP until the hydrocephalus can be surgically relieved. Rapid sequence induction and intubation should be used in any child with nausea or vomiting secondary to elevated ICP. Drugs that elevate ICP should generally be avoided. If the patient is unable to tolerate awake IV placement of if IV placement is difficult, a careful inhalation induction with the head of the bed elevated and application of cricoid pressure are acceptable. An IV catheter should be placed as soon as possible, and time to tracheal intubation should be minimized to decrease the risk of aspiration [48]. A patient should always be extubated awake to avoid the risk of aspiration.

Treatment of hydrocephalus usually includes surgical placement of an extracranial shunt unless the hydrocephalus rapidly resolves after treating the underlying disease. The most common type of shunt diverts CSF from the lateral ventricles to the peritoneal cavity (ventriculoperitoneal shunt). If the peritoneal cavity is unable to absorb the CSF, the shunt can also be placed into the right atrium or the pleural cavity. If a ventriculoatrial shunt is placed, precautions against venous air emboli should be taken. Shunts have programmable valves that can moderate the rate of CSF drainage and can be manipulated using a remote control device which eliminates the need for repeat surgeries.

Ventricular shunts are often used for long periods of time and can become infected. This requires the entire shunt system to be removed and an external ventricular drain to be placed temporarily while the infection is treated with antibiotics. Once the infection clears, the external drain is removed, and a new ventricular shunt is surgically placed. The temporary ventricular drain is not as well anchored, and care must be taken to avoid accidental dislodgement. The drainage of CSF in this drainage system is completely dependent on gravity; therefore the height of the drainage bag should always be kept level compared to the tragus of the ear to avoid sudden, and dramatic, changes in CSF drainage.

Endoscopic ventriculostomy is an alternative to extracranial shunt placement. A flexible neuroendoscope is passed through a burr hole in the skull, and a communication is made, most commonly in the septum pellucidum or the floor of the third ventricle, by a blunt probe inserted through the endoscope [49, 50]. This allows CSF to bypass the obstruction and restores normal CSF flow. Complications of this surgery include large volume blood loss from injury to the basilar artery, and adequate resuscitation materials

should be readily available at all times. Neurologic injury may occur if cranial nerves or vital brain tissue is damaged during surgery, and the anesthesiologist should always assess for adequate resuscitation as well as feasibly of extubation. If the surgery is lengthy, large volumes of cold irrigating solution may cause hemodynamic instability; thus the anesthesiologist must always keep track of the amount of irrigation fluid used.

Patients with treated hydrocephalus are at risk for a condition known as slit ventricle syndrome. This syndrome develops in 5–10% of children with CSF shunts and is due to over drainage of CSF causing small, slit-like lateral ventricles. CT scans can reliably and quickly identify this condition. Children with this syndrome have very little CSF and cannot compensate for alterations in brain or intracranial blood volume. In order to avoid life-threatening brain swelling, judicious administration of intravenous fluids and avoidance of hypotonic intravenous fluids should be considered. Postoperative brain herniation has been reported despite uneventful surgical procedures [51].

20.7.2 Congenital Anomalies

Congenital anomalies of the CNS occur most frequently as midline defects along the neural axis involving the head or spine. Defects range from minor bony or soft tissue structure to major malformations of neural tissue with debilitating effect.

Encephalocele Encephaloceles can occur anywhere along the cranium from the frontal area to the occiput. The size of encephaloceles varies from small nasal polyps extending out of the cribriform plate to large CSF-filled sacs that are as large as the head itself. Large defects pose significant challenges to positioning and tracheal intubation. Large occipital encephaloceles can cause enough flexion of the head that head extension, to facilitate tracheal intubation, is impossible. In these cases, elevating the child's torso and limbs up on blankets and rolls so the body is level with the head can help create enough neck extension to facilitate tracheal intubation. Large volume blood loss may occur from prolonged surgical time, and acute blood loss should be expected if venous sinuses are involved in the encephalocele. Adequate IV access, arterial line, and blood products should be readily available in all cases where there is anticipated blood loss.

Myelodysplasia Defects of the spinal cord are a series of diseases known grouped under the term spina bifida. Hydrocephalus is often present and is associated with Chiari II malformations. Meningomyeloceles are lesions with CSF and spinal tissue. Meningoceles are lesions with only CSF. Open neural tissue is known as rachischisis.

Most neonates with a meningomyelocele will present for surgical repair within the first 24 h of birth to minimize the risk of infection. Most defects are prenatally diagnosed, as the defects are easily identified on prenatal ultrasound. Some centers are repairing the defect while the fetus is intrauterine as a way to minimize the neurologic impairment [52–54]. While evidence is encouraging, it has not yet become widespread practice.

Positioning for induction of anesthesia can be done in the supine position with a donut ring or rolled blankets to support the baby's back and take pressure off the meningomyelocele. If the defect is too large to position the patient supine, intubation can be done with the patient in the right lateral decubitus position. Succinylcholine can be used since muscle denervation and hyperkalemia are not a concern [55]. Neonates with concurrent severe hydrocephalus can have significant of facial and cranial structures that may make mask ventilation and intubation difficult. In such cases difficult airway equipment should be available, or, alternatively, awake intubation should be considered. Blood loss can be minimal for small defects, but can be extensive for larger defects. During the initial repair, some neurosurgeons will insert a ventriculoperitoneal shunt,

while others will wait for signs of hydrocephalus before inserting a shunt.

Children with myelodysplasia are at high risk for latex sensitivity and anaphylaxis and should be treated with latex-free equipment starting at birth [25]. This sensitivity is thought to be related to repeat exposure to latex from surgical procedures and products used for bladder catheterization [56]. There should be a low threshold to treat for latex allergy during surgery.

Chiari Malformations Several types of Chiari malformations exist. Type I Chiari malformations involve caudad displacement of the cerebellar tonsils below the foramen magnum and can occur in healthy children without myelodysplasia. Symptoms are usually mild and may include headaches or neck pain. Treatment is usually surgical decompression with a suboccipital craniectomy and cervical laminectomies.

Type II Chiari malformation, also known as Arnold-Chiari malformation, is usually also present in children with myelodysplasia. The defect consists of a bony abnormality in the posterior fossa and upper cervical spine along with resultant caudal displacement of the cerebellar vermis, the fourth ventricle, and lower brainstem below the level of the foramen magnum. Cervical cord compression can occur. Due to the structures present in the area affected, common signs and symptoms include vocal cord paralysis with possible stridor, aspiration, apnea (swallowing may be affected) and other cranial nerve deficits. Children may have altered response to hypoxia and hypercarbia, and the anesthetic plan should take this into account [57, 58]. Care must be taken to keep the neck neutral as extreme head flexion may cause brainstem compression.

Other Spinal Defects Tethered cord syndrome includes several spinal anomalies where the spinal cord is tethered at the base of the spinal canal typically over the lumbar region. These anomalies include lipomeningocele, lipomyelomeningoceles, diastematomyelias, dermoid tracts, and dermoids. Skin defects or dimples, midline hair tufts, and fat pads are frequently found external signs of tethered cord. Clinical signs and symptoms include difficulty walking, toilet training, or back pain. Diagnosis is made by MRI, and early surgical intervention is performed to prevent neurologic damage.

Anesthetic management for surgical release of tethered cord involves a standard general anesthetic with an endotracheal tube. The child is placed in the prone position. Muscle relaxation should be avoided or worn off by the time surgery begins. Surgeons often use nerve stimulators and rectal electromyelograms or manometry to test for nerve function during the surgery.

20.7.3 Tumors

Brain tumors are the most common solid tumors in children and the second most common pediatric malignancy [59]. The most common brain tumors in children are infratentorial, posterior fossa tumors (e.g., medulloblastoma, cerebellar astrocytoma, brainstem glioma, and ependymomas). Due to the location of the tumors in the posterior fossa, obstruction of CSF flow is common, and children often present with signs and symptoms of increased ICP. If ICP is elevated, care should be taken to avoid further increases in ICP, and in severe cases a ventricular drain should be placed emergently prior to surgery. Arrhythmias and hemodynamic variability are common during surgical resection of tumors in close proximity to the brainstem. Attention must be paid to ventilation and oxygenation in the preoperative and postoperative time period as the patient may have altered responses to hypoxia and hypercarbia. VAEs may occur during surgery even if the patient is not in the beach chair position since patients are often placed slightly head up to facilitate venous drainage from the head.

Supratentorial tumors common in children include craniopharyngiomas, optic gliomas, pituitary adenomas, and hypothalamic tumors. Hypothalamic tumors often present as precocious puberty. Craniopharyngiomas are the most

common para-sellar tumors in children and may be associated with hypothalamic and pituitary dysfunction. Symptoms often include visual impairment (from compression of the optic nerve), growth failure, and endocrinopathies. Thyroid function should be checked and replacement initiated if needed. Corticosteroids should be given if there is potential involvement of the hypothalamic-pituitary-adrenal axis. Diabetes insipidus (DI) is common pre-, intra-, and postoperatively.

Diabetes insipidus often presents preoperatively and extends postoperatively. If DI is not present preoperatively, it is unlikely to develop intra-op because there is a reserve of antidiuretic hormone in the posterior pituitary gland which will last for many hours. Postoperative DI can occur without preoperative symptoms and involves sudden increase in dilute urine output, with lab findings including hypernatremia and hyperosmolality. Vasopressin infusions can be initiated and titrated to specific targets of urine output, serum sodium, and osmolality values until the return of normal antidiuretic hormone (ADH) activity. Frequent monitoring of electrolytes, specifically serum sodium, osmolality, and urine output should continue until stabilization of ADH activity postoperatively. Return of ADH will cause a significant decrease in urine output, and cerebral edema and seizures can ensue if fluid administration is not adjusted to reflect these changes.

Transsphenoidal surgery for pituitary adenoma resection may be performed in older children, and the same care should be taken as for any other intracranial tumor resection. Nasal intubation should be avoided as this passage is needed for surgical access. Should massive bleeding occur, the surgery should be rapidly converted to an open craniotomy. Due to potential post-op bleeding from the nasal passage, all patients should be extubated awake.

Optic gliomas present with visual changes and proptosis, though signs and symptoms of elevated ICP or hypothalamic dysfunction can occur later in the disease process. Children with neurofibromatosis have an increase frequency of developing optic gliomas which can be highly vascularized. In instances where such lesions are involved, anesthetic preparation should include resuscitation for blood loss.

Tumors involving the cerebral hemispheres include astrocytomas, oligodendrogliomas, ependymomas, and glioblastomas. Seizures and focal deficits are more likely to occur in these tumors. If motor weakness is present, succinylcholine should be avoided due to the risk of hyperkalemia. Nondepolarizing NMBDs are safe to use but may be rapidly metabolized due to upregulation of hepatic enzymes from chronic antiepileptic drug therapy.

Anesthetic management of craniotomy for tumor resection includes a secure airway with an endotracheal tube, large-bore peripheral IV catheters for resuscitation in the event of blood loss, and arterial line for hemodynamic monitoring. If motor or somatosensory evoked potentials are used during the surgery, care should be taken to use anesthetic agents with minimal effect to monitoring, and paralysis should be avoided. In the event an intraoperative MRI or CT scan is required, the patient should be kept under general anesthesia and transported to the scanner and back to the operating room fully anesthetized. A complete IV anesthetic is usually the best way to facilitate the transfer while maintaining and adequate depth of anesthesia. Emergence and extubation should be kept hemodynamically stable with the goal of having the child awake enough to perform a neurologic exam after extubation.

20.7.4 Trauma

Head Injury Trauma is the primary cause of death in children, and head injury carries the highest mortality for children with traumatic injury [60–62]. Unlike adults children are more likely to develop cerebral edema rather than intracranial hematomas [63]. The mechanism of brain injury occurs in two stages. The first stage is the primary physical insult that causes tissue destruction. The second stage is caused by the pathologic sequelae of the injury which include hypotension, hypoxia, cerebral edema,

and intracranial hypertension. The anesthesiologist plays a pivotal role in managing the second stage of brain injury.

Scalp Injuries Scalp lacerations are very common head injuries in children and often are mild, but large wound may cause significant blood loss due to the larger fraction of cardiac output that perfuses the head in children. Preoperative evaluation of any scalp injury should assess for signs of hemodynamic instability from blood loss. A quick CT scan should be used to diagnose other injuries that may be unrecognized following head trauma.

Skull Fractures Skull fractures are common in children, and most do not require surgical treatment. Linear fractures are of concern only if there is potential damage to the underlying brain or vascular structures which may cause blood loss or cerebral contusions. Most children with skull fractures heal without intervention. On occasion a leptomeningeal cyst or growing fracture may result which requires surgical intervention. Child abuse should be included in the differential for any trauma injury to a child with multiple skull fractures or fractures in various states of healing.

Depressed skull fracture often requires surgical repair. Usually more force is required to produce a depressed skull fracture, and there is a higher likelihood of damage to underlying brain tissue and vasculature. One third of all depressed skull fractures are uncomplicated, one third are associated with dural lacerations, and one third are associated with cortical lacerations. Morbidity and mortality depend on the amount of cortical brain injury.

Basilar skull fractures are uncommon in children and usually do not require surgical intervention. Signs of symptoms of basilar skull fractures include periorbital ecchymoses, retroauricular ecchymoses, otorrhea, hemotympanum, altered mental status, and seizures. If the patient requires surgery, instrumentation of the nose should be avoided unless absolutely necessary (e.g., nasogastric tubes and nasotracheal tubes). There is a risk of these tubes passing through the skull fractures and entering the cranium [64–66].

20.8 Neurovascular Lesions

Arteriovenous Malformations Arterial venous malformations are made up of large arterial feeder vessels, dilated communicating vessels, and large venous draining vessels with arterial blood that have not gone through a capillary system. Large posterior cerebral or vein of Galen malformations usually present early and may cause congestive heart failure via high cardiac output in neonates. If heart failure is present with or without pulmonary hypertension, the prognosis is very poor. Smaller saccular dilations of vein of Galen malformations may present later in childhood and cause hydrocephalus from obstruction of the aqueduct of Sylvius. Malformations that are smaller and nonobstructing are usually undiagnosed until they rupture [67]. Intracranial hemorrhage is the most common presentation in these silent malformations, and the mortality rate is 25%.

Treatment can involve embolization of the malformation, surgical excision, or a combination of the two procedures. Neonates in heart failure often present for embolization already intubated, sedated, and on vasopressor support. Anesthesia for these neonates should be aimed at maintaining hemodynamic stability, paralysis, and careful monitoring of fluid status. Large amounts of contract agent are often used to identify the vessels prior to embolization; sometimes embolization needs to be done in stages due to the amount of contract agent used. Different types of embolic agents are used, and each has different potential complications. Generally, no matter the material used, there is a risk of bleeding and rupture of the malformation during embolization. Bleeding is brisk, and the anesthesia team should always be ready to handle sudden large blood loss and intracranial hypertension from the bleeding. The anesthesiologist must stabilize and resuscitate the patient until an emergent craniotomy can be performed to stop the bleeding.

Aneurysms Most aneurysms in children form as a malformation in the arterial wall. Children with polycystic kidney disease and coarctation of the aorta have an increased incidence of intracranial aneurysms. Most aneurysms are asymptomatic and present as an acute rupture with a high mortality rate. Treatment of intracranial aneurysms usually involves surgical ligation or clipping [68].

Anesthetic management for intracranial aneurysm resection can be difficult. Adequate IV access and blood products should be readily available in the operating room. Fluid and blood warmers should be set up in the operating room. Arterial line should be placed for hemodynamic monitoring. The patient should be fully anesthetized under general anesthesia with a secured airway. ICP should be aggressively managed to prevent intracranial hypertension. Occasionally, the surgeon may request some degree of controlled hypotension for short periods of time to decrease the risk of bleeding [69]. This should be done carefully as hypotension in a child with elevated ICP will impair cerebral perfusion pressure and may cause or worsen ischemic injury. In the event of bleeding, the surgeon may ask for adenosine administration to stop the heart, decrease bleeding, and facilitate a surgical field conducive to stopping the bleeding. This should be done with caution and only in older teenagers.

Emergence and extubation is a critical period. Hemodynamic stability, without hyper- or hypotension, is required. Coughing, straining, and untreated pain can all cause hypertension which can increase the risk of bleeding. Hypotension should also be avoided as it can worsen ischemia and slightly higher blood pressure can minimize the risk of vasospasm. Post-aneurysm clipping, a phenomenon known as normal perfusion pressure breakthrough, may cause cerebral edema with increased ICP. This is thought to be due to hyperemia in the areas around the arteriovenous malformation site which cannot vasoconstrict appropriately. Treatment is controversial but involves a combination of treating the elevated ICP, maintaining adequate CPP, moderate hypotension, and moderate hypothermia. Postoperatively patients should be taken to the ICU for neurologic monitoring as well as strict hemodynamic monitoring.

Moyamoya Disease Moyamoya disease is an arteriopathy that results in progressive occlusion of intracranial vessels, particularly those in the distribution of the internal carotid artery [70]. As a result of this occlusion, a network of small collateral vessels develops at the base of the brain. On angiography these vessels have a distinct appearance, and it was described by the Japanese name Moyamoya, which means "puff of smoke." Congenital forms of this arteriopathy can involve other systemic vasculature, including the renal, coronary, pulmonary vessels. Moyamoya syndrome is the acquired form of the disease and is associated with neurofibromatosis, Down syndrome, connective tissue disease, radiation, chronic inflammation, meningitis, and sickle cell disease [71]. Children of Japanese ancestry have a higher incidence of Moyamoya disease. Ten percent of adult patients have associated intracranial aneurysms, but it rarely occurs in children.

The initial signs and symptoms of Moyamoya disease are often transient ischemic attacks with progression to strokes and permanent neurologic deficits. Morbidity and mortality are high in patients with untreated disease. Medical management consists of antiplatelet therapy and/or calcium channel blockers. Surgical treatment includes a variety of direct and indirect arterial anastomosis. The most common surgical procedure is the pial syangiosis, which is done by dissecting and then suturing a scalp artery directly onto the pial surface of the brain to encourage angiogenesis and improve perfusion [72].

Anesthetic management for surgery includes maximizing cerebral perfusion. Maintaining normocarbia to mild hypercarbia is important in maintaining cerebral blood flow [73, 74]. Maintenance of adequate intravascular volume and maintenance of normal blood pressure are also important. Patients are often admitted the night before for administration of 1.5 times the

amount of maintenance IV fluids for the duration of preoperative fasting time. Arterial access should be obtained for strict hemodynamic monitoring. Intra-op EEG monitoring can help identify early ischemia, and immediate treatment should be initiated. Children should be maintained with normothermia throughout the surgery to prevent the stress response from shivering as well as increase oxygen consumption from hyperthermia. Emergence and extubation should be smooth without coughing or bucking which can cause intracranial hypertension. The risk of stroke remains high in the immediate postoperative time and does not begin to decrease significantly until 6 months after surgery.

20.9 Seizure Disorders

Seizure disorders are some of the most common neurologic disorders in children. The disease can range from mild febrile seizures to intractable epilepsy. The past few decades have seen dramatic advances in the treatment of seizure disorders, but the prevalence of the disease remains high. Current neuroimaging techniques combined with EEG monitoring can locate seizure foci that are amenable to surgery.

Children presenting for surgical management of seizure often take multiple antiepileptic drugs (AEDs). These medications can have serious side effects which include hepatic dysfunction or upregulation, impaired hematopoietic function, coagulation abnormalities, as well as potential toxic overdose. The upregulation of hepatic enzymes can result in rapid metabolism of nondepolarizing neuromuscular blocking drugs and opioids.

Planning for seizure foci resection involves identification of abnormal brain tissue and preservation of healthy brain tissue. External EEG leads can facilitate the location of seizure foci prior to surgery. In cases where epileptogenic foci are difficult to identify, a craniotomy under general anesthesia can be performed to place intracranial EEG monitors (aka grids and strips) directly on the surface of the cerebral cortex. The EEG monitors are left on the cortex, and the craniotomy is closed. The children are monitored in the hospital for several days until the foci of the seizures are identified, and then patients return to surgery for removal of the "grids and strips" and resection of the seizure foci.

Children with grids and strips in place should be monitored carefully. Pneumocephalus is a potential concern as air may remain in the skull for weeks after a craniotomy [75]. If patients receive nitrous oxide for other surgeries, there is a risk of tension pneumocephalus. On rare occasions the placement of the grids and strips can cause worsening of the seizures and even precipitate status epilepticus. In such instances, the seizures must be managed medically, and the patient should go to surgery emergently for grids and strips removal.

Recent advancements have seen the rise of thermal ablation of seizure foci. This is a less invasive method of seizure foci ablation compared to an open craniotomy. A stereotactic frame is placed on the child's head under CT guidance. Electrodes are inserted via burr holes into specific areas of the brain, and seizure activity is measured over the course of several days. Once epileptogenic foci are identified, the electrodes are removed, and laser electrodes are placed into each seizure focus under MRI guidance. Once placement is confirmed, the laser electrodes thermally ablate the seizure foci.

Anesthesia for both stages of the thermal ablation procedure involves general anesthesia. Adequate IV access should be obtained, and an arterial line should be placed for hemodynamic monitoring. Maintenance of anesthesia can be done via inhalational agents or IV agents. These procedures often involve transport between different locations (e.g., CT to operating room, operating room to MRI), and emergency airway equipment, emergency drugs, and anesthesia machine should all be available in all anesthetizing locations. Emergence extubation should be smooth with the goal of obtaining a reliable neurologist exam.

Key Points

- Increases in intracranial pressure may not be appreciated until very late in the disease process due to open fontanelles in neonates and lack of appreciation for earlier subtle signs in younger pediatric patients.
- Brain tumors are the most common solid tumor malignancy in children, and infratentorial posterior fossa tumors are more common in children than supratentorial tumors. Due to the location in the posterior fossa, patients present more often with cranial nerve deficits, elevated intracranial pressure, as well as respiratory depression and arrhythmias and may rapidly progress to death if not treated.
- Induction of anesthesia for pediatric neurosurgical patients may require a multimodal approach. Care should be taken to assess for the severity of the disease process and the induction plan tailored to both the developmental and physiologic condition. Care should be taken to maintain normal intracranial pressure and normal cerebral perfusion, avoid excessive agitation, and facilitate a hemodynamically stable patient.
- Pediatric patients require special positioning. Care needs to be taken to ensure all pressure points are padded, all lines and tubes are securely fastened, and precautions to prevent venous air emboli are taken.

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Geriatric Neuroanesthesia

21

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21.1 Introduction

The exact age for defining geriatric patient is still unknown, as aging is not a sudden phenomenon but is a continual process that is influenced by various factors such as coexisting diseases that can hasten process of aging. In recent era, the development of advanced technology, new equipment, and neuroanesthesia/neurointensive care has expanded and revolutionized the daily neurosurgical practice [1]. These techniques have enlarged the spectrum of conditions that are amenable to neurosurgical management. The proportion of geriatric population is following an increasing trend. Despite this, the literature regarding various interventions and their outcome in geriatric patients is limited [2–5].

The optimal management of geriatric patients is a challenge due to their depleted systemic reserves, polypharmacy, and geriatric syndromes. As compared to the younger patients, geriatric patients are at higher risk of adverse perioperative outcomes. Strong evidence is required to conclude whether neurosurgical intervention actually benefits these elderly patients or just increase the risk of perioperative morbidity and mortality. Previous study by Whitehouse et al. has reported that elderly patients should not be denied of neurosurgery just because of their age alone, as they have found improvement in general condition after neurosurgery [6]. A multidisciplinary team approach involving emergency medicine experts, geriatricians, surgeons, anesthetists, and intensivists should work together to improve outcome in these patients. For optimal management during perioperative period of these patients, we must be aware of the physiological changes associated with aging.

21.2 Physiological Changes of Aging

Under normal circumstances, aging takes place in all the organ systems spontaneously and gradually, beginning at conception [7]. The rate and course of aging vary widely from individual to individual and are influenced by their genetic makeup and environmental, socioeconomic, and psychological factors. There is a reduction in systemic reserve that reduces the normal physiological response during acute stressors, including anesthesia, surgery, and critical illness. Functional decline of various organ systems including cardiovascular (CVS), pulmonary, renal, central nervous (CNS), hematological/immunological, and musculoskeletal systems may influence perioperative outcomes. Table 21.1 summarizes various physiological changes with aging and their clinical relevance.

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Table 21.1 Physiological changes and their clinical significance

Organ system	Physiological change	Clinical significance
Cellular	Reduced lean body weight Intracellular fluid is reduced	Risk of dehydration
Neurological	Diminish cerebral volume Reduced cerebral perfusion Reduced neuronal conduction Reduction in all senses including vision, hearing, tactile, balancing Aging of hypothalamus makes these patients susceptible to hypothermia	Increased risk of confusion and delirium Increased sensitivity to hypoxia and hypotension Complicates the neurological examination Increased sensitivity to sedative and hypnotic agents Risk of delayed awakening Hearing aids and glasses should be kept on while examining the patient in awake craniotomy
Cardiovascular	Myocytes start to degenerate and replaced by connective tissues or fats Stiff ventricles Blood vessel wall also gets stiffened Autonomic system involvement leading to low fixed heart rate	Increased risk of conduction defects, arrhythmias, and heart block Lesser cardiac output High risk for pulmonary edema Increased risk of hypertension Compensatory response to blood/fluid loss is obtund High risk for hypotension in extremes of positions (sitting/prone)
Pulmonary	Reduction in lung and chest wall compliance Decreased number of functioning alveoli Weakness of respiratory muscles Poor mucociliary function	Early decompensation during hypoxia due to poor reserve Ventilation perfusion mismatch progressively increases with age High-risk postoperative pulmonary complications including pneumonitis and atelectasis
Renal system	Decreased renal blood flow and glomerular filtration rate Decreased concentration ability of urine and to conserve sodium	Vulnerable for ischemia during perioperative hypotension Increased sensitivity to potential nephrotoxic drugs like nonsteroidal anti-inflammatory drugs Risk of perioperative renal failure Altered pharmacokinetics and pharmacodynamics of the drugs Exaggerated response to diuretics leading to excessive dehydration
Musculoskeletal	Sarcopenia	Risk of residual muscle paralysis
	Osteopenia	Increased risk of fracture while positioning
	Stiff joint and tendons	Risk of spinal cord trauma in the presence of osteophytes
	Degenerative changes in spine and disc spaces	
	Decreased mobility	Increased risk of deep vein thrombosis
Integumentary	Epidermis atrophy	Delayed re-epithelisation of skin injuries
	Loss of subcutaneous adipose tissue	Diminished thermoregulation
	Easy separation of dermis and epidermis	Increases the risk for shear injuries pressure ulcers

21.2.1 Cellular Changes

The number of cells gradually reduces with aging, and these changes at cellular level influence all the physiological functions. Aging cells lack certain enzymes that may slow the effects of cell aging leading to age acceleration. There is a reduction in myocytes of skeletal muscles leading to loss of muscle mass [8]. These changes result in reduced lean body mass and increased total body fat [9]. In elderly patients, there is less total body fluid, cellular solids, and bone mass. Extracellular fluid is usually maintained, but intracellular fluid is reduced, rendering these patients at risk of early dehydration [10]. Administration of diuretics (mannitol) aggravates dehydration and might cause exaggerated hemodynamic instability intraoperatively.

21.2.2 Neurological Changes

With aging intelligence is not diminished, but cerebral volume and cerebral perfusion will decrease that may manifest as concentration difficulties, memory loss, and slowed reaction time [11–13]. The loss of neurons and slowing of nerve fiber conduction velocity decrease motor function, hearing, and vision. The dementia might mask acute neurological changes and further complicates the neurological examination [14]. Aging in the hypothalamus makes these patients susceptible to hypothermia. Performance of various sensory organs also gets weakened [10, 15]. Visual acuity is altered, visual field narrows, and pupillary reactions to light slow down as the pupil sphincter hardens (interferes with neurological examination). There is a progressive hearing loss due to the changes in inner ear. Degeneration of the vestibular apparatus results in loss of equilibrium and balance and tendency to fall. Tactile sensation is also reduced to sense pressure, pain, and temperature.

Age-related reduction in cerebral and cerebrovascular reserve results in a relatively high prevalence of postoperative delirium and cognitive dysfunction that delays discharge and functional recovery. Due to decreased CNS reserves, these patients are at risk of delayed awakening after anesthesia, and it must be distinguished from delayed awakening secondary to intracranial cause due to brain insult.

Hypertension is commonly encountered comorbidity in geriatric patients. Due to which cerebral autoregulation curve shifts toward right side, suggesting that lower limit of autoregulation is higher in these patients and the brain becomes ischemic at a higher mean arterial pressure.

21.2.3 Cardiovascular Changes

Cardiovascular diseases are the leading cause of death in this group of patients [16]. Aging alters both the anatomy and physiology of cardiovascular system [17]. The number of myocytes declines progressively, and myocardial collagen starts increasing [18]. Thus, myocardium becomes weak resulting in reduced contractile strength and cardiac output. The myocardium becomes stiff due to increased myocardial interstitial fibrosis [17, 19]. Slowly, myocytes are replaced by connective tissue and fat, that causes conduction defects, risk of sick sinus syndrome, atrial arrhythmias, atrioventricular blocks, and bundle branch blocks [19, 20]. Similarly, blood vessel walls also get stiffened and consequent in increased afterload and myocardial hypertrophy [17]. Both systolic and diastolic blood pressures rise with age to compensate for high peripheral resistance and low cardiac output. Due to lower cardiac output state, their myocardium is at risk of ischemia during increased metabolic demand situations [21].

The physiological changes in the autonomic nervous system result in decreased cardiovascular responsiveness to stress [22]. Elderly patients are effectively "beta-blocked" due to the decreased sensitivity of beta-receptors that limits the capability to increase cardiac output in response to fluid/blood losses. In the same manner, decreased sensitivity of baroreceptors and angiotensin-II responsiveness may further limit the response to hypovolemia. Consequently, it is crucial to maintain adequate circulating volume in geriatric patients.

Due to autonomic involvement, geriatric patients may develop severe hemodynamic instability during sitting or prone positions.

21.2.4 Pulmonary Changes

Aging affects both structure and function of respiratory system. There is a reduction in chest wall and lung compliance as age progresses. Various changes in ribs and costal cartilages (osteoporosis and calcification of the costal cartilage) make the trachea and rib cage more stiff and difficult to ventilate. Along with stiffness, there is a weakness of inspiratory and expiratory muscles that results in the use of accessory muscles even during normal breathing. These patients are high risk for developing pneumonia due to various age-related changes, including blunting of cough and laryngeal reflexes, decreased number of cilia, bronchial mucus gland hypertrophy, and decreased ability to expel pooled mucous and debris [23].

Pulmonary function is also affected due to reduced number, elasticity, and surface area of alveoli [17, 19]. These changes lead to decreased area available to gas exchange and lower the partial pressure of oxygen in arterial blood (PaO_2) [10]. In contrast, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) remains unchanged with aging; therefore, hypercarbia is always considered pathological [17]. Due to these alterations, elderly patients are at risk of sudden decompensation in the presence of hypoxia and hypercapnia. Associated pulmonary diseases and smoking might complicate the situation further. With aging ventilation-perfusion mismatch increases.

21.2.5 Renal System

As age progresses there are structural and functional changes in the kidney that cause decreased renal blood flow and glomerular filtration rate (GFR) [24]. There is approximately 50% reduction in renal blood flow by the age of 80, because of decreased renal tubular mass and arteriole atrophy [19–21]. With aging there is a reduction in the capacity to concentrate urine and conserve sodium resulting in fluid and acid-base imbalances [25]. By the age of 85 years, GFR decreases by approximately 45% [19–21].

Various comorbidities such as hypertension and diabetes and the use of nephrotoxic drugs (particularly nonsteroidal anti-inflammatory drugs and ACE inhibitors) also lead to decline in renal function [26]. Renal function directly affects the pharmacokinetics and pharmacodynamics of anesthetic drugs and therefore should be assessed routinely in elderly patients before elective or emergency surgeries.

21.2.6 Gastrointestinal Changes

With aging, there is a decrease in the feeling of hunger and increase in the feeling of satiety [27, 28]. Other physiological changes are altered swallowing caused by oropharyngeal dysmotility, gastric and intestinal mucosal atrophy, reduced gastric acid and digestive enzyme secretion, and decreased esophageal and gastric motility [24, 28]. All these factors lead to the malabsorption of fats and vitamin B12 resulting in undernourishment, weakness, and debilitation.

The liver also reduces in weight, volume, and function with age that reduces the capacity to metabolize the medications [29]. Laboratory tests might show normal liver function tests. Impaired insulin secretion and increased peripheral insulin resistance render these patients high risk for glucose intolerance and type 2 diabetes [30].

21.2.7 Musculoskeletal Changes

Aging induced changes of musculoskeletal system, such as senile sarcopenia and loss of muscle mass which begins as early as the age of 30 years [20]. Various factors influence this degeneration including environmental, nutritional, hormonal, and immunological factors and physical activity. The myocytes are gradually replaced by fibrous connective tissue which results in reduced muscle mass, tone, and strength. With aging tendons, ligaments, and cartilage lose elasticity and joints become stiffer. Bone mass declines progressively with aging resulting in more susceptibility to fractures, tears, and dislocations [20]. The intervertebral discs also show degenerative changes, and these changes can cause neural compression during positioning under anesthesia [31]. Immobility contributes to a greater prevalence of thromboembolism and pressure necrosis [17].

21.2.8 Integumentary Changes

Various skin changes include epidermis atrophy, dermal collagen stiffening, loss of subcutaneous adipose tissue, and elastin calcification [32]. These changes lead to slow healing, reduced barrier protection, and delayed absorption of medications. Thinning of epidermis causes easy separation of dermis and epidermis and increases the risk for shear injuries and pressure ulcers. Age-related changes to the dermis such as decreased number of sweat glands, blood vessels, and nerve endings cause diminished thermoregu-

lation. There is delayed reepithelization of skin injuries in elderly patients [20].

The neurosurgical procedures are done in diverse positions including supine, prone, sitting, and park-bench, and these procedures are usually of prolonged duration. If pressure points are not adequately padded, then chances of injuries to skin and peripheral nerves may increase.

21.3 Preoperative Assessment

"Perioperative risk" is defined as likelihood of adverse events related to surgery or anesthesia. Various factors contributing to the perioperative risk include modifiable or non-modifiable factors related to patient's comorbidities and deranged physiology and factors related to surgical procedure and anesthesia. Even though there are various risk stratification scores for perioperative morbidity, Portland modification score has been successfully used applied in neurosurgical patients [33]. Preoperative identification and optimization of modifiable risk factors decrease perioperative risk and improve surgical outcome.

21.3.1 Risk Related to the Surgical Procedure

Observational studies are conducted to estimate the surgical risk factors, but these vary from surgeon to surgeon and are influenced by institutional practices [34]. Adverse events are more common during emergency surgery as compared to elective surgeries [35]. Procedural risk may be decreased by using more meticulous surgical techniques, multidisciplinary perioperative approach, and better postoperative and rehabilitation care [36].

21.3.2 Risk Related to the Patient [37]

Aging is commonly associated with physiological decline, multiple comorbidities, and frailty, and these are independent risk factors for increased perioperative risk. Hence, preoperative assessment should involve a structured multifactorial approach in geriatric patients [38].

Table 21.2 enumerates the minimum criteria for preoperative geriatric patient's assessment based on recommendations given by the experts [33, 39–41].

21.4 Preoperative Optimization of the Older Surgical Patient

Preoperative assessment alone is insufficient without attempting the preoperative optimization. At the same time, we must balance the risks of delay in surgical procedure and benefits of optimization. It is suggested that optimization and surgery should take place simultaneously rather than consecutively in emergency setup [36]. Pre-optimization should be focused on reducing the risk of complications, mentioned in Table 21.3.

21.5 Decision-Making

Preoperative assessment allows us the determination of the risk to a patient of undergoing a particular intervention compared with the intended benefits [45].

21.6 Intraoperative Management

The general goals of neuroanesthesia are the same in elderly patient as in other group of patients, including maintaining appropriate intracranial pressure (ICP) and cerebral perfusion pressure (CPP); smooth induction and reversal techniques; avoidance of large hemodynamic fluctuations; and maintaining normocapnia and normoxia. Premedication must be given carefully and under monitoring as geriatric brain is more sensitive to the sedative/hypnotics and the response of these drugs aggravates in the presence of intracranial lesions. Invasive monitoring may be required to provide a beat-to-beat control of ICP and CPP. Intraoperative management of geriatric patients is described in Table 21.4.

Table 21.2 Preoperative assessment of geriatric patients

Domain	Items to be assessed	Appropriate assessment tools
Medical illness	Comorbidity/severity	
	• Cardiovascular	• Vital signs, ECG, echocardiography (if applicable), CPET
	• Respiratory	• Chest X-ray, SpO_2, pulmonary function tests, and arterial blood gases if required
	• Hematological	• Full blood count
	• Renal	• Urea and electrolytes, estimated glomerular filtration rate
	• Endocrinological	• Blood sugar
	• Nutritional	• Weight, body mass index, albumin (liver function tests)
	Previous anesthesia	Enquire about problems during previous exposure (difficult airway, cardiovascular liability, emergence delirium, delayed awakening)
	Presenting pathology	Radiological
Medication	Medication review	
	Anticoagulant therapy	Coagulation screen
	Relevant allergies	
Cognitive functions	Decision-making capacity	Abbreviated mental test score
	Communication	
	Preoperative depression	Vision, hearing, speech
	Alcohol dependence	
	Risk factors for postoperative delirium	
Functional capacity	Gait and balance	6-m walk
	Mobility	Walks unaided/with stick/with frame/does not walk Home-bound? (yes/no)
Use of functional aids	Visual Hearing Mobility Dentures	Glasses Hearing aids Walking stick, frame, wheelchair

ECG electrocardiogram, *CPET* cardiopulmonary exercise test

Table 21.3 Perioperative optimization

Postoperative complications	Measures to optimize
Organ-specific morbidity	Comorbidities should be optimized as per various guidelines for specific disease These guidelines might need to be tailored as per patient's needs, and risk of over-investigations and interactions of polypharmacy should be kept in mind
Ischemia	Age-related physiological is associated with organ-specific and generalized ischemia The brain and heart have high metabolic demands, and perioperative ischemia leads to dysfunction of these organs. So, interventions should be aimed at reducing oxygen demands and improving oxygen delivery These aims are achieved by maintaining adequate depth of anesthesia and analgesia, adequate thermoregulation, oxygenation, blood pressure, fluid balances, and hematocrit
Postoperative cognitive disorders (delirium and cognitive decline)	High-risk patients should be identified and optimized Intraoperative oxygenation and hemodynamics should be tightly controlled Early detection and management helps in reducing the prevalence, severity, and duration of POCD
Malnutrition	Adequate oral nutrition and supplementation of hematinics (if required) and vitamins should be started at least 28 days prior to elective surgery [42, 43] Prolonged fasting should be avoided preoperatively [44]
Functional decline	Currently there is inadequate evidence on postoperative rehabilitation of geriatric patients There should be a multimodal approach involving patient information and encouragement, recovery protocols, maintaining hemodynamic goals, employment of postoperative care bundles, and rehabilitation

Table 21.4 Intraoperative management of geriatric patients

Preoperative checklist	Sign in: before induction of anesthesia	Time out: before surgical incision
WHO Surgical Safety Checklist modified the checklist for geriatric patients	• Have vital signs been recorded (heart rate, blood pressure, heart rhythm, SpO_2, temperature)? • Is the patient's resuscitation status known? • Does the patient have dentures? • Does the patient have any preoperative pressure sores? • Has the site of any nerve block been confirmed and marked?	• Have possible areas of pressure damage been padded? • What is the patient's hemoglobin concentration? • What is the patient's eGFR?
Temperature control	Geriatric patients are more at risk of hypothermia Hypothermia is associated with increased risk of complications including [46, 47] • Postoperative delirium • Cardiac dysfunction • Prolonged hospital stay • Poor wound healing Measures should be taken to maintain temperature including [47] • Appropriate monitoring • Forced air warming/fluid warming	
Monitoring	Besides standard intraoperative monitors • Electrocardiography • Noninvasive blood pressure • Pulse oximeter • End-tidal carbon dioxide monitor Advanced and invasive monitors might be needed depending upon the presence of comorbidities and invasiveness of surgery (a) *Central venous pressure* • Due to poorly compliant ventricles and vasculature, central venous pressure does not correlate with actual blood volume [48] • Its use is more limited to the administering vasoactive drugs and parenteral nutrition (b) *Cardiac output monitor* • Esophageal Doppler (directed at aorta) directed guided cardiac output monitoring may be less accurate in the geriatric patients • Flow through stiff artery might overestimate cardiac output • Results in suboptimal fluid resuscitation [49, 50] (c) *Cerebral oxygen saturation* • Still under research and might decrease the prevalence of POD/POCD (d) *Bispectral index monitors (BIS) or entropy monitors* • Requirement of anesthetic agents reduces with age [51, 52] • If dosage of anesthetic agents is not tailored as per needs, it results in relative overdose and leads to prolonged recovery time and significant hypotension [53] • If these monitors are not available, then age-adjusted MAC values should be used [51] • "Triple low" (low BIS, low hypotension, and low inspired inhalational agent) is associated with higher mortality and prolonged inpatient stay [54] (e) *Peripheral nerve stimulation* Altered pharmacokinetics and pharmacodynamics of the drugs might lead to prolonged neuromuscular blockade, suggesting that neuromuscular function monitoring should be used routinely [55, 56]	
Fluid and electrolyte management	• Fluid and electrolyte therapy is challenging as there is weak cardiac compensation • There is no tachycardia of blood and fluid losses • Slight overhydration causes pulmonary edema • Prolonged preoperative fasting should be avoided	

(continued)

Table 21.4 (continued)

Preoperative checklist	Sign in: before induction of anesthesia	Time out: before surgical incision
Positioning	• Positioning should be made with care as there are associated skeletal deformities and osteoporosis • Elderly skin can be friable • Peripheral nerve injuries are common • All pressure sites should be well padded • Care should be taken during transfer of the patient on the operating table • Their skin is at risk of thermal damage. Warming devices should be carefully placed	
End-of-surgery checklist WHO Surgical Safety Checklist "sign out" [57]	Sign out: before patient leaves the operating theatre • What is the patient's core temperature? • What is the patient's hemoglobin concentration? • Have age-adjusted and renal function-adjusted doses of postoperative analgesia been prescribed? • Has a postoperative fluid plan been prescribed? • Can the patient be returned safely to a general care? • Ward?	
Perioperative analgesia	• Must be titrated carefully • Respiratory compromise may be a risk preoperatively • Inadequate analgesia may lead to postoperative delirium	
DVT prophylaxis	Must be started as soon as feasible	

DVT deep vein thrombosis, *POD* postoperative cognitive disorders, *POCD* postoperative cognitive decline

Additionally, functional aids (hearing aids, glasses, dentures) should remain in place until just prior to the induction of anesthesia. During awake craniotomy, we need to keep hearing and visual aid in place to examine patient's neurological status intraoperatively.

21.7 Specific Concerns for Common Neurosurgical Conditions (Table 21.5)

Various neurosurgical lesions commonly encountered in geriatric patients are listed in Table 21.5.

Table 21.5 Spectrum of lesions in geriatric patients

Intracranial lesions
Intracranial space-occupying lesions
• Intrinsic tumors
• Meningioma
• Metastatic malignant disease
• Cerebral abscess (less common)
Vascular
• Vascular disease, e.g., cerebellar infarction
• Stroke-ischemic/hemorrhagic
• Chronic subdural hematoma
• Arteriovenous malformation (less common)
Spinal cord and column
Degenerative diseases
• Lumbar canal stenosis
• Rheumatoid arthritis
• Prolapsed intervertebral disc (less common)
Metastatic tumors

21.7.1 Vascular Disease

In geriatric neurosurgery, vascular diseases are commonly divided into two main groups. One of them is where surgery is performed directly on the vessels such as aneurysm and carotid stenosis. Another category is where surgery is performed because of the consequences of vascular involvement, such as shunt placement in acute hydrocephalus following cerebellar infarction or decompressive hemi-craniotomy after complete middle cerebral artery territory infarct.

21.7.2 Carotid Artery Surgery

The degenerative diseases constitute a major burden of neurovascular diseases, particularly stroke, related to carotid stenosis [58]. A multicenter trial showed that in symptomatic patients with greater than 70% stenosis surgical interventions are superior over medical treatment. This leads to an increase in number of patients presenting for carotid endarterectomy (CEA) or carotid stenting. This group of patients

usually has multiple comorbidities including hypertension, diabetes, ischemic heart disease, peripheral vascular disease, and smoking-related lung disease and might be on multiple pharmacological agents. Because of these comorbidities, anesthesia becomes challenging in these patients [59, 60]. The goals of anesthesia during these surgeries are maintenance of adequate cerebral perfusion pressure and avoidance of hypocapnia (leads to cerebral vasoconstriction and aggravates ischemia) and hypotension/hypertension (leads to myocardial ischemia and stroke, cerebral hyperperfusion, rupture of vascular suture line). Patients should be counselled regarding the perioperative risks of major complications such as myocardial infarction and stroke and the purpose of surgery. Myocardial infarction is the most common cause of perioperative death during these procedures. In patients over 75 years of age undergoing surgery, the risk of perioperative stroke rate is reported as 3.3% and total mortality as 2.1%. Surgery will not reverse the pre-existing deficit but will prevent future stroke and debilities that might occur due to major stroke [59]. In patients with severe degrees of stenosis, one should balance the risk firmly in favor of surgery.

21.7.3 Subarachnoid Hemorrhage (SAH)

In patients over 70 years of age, the incidence of SAH is about 3/100,000, and out of these, approximately 75% occur due to ruptured aneurysm. Other causes of hemorrhagic stroke such as arteriovenous malformation are more common in younger patients [61]. Perioperative management goals are the same as described in previous section. Hemodynamic management of vasospasm should be guarded as the risk of cardiopulmonary decompensation is high in the presence of stiff ventricles.

21.7.4 Chronic Subdural Hematoma

Chronic subdural hematoma (SDH) is common with increasing age. Due to loss of brain mass, the bridging veins between the dura and brain rupture easily leading to a chronic SDH. Patients with SDH usually present with dementia or gradual worsening of an existing mental status. The mechanism of the acute SDH is distinct from chronic SDH that usually occurs due to major head trauma, but in geriatric patients, acute SDH may follow a seemingly trivial trauma. Chronic SDH is managed by evacuation through burr holes under minimal sedation and local anesthesia or scalp block.

21.8 Intracranial Neoplasms

21.8.1 Malignant Tumors

Metastatic intracranial deposits depressingly form a larger proportion of neurosurgical cases in geriatric age group [62, 63]. The removal of metastasis deposits may result in extension of life to some extent and may improve quality of life. Excision of metastatic tumors is a usual neurosurgical procedure with a little blood loss and is managed in similarly as in younger patients.

21.8.2 Benign Tumors

The common benign tumors in geriatric age group are meningiomas and tumors of the eighth nerve. Slow-growing tumors might acquire a larger size before presentation in geriatric patients due to larger space available secondary to loss of brain volume. The strategy in surgical excision may be different in this age group [64]. One might go for attempted complete excision of a medium-sized acoustic neuroma in a young adult, while in the older patients, a debulking procedure with preservation of the facial nerve may be more sensible. These slow-growing tumors usually take time to recur, and patients may die due to some other associated pathology in natural course of disease before the recurrence. It might be technically easy to remove extra-axial tumors like meningiomas in the elderly patients, as atrophied brain allows a good exposure with lesser retraction and lesser need

for decongestive measures such as mannitol and hyperventilation [65]. The slowly growing tumors may present with progressive intellectual deterioration in the elderly patients, and it may be confused with degenerative diseases like Alzheimer-type dementia. The intellectual capacity recovers satisfactorily following excision of such tumors. Preoperative embolization of vascular tumors can be considered to reduce blood loss and morbidity.

21.9 Spinal Diseases

The spectrum of spinal pathology is also different in young and elderly patients. Approximately 30% of neurosurgical interventions are related to spinal diseases in elderly patients, and out of which, 45% are related to degenerative spinal diseases such as cervical spondylotic myelopathy and lumbar canal stenosis [66]. Most common cause of spinal trauma is simple fall in the elderly, while road traffic accident is the leading cause in the young patients. Another category of disease predominantly seen in this group of patients is metastatic tumors. These lesions may be extremely vascular and might bleed torrentially intraoperatively. Neurofibroma and meningioma are commonly seen benign spinal tumors and are managed in a conventional way.

Intubation might be challenging in geriatric patients due to the presence of cervical osteophytes (causes cervical compression myelopathy) or rheumatoid arthritis (might be associated with atlanto-axial dislocation). Also, stiff and osteoporotic spine at this age might endanger spinal cord during intubation. Hence, care should be taken to prevent injuries to the spinal cord during intubation.

21.10 Trauma

As far as function is concerned, the elderly traumatic brain and spinal cord usually do not recover well following injury, and both the morbidity and mortality are much greater than the younger patients. In other neurosurgical diseases, patient's physiological state is more important than the chronological age in predicting the outcome. The mechanism of injury and outcome following evacuation of acute SDH are markedly different in young and old alike [67]. As in spinal trauma, the mechanism of injury is commonly a high-impact road traffic accident in younger population, whereas in elderly it may be a simple fall (approx. 55%) leading to the same severity of trauma.

After acute head injury, geriatric patients usually have poor outcome despite full resuscitation, including adequate ventilation, neuroprotection, maintaining an adequate cerebral perfusion pressure, and timely surgical intervention. In contrast, chronic SDH has a better outcome. A study comparing the mortality of patients over 65 years of age and under 40 years of age with GCS of <12 found that mortality was 75–100% in the former group while 18% in the latter group.

As with brain trauma, spinal injuries are also poorly tolerated by elderly patients as compared to younger patients. Spinal injuries are associated with mortality rates between 30% and 100% in patients with new onset tetraplegia in the over 65 years of age.

21.11 Trigeminal Neuralgia (TGN)

TGN is seen in middle-aged to elderly patients. TGN is successfully treated by three approaches including medical, surgical decompression of the trigeminal nerve in the posterior fossa, and percutaneous ablation of trigeminal nerve. Initially the patients are treated with pharmacological agents, but if pain is not controlled with pharmacological agents or side effects of drugs are intolerable, then surgical treatment is needed. The surgical technique involves posterior fossa exploration, exposure of the trigeminal nerve, and revealing of a microvascular compression (by a loop of superior cerebellar artery), and a graft is inserted between vessel and nerve. The complications of the procedure include all the hazards of posterior fossa surgery and most serious being the potentially fatal posterior fossa hematoma postoperatively.

The percutaneous approaches include ablation of trigeminal ganglion by injection of glycerol, balloon compression, or radio-frequency lesioning (RFL) by thermocoagulation. Insertion of the needle and lesion ablation are painful and may require general anesthesia or can be done in conscious patient. If general anesthesia is used, recovery should be rapid and complete after procedure to allow assessment of success of the treatment. Depending upon anatomy of patient and operator's experience, the needle placement may take a few seconds to minutes; hence a square-wave pattern of anesthesia is required. If sedation is planned, then one should be careful about apnea due to oversedation. During the procedure, as needle enters the ganglion, patient may develop hypertension, severe bradycardia, and even asystole. Close communication with patient is required during procedure, but the presence of hearing difficulty (deafness, dementia, residual anesthesia) might interfere with the assessment.

21.12 Interventional Neuroradiology

Intervention neuroradiology (INR) is being increasingly used for neurosurgical procedures. Being minimally invasive, INR is beneficial in the situations where either surgery is high risk such as basilar-top artery aneurysms or where patients are high risk due to associated comorbidities [68]. In carotid stenosis, the patients having severe cardiac disease and other associated systemic diseases that increase the perioperative risks are treated by carotid stenting in INR suite rather than carotid endarterectomy. INR involves lesser hemodynamic changes and better outcome.

Preoperative embolization of vascular tumors prior surgery may reduce intraoperative blood loss and decrease morbidity greatly. Anesthetic plan varies as per the procedure; preoperative embolization of tumors is usually done under local anesthesia and minimal sedation, whereas coiling of aneurysm is preferentially done under general anesthesia. INR becomes challenging when patient have associated cardiac and renal dysfunction. Flush fluids, intravenous fluids, and the use of contrast should be used in restricted dosage in patients with such comorbidities. Temperature should be monitored, and rewarming devices should be used as INR suites are usually kept at lower temperature to maintain proper functioning of machines, and elderly patients rapidly lose heat due to poor compensatory mechanisms.

21.13 Functional Stereotactic Neurosurgery

Therapeutic electrical stimulation of the CNS is being practiced in various diseases such as Parkinson disease, severe depression, chronic pain, and movement disorders. These procedures are usually performed under monitored anesthesia care and minimum sedation. Complications may arise during the procedure due to the preexisting comorbidities and drug interactions. Intraoperative complications include hypertension, airway obstruction, and seizures. Good preoperative preparation, proper patient selection and counselling, and increased vigilance intraoperatively will prevent or minimize these events [69].

21.14 Postoperative Management

Pre-existing systemic diseases, type of intracranial pathology, and local postoperative complications affect the postoperative course and outcome of geriatric patients. Advanced neuro-monitoring modalities including ICP and transcranial Doppler ultrasonography might help in early detection of intracranial complications [70]. Major postoperative complications are described wide infra.

21.14.1 Respiratory Complications

Due to diminished physiological reserve, geriatric patients are at increased risk of postoperative pulmonary complications. In addition to these

changes, in patients with posterior fossa lesions and upper cervical spine, there is decreased cough and pharyngeal reflex that may increase the risk of postoperative aspiration. Adequate analgesia incentive spirometry, chest physiotherapy, and toileting or protection of airway (endotracheal tube/tracheostomy) might prevent aspiration.

21.14.2 Postoperative Delirium and Cognitive Decline

Causes of postoperative delirium are multifactorial including urinary tract infection, hypoxia, hypercarbia, hyperthermia, fluid shifts, and electrolyte imbalance.

21.14.3 Rehabilitation

A multidisciplinary team involving medicine experts, geriatricians, surgeons, anesthetists and intensivists helps to bring these patients to the premorbid functional states.

21.15 Conclusion

As we are growing grayer, our expectations are also growing, and neurosurgical interventions are also being increasingly done in the elderly patients. There are various studies that show surgeries in elderly patients are successful most of the times and can avoid long-term disability and dependence, and age alone should not be the criteria to decide in favor or against the surgery. It is the presence and severity of coexisting pathology that also affects the outcome in these patients rather than age alone. In traumatic and emergency surgeries, age directly affects the outcome, and geriatric patients with severe trauma usually carry a poor prognosis. In patients with compromised physiological reserve, where surgery is associated with higher intraoperative morbidity and mortality, INR plays a major role. With adequate preoperative optimization, skillful perioperative management, and clinical common sense, a good outcome can be achieved in elderly neurosurgical patient.

Key Points

- The perioperative management of geriatric patients is challenging due to their depleted systemic reserves, polypharmacy, and geriatric syndromes.
- A multidisciplinary team approach involving emergency medicine experts, geriatricians, surgeons, anesthetists, and intensivists should work together to improve outcome in these patients.
- Preoperative identification and optimization of modifiable risk factors decrease perioperative risk and improve surgical outcome.
- Premedication must be given carefully and under monitoring as geriatric brain is more sensitive to the sedative/hypnotics and the response to these drugs is intensified in the presence of intracranial pathology.
- Functional aids (hearing aids, glasses, dentures) should remain in place until just prior to the induction of anesthesia and intraoperatively during awake craniotomy.

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Part VI

Allied Considerations

Interventional Neuroradiology

22

Ravi Bhoja, Meghan Michael, Jia W. Romito, and David L. McDonagh

22.1 Introduction

Interventional neuroradiology (INR) has remarkably evolved over recent years and serves as an alternative to many open neurovascular procedures. Endovascular therapy is less invasive and allows for some interventions that simply cannot be performed with open surgery, making it a primary approach for treating a host of thrombo-occlusive and hemorrhagic neurovascular conditions. To that end, INR also poses many challenges for the anesthesiologist from caring for fragile or critically ill patients in an off-site location to having to navigate through various physical obstacles within the interventional suite.

This chapter will (1) explore the challenges met with working in an angiography suite, (2) discuss a basic approach to the anesthetic regimen and management of common INR procedures, (3) review the uses of endovascular therapy in the treatment of various neurological conditions (both elective and emergent), and (4) discuss some of the common complications encountered in INR.

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22.2 Angiography Suite Considerations

The angiography suite itself can be an extreme test for the anesthesiologist. Depending on the institution, these suites are often located off-site with limited accessibility to anesthesia personnel and resources, which can be a particular challenge in emergent situations. A biplanar fluoroscope with two juxtaposed C-arms for anterior-posterior and lateral images occupies a significant amount of room centrally within the suite. All personnel and equipment are situated circumferentially around the fluoroscopy unit, decreasing accessibility to the patient and creating physical obstacles to obtain equipment in a timely manner. Also, the presence of digital imaging screens poses a barrier to communication as it is often located directly between the interventionalist and the anesthesiologist (Figs. 22.1 and 22.2).

The patient is situated such that the head is often positioned in the far end of the room between the two C-arms which must have enough unobstructed room to allow rotational movement. This essentially pushes the anesthesia machine to the distal end of the patient, allowing access to just the lower half of their body. More importantly, this also limits access to the patient's airway and torso both during intubation and during the procedure. The INR table itself poses additional challenges. While it can be maneuvered into Trendelenburg and reverse

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Fig. 22.1 Angiography suite from the side of the interventionalist

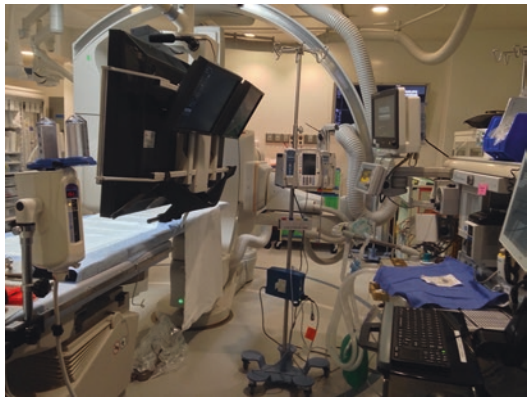

Fig. 22.2 Angiography suite from the side of the anesthesiologist

Trendelenburg positions, more nuanced positions such as head up cannot be obtained. This may make it difficult to place the patient into an optimal sniffing position for intubation. The table also does not have built-in arm boards. Boards such as these (Fig. 22.3) can be used for arterial line placement but must be removed and the arms must be tucked to allow the C-arms necessary access to the patient. Finally, the bed is firmer than a conventional operating room table, which can pose a challenge in keeping a patient comfortable for any cases done under sedation/monitored anesthesia care.

It is for these considerations that precise planning is required. Extension tubing for the circuit and end-tidal gas sampling line is often needed to allow for the added distance between the patient and the anesthesia machine. Care should

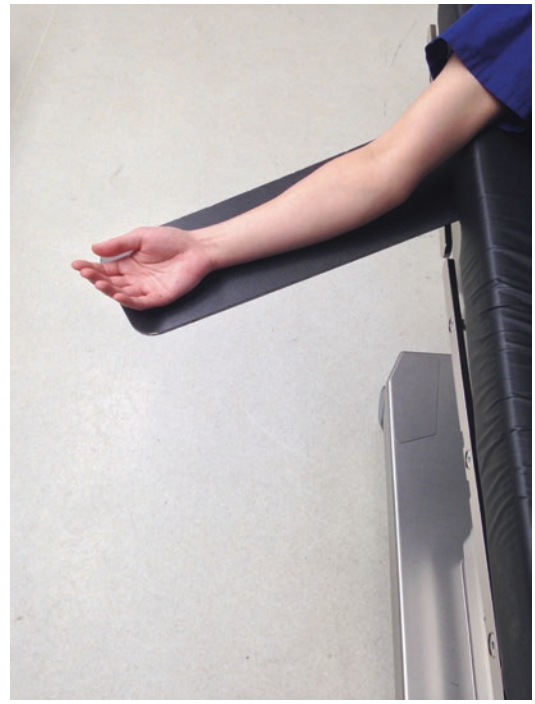

Fig. 22.3 An arm board can be used for arterial line placement; however it must be removed before the procedure begins

be taken to ensure that the circuits, monitor cables, and IV tubing are not hanging in the path of the rotational C-arms. Also, as there is often significant distance between the patient's IV site and the anesthesiologist, IV extension tubing should be utilized with consideration given to the increase in dead space when initiating any vasoactive or anticoagulant infusion therapy [1]. Finally, radiation exposure necessitates the utilization of lead garments and leaded shields and complicates navigating an already restricted environment.

22.3 Radiation Safety

In the neurointerventional suite, radiation exposure is a significant occupational hazard. The four factors that affect occupational radiation exposure are the amount of radiation used, duration of exposure, shielding from the radiation, and distance from the source. Embolizations of cerebral aneurysms and arteriovenous malformations are considered high-dose radiation

procedures due to the interventional technique of digital subtraction angiography requiring more ionizing radiation than standard fluoroscopy. The two controllable methods of protection from radiation for anesthesiologists are appropriate shielding and increased distance from the source. Appropriate personal shielding includes radiation-protection aprons, thyroid collars, and radiation-protection eyewear. Lead-plated glass/plexiglass shields can also be positioned to reduce direct exposure to the fluoroscopy equipment. The concept of increased distance from the radiation source stems from the inverse-square law: radiation concentration is inversely proportional to the square of the distance from the radiation source [2].

Radiation exposure can lead to acute and chronic effects. Directed acute effects can cause skin erythema and dermatitis. Generalized whole-body radiation exposure can cause nausea, vomiting, diarrhea, weakness, and possibly death. Chronic effects can lead to skin cancer, bone marrow suppression, and reproductive issues. Dosimeters should be utilized routinely, and exposure to the anesthesiologist should be kept lower than the annual limit for healthcare workers set by the United States Department of Labor's Occupational Safety and Health Administration [3].

22.4 INR Procedure

INR procedures routinely begin by obtaining arterial femoral sheath access, most often with a 6 or 7 French catheter [4]. Alternative access can also be obtained via the radial, brachial, or carotid arteries [4–6]. Through the femoral sheath, a smaller coaxial guide catheter is introduced and advanced to the common carotid artery. This is followed by a diagnostic cerebral angiogram, where contrast medium is bolused to outline the cerebral vasculature. The radiological imaging is produced via high-resolution fluoroscopy and high-speed digital subtraction angiography (DSA) with a "roadmapping" feature (Fig. 22.4a) [4, 7]. While performing live fluoroscopy, a computer will superimpose these live images on those acquired in the "roadmapping" process (inversion of the black vessels on angiography to make them white) to allow visualization of the progress of the radiopaque catheter tip into the target vessel [4, 7].

If the visualized neurovascular lesion is deemed treatable by an interventional route, a microcatheter is advanced into the cerebral vasculature and navigated to the neurovascular lesion. The lesion is then treated with detachable coils, stents, or embolization agents as deemed necessary by the interventionalist (Fig. 22.4b).

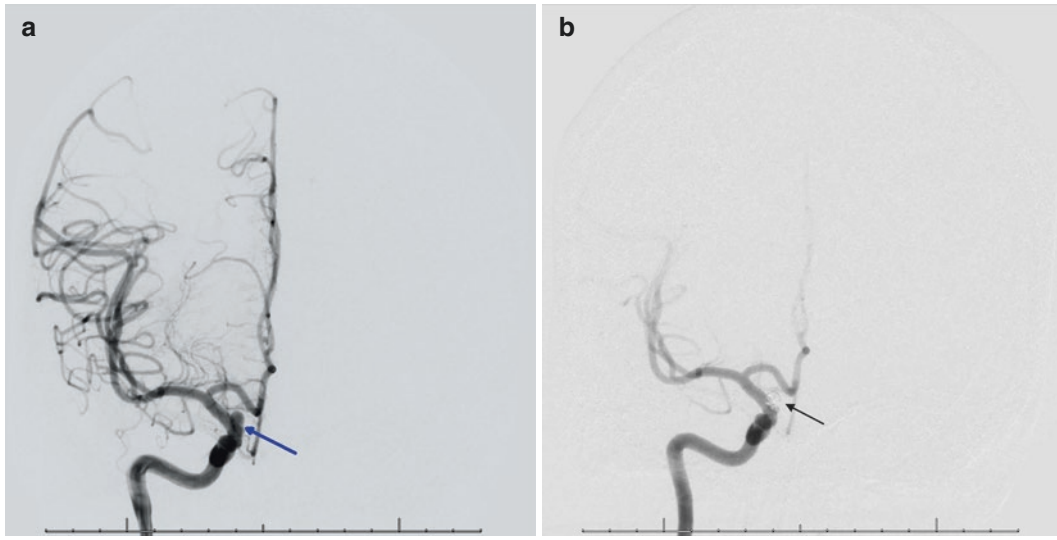

Fig. 22.4 Coil embolization of a type II right ophthalmic artery aneurysm. (**a**) Pre-procedure diagnostic angiography obtained using digital subtraction angiography (DSA). (**b**) Post-procedure DSA angiography performed after successful coil embolization of the aneurysm. Arrow denotes the coil

After the procedure is complete, the interventionalist will obtain hemostasis and may insert an arterial closure device to prevent post-procedural bleeding from the arteriotomy. This process is variable and may require several minutes of direct pressure to the groin. Closure devices work through various mechanisms that may include a disc deployed on the intravascular side of the arteriotomy, a collagen plug or polyethylene glycol sealant applied on the extravascular side of the arteriotomy, a clip, sutures, or some combination of the abovementioned components [8]. Many of these techniques will require the patient to lay flat with the ipsilateral leg to the arteriotomy extended at the hip for a certain period of time, up to several hours. It is important that the anesthesiologist and interventionalist communicate prior to emergence regarding the needs for each patient.

22.5 Anesthetic Management

The anesthesiologist's involvement in INR cases is vital for a number of reasons. (1) The anesthetic can provide partial or complete immobility, which is essential while the interventionalist navigates through delicate cerebrovascular structures. (2) Since the majority of INR procedures involve manipulation of the cerebral vasculature, precise hemodynamic monitoring and control are critical in order to complement the intervention being performed. (3) A rapid emergence is essential to allow for neurological monitoring in the post-procedural period, which is largely determined by the anesthesiologist's choice of drugs.

22.5.1 Lines and Monitors

Neurovascular disease can often call for extremes in the patient's blood pressure parameters. Generally speaking, hemorrhagic disease calls for deliberate hypotension or controlled normotension, while thrombo-occlusive or spastic disease requires deliberate hypertension. Moreover, the anesthesiologist may need to manage intracranial pressure (ICP) and cerebral perfusion pressure (CPP) when a ventriculostomy or other ICP monitor is in place. Communication regarding hemodynamic targets is of the utmost importance between the anesthesiologist and the interventionalist.

Intra-arterial blood pressure monitoring allows for precise measurement of the arterial pressure during the procedure as well as for post-procedural care in the intensive care unit. For the critically ill, placement of the arterial line should be considered prior to induction (such as for the aneurysmal subarachnoid hemorrhage patient). Note that certain femoral sheath catheters possess a side port which allows a line to be added ("piggy-backed") for blood pressure monitoring, although these ports often provide dampened waveforms. Also, once the sheath is removed, monitoring will not be available for emergence and post-procedural care.

The necessity of vasoactive infusions and the risk of blood loss, should a complication occur, make a second IV line useful in many cases. In the nondiabetic patient, the legs (saphenous vein) and feet are a convenient location as they are easily accessible to the anesthesiologist during the procedure. Central venous access is usually not needed unless the patient is critically ill, such as the aneurysmal SAH patient with vasospasm.

Urinary catheters are usually deemed necessary to monitor the increased urine output that can develop from the contrast-induced diuresis. This also helps the anesthesiologist determine volume status and maintain adequate hydration to help prevent nephropathy induced by contrast medium [9].

22.5.2 Type of Anesthesia

For diagnostic cerebral arteriograms, conscious sedation is typically the preferred approach as this procedure simply entails imaging the cerebral vasculature, assuming the patient is cooperative enough for the procedure. However, for more complicated interventional procedures involving coiling, embolization, stenting, or thrombolysis/clot retrieval, patient movement in the angiography suite can be potentially disastrous, especially

if the motion comes at a critical portion of the case. This can lead to impaired radiographic imaging, perforation of a cerebral vessel, or drastic elevations in intracranial pressure. As a result, immobility is usually preferred [10]. The choice between conscious sedation (CS)/monitored anesthesia care (MAC) and general endotracheal anesthesia (GETA) is often left to the discretion of the anesthesiologist and interventionalist.

CS/MAC offers the option of intra-procedural monitoring of the clinical neurological exam [11], which is preferable in a carotid stenting procedure for example. However, this comes at the expense of potential patient movement, increased procedural difficulty, and motion artifact. Moreover, CS/MAC may be preferable in those presenting with other significant comorbidities which would make them less amenable to GETA [12]. Relieving an obstructed airway with jaw thrust/chin lift can be extremely challenging and can impair the fluoroscopic views as the patient's head/airway is away from the anesthesiologist and in the field of radiation. GETA is a preferable alternative as it can provide complete immobility, especially in lengthy procedures or in patients with an inability to lay flat. It can also be of value in that it provides a protected airway and gives the ability to hyperventilate a patient to reduce ICP or, alternately, hypoventilate to dilate the cerebral vasculature in appropriate scenarios. Moreover, GETA provides more flexibility for the anesthesiologist to focus on other matters such as hemodynamic monitoring during the procedure. On the other hand, being under GETA during an INR procedure, which is minimally stimulating, can lead to hemodynamic lability with drops in blood pressure and/or heart rate, requiring titration of the depth of anesthesia and the addition of vasopressor infusions.

22.5.3 Anesthetic Medications

Induction Induction can be a very labile period, especially in critically ill neurological patients who need to stay within a range of specific hemodynamic parameters. Performing a smooth and controlled induction can be a challenge. Pre-induction arterial access to allow invasive blood pressure monitoring can be of value, although obtaining such access can be a challenge in the setting of time-sensitive conditions such as acute ischemic stroke. Patients typically need to maintain blood pressure with some degree of induced hypertension in conditions such as ischemic stroke and cerebral vasospasm. The use of hemodynamically stable agents such as etomidate and a pre-induction fluid bolus can help reduce lability. The induction in those with hemorrhagic lesions, who need minimal surges in blood pressure, can be accomplished with agents that achieve a deep level of anesthesia in a short period of time such as propofol and remifentanil.

Maintenance A rapid, clear emergence and wake-up are crucial to allow for an adequate neurological examination post-intervention. Intracerebral bleeding or thrombotic complications as a result of INR procedures can be detected by neurological examination and could necessitate, depending on the situation, an emergent head CT, anticoagulation, reversal of anticoagulation, surgical hematoma evacuation, or endovascular thrombectomy. Thus, using short-acting anesthetic agents is vital to allow for more effective surveillance for these complications (Table 22.1). Time is critical in these situations, and the use of longer-acting agents can delay their recognition. Nitrous oxide should be avoided in neurointerventional procedures since this agent will enlarge any gaseous/air microemboli that may have complicated the interventional procedure. If an air embolus does complicate the procedure, hyperoxia is the treatment (1.0 FiO_2 then emergent transfer to a hyperbaric treatment facility) [13].

Most INR procedures do not provide a great deal of intraoperative stimulation or postoperative pain. Manipulation of cerebral vessels can be painful for an awake patient but does not provoke much of a response under general anesthesia. A typical approach is 0.6 MAC (minimum alveolar concentration) halogenated inhalational agent with a remifentanil infusion

Table 22.1 Select anesthetic drugs in the INR suite

Anesthetic drug (drug class, dose range)	Advantage for INR	Disadvantage for INR	Acceptable substitutes	Other aspects
Desflurane (volatile anesthetic, ~0.6 MAC)	Rapid titration and emergence	Potential for airway irritation leading to coughing; Theoretical risk of cerebral steal in certain disease states (such as moyamoya)	Sevoflurane Isoflurane	Avoid nitrous oxide (due to potential for intra-arterial air emboli)
Remifentanil (opioid, 0.1–0.3 mcg/kg/min)	Deep plane of anesthesia, smooth emergence No context sensitivity	Potential for hypertension and tachycardia after emergence	Sufentanil Fentanyl	Bolus dosing effective to blunt the response to intubation (1–2 mcg/kg)
Dexmedetomidine (α-2 agonist, 0.2–0.7 mcg/kg/h)	Sedation and analgesia for procedures	Potential for hypotension, bradycardia, somnolence	Low-dose clonidine	Prevents emergence agitation and hypertension
Midazolam (benzodiazepine, 0.5–5 mg)	Anxiolysis; sedation for procedures	Potential for somnolence, alteration of neurological exam	Propofol bolus or infusion	
Propofol (intravenous anesthetic, 25–200 mcg/kg/min)	Sedation for procedures	Potential for hypotension; loss of anesthetic depth (or awareness) due to IV infiltration		Does not exacerbate ICP; should not cause "cerebrovascular steal"

Table 22.2 Vasoactive medications useful in the INR suite

Pressors/inotropes (drug class, dose range)	Antihypertensives (drug class, dose range)
Phenylephrine (α-1 agonist, 0.1–1 mcg/kg/min)	Nicardipine (calcium channel blocker, 5–15 mg/h)
Ephedrine (indirect sympathomimetic, 5–10 mg IV bolus)	Clevidipine (calcium channel blocker, 4–6 mg/h)
Epinephrine (dose-dependent α and β agonist, 0.01–0.5 mcg/kg/min)	Labetalol (α-1 and β-1,2 blocker, 5–20 mg IV bolus Q 5 min)
Norepinephrine (α-1 and β-1 agonist, 0.02–1 mcg/kg/min)	Esmolol (short-acting β-1 blocker, 10–30 mg IV bolus)
Vasopressin (V1 and V2 receptor agonist, 0.01–0.04 units/min IV)	Hydralazine (vasodilator, 5–10 mg IV Q 20 min)

(0.1–0.3 mcg/kg/min), with or without neuromuscular blockade. For CS/MAC cases, various techniques may be employed depending upon the patient, the need for the interventionalist to communicate with the patient, and the hemodynamic goals of the procedure. A propofol infusion would be a typical approach. Whether the procedure is to be performed under CS/MAC or GETA, vasoactive infusions targeted toward the patient's hemodynamic goals should be available for both bolus and infusion throughout induction, maintenance, and emergence (Table 22.2).

Emergence Special considerations may be involved as the patient emerges from anesthesia. Depending upon the type of closure performed on the groin, the proceduralist may need to hold pressure on the groin for several minutes after the procedure is complete. The patient may also be required to lay flat for a certain period of time to prevent damage to the femoral artery. This may be an uncomfortable position for the patient and may even provide a challenge in achieving extubation criteria. As mentioned before, vasoactive medications via both bolus and infusion should be available to maintain tight adherence to the

agreed-upon hemodynamic goals. A typical approach to emergence is the "remifentanil wake-up" where the inhalational agent is turned off and blown off (to less than 0.25 MAC) prior to stopping the remifentanil. The patient will typically awaken 5–10 min after discontinuation of the remifentanil (and flushing of the IV line).

For patients with an obese body habitus, laying flat may prove detrimental, especially as it relates to their pulmonary mechanics. Discussions should take place between the interventionalist and the anesthesiologist regarding post-procedure positioning and the allowance for a head up or a reverse Trendelenburg position in this subset of patients. Moreover, the use of airway adjuncts such as nasal trumpets should be considered (caution with anticoagulation), to more effectively enable oxygenation and ventilation in patients at risk for suffering from obstructed airways especially in the flat position.

22.5.4 Anticoagulation

A heparinized saline infusion is continuously administered through a side port of the intra-arterial catheters to prevent thrombotic complications from the procedure. Moreover, systemic anticoagulation with heparin is generally required during the procedure, with a dose of ~70 IU heparin/kg being administered upon insertion of the arterial sheath and re-dosing with ~1000 units of IV heparin every hour after the bolus. The goal of this anticoagulation regimen is to achieve an activated clotting time (ACT) of two to three times the patient's normal value [4].

Patients are also often treated with antiplatelet therapy, such as aspirin and clopidogrel, prior to arrival for elective procedures. Adequate antiplatelet activity should be assayed preoperatively. These agents are used most often for procedures involving intra-arterial stents in order to prevent stent thrombosis. They are continued for months postoperatively. Acute intra-procedural thrombi can potentially occur, are platelet rich, and are treated very effectively with intravenous antiplatelet agents (with glycoprotein IIb/IIIa inhibitors such as tirofiban) (Table 22.3).

Table 22.3 Mechanism of action of common anticoagulants

Anticoagulant(s)	Mechanism of action
Aspirin	Inhibitor of cyclooxygenase
Clopidogrel	ADP receptor inhibitor
Abciximab, eptifibatide, tirofiban	Glycoprotein IIb/IIIa inhibitors
Heparin	Binds antithrombin III

22.6 Procedure-Specific Management

22.6.1 Aneurysms

It is estimated that 2–5% of the general population develop cerebral aneurysms [14]. Patients with either unruptured (elective) or ruptured (emergent) aneurysms may present for INR treatment. With spontaneous rupture, about 12% of patients die before arriving to the hospital [15]. For those who survive to hospital admission, the mortality rate is 26–44%, the rate of severe disability is 19%, and the incidence of a favorable outcome is 55% [16]. Aggressive early intervention is standard of care to reduce the risk of rebleed.

The International Subarachnoid Aneurysm Trial has demonstrated the utility of endovascular treatment of cerebral aneurysms [17, 18]. Aneurysms which were historically treated with surgery using clips are now being secured with the utilization of Guglielmi platinum detachable coils, often with stent assistance. While preserving flow through the parent vessel, these coils are introduced into the aneurysm with the goal of inducing stagnant flow in the aneurysm sac and in turn generating a thrombotic reaction to occlude the aneurysm [19]. The thrombogenic fibers of the coils also aid in promoting this reaction [20]. Multiple coils may be required to achieve an adequate coil packing density of at least 20–30% or more depending on the aneurysm size, type, and location [19]. Thrombosis of the parent vessel is a concern when performing an aneurysm coiling. An acute thrombotic event often requires the initiation of intra-procedural antiplatelet therapy such as tirofiban.

These techniques were initially used in the treatment of berry aneurysms as the narrow neck would retain the coils. However, stent-assisted coiling now allows for coil placement in wider-necked aneurysms using the stent to keep the coils within the sac. Some types of aneurysm morphology still require open surgical treatment including wide-necked and fusiform aneurysms or those with proximal vessels that are occluded.

A new approach to aneurysm management has emerged which involves endoluminal reconstruction of the cerebral aneurysm with a flow-diverting stent (such as the Pipeline™ stent or Pipeline™ embolization device [PED]) (Fig. 22.5). This technique allows interventionalists to treat giant aneurysms and those with complex morphologies that were previously only amenable to vessel occlusion followed by extracranial to intracranial bypass. This is a considerably different approach to the classic coiling procedure. A low-porosity self-expanding tubular mesh stent promotes blood flow along the typical course of the parent artery, thus diminishing the flow within the aneurysm [21]. Over time the aneurysm thromboses around the stent, and the flow-diverter stent slowly incorporates into the parent artery with neointimal overlay; endoluminal reconstruction takes place

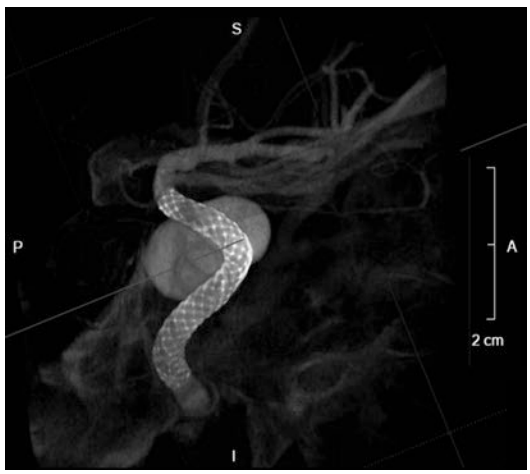

Fig. 22.5 Pipeline TM embolization device (PED) deployed across a large cavernous left internal carotid artery aneurysm

[21]. Dual antiplatelet therapy is required (for ~6 months) until the stent is fully endothelialized.

Potential complications are inherent to all of these procedures. Not filling the aneurysm with enough coils, or with a low packing density, can lead to coil compaction and a residual aneurysm with risk of future rupture [19, 22]. Thus, serial follow-up with surveillance angiography is required to monitor for these issues. Vessel perforation with a catheter or overpacking an aneurysm with coils can lead to aneurysm rupture during the procedure [19]. The risk of thrombosis in the parent vessel is also of concern.

22.6.2 Angioplasty and Stenting

Treatment of intracerebral and carotid atherosclerotic disease can be accomplished with angioplasty and/or stenting procedures. For carotid stents, activation of the carotid body can cause a bradycardic or asystolic response (with hypotension) for which the anesthesiologist should be prepared. Chronotropic agents should certainly be available, and the preemptive placement of transcutaneous pacing pads should also be considered as a precaution. Strict blood pressure control should also be maintained to promote flow through any stenotic regions. As with carotid endarterectomies, the blood pressure should be kept at or above baseline pressures prior to stent deployment (i.e., prior to expanding the stenotic lesion) and then controlled at or below baseline following stent expansion to avoid a cerebral hyperperfusion syndrome (which could cause cerebral edema or hemorrhage). To allow for intraoperative neuromonitoring, these procedures are frequently performed under CS/MAC. This provides the added benefit of curtailing some of the hypotension that may be associated with GETA. Complications of carotid stents include thrombosis, vessel dissection, dysrhythmias, vasospasm, vessel perforation, cerebral hemorrhage from hyperperfusion, and cerebral embolism (ischemic stroke) [1].

22.6.3 Cerebral Vasospasm

Patients may present to INR for treatment of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. The onset of vasospasm is typically about 5 days after the initial hemorrhage, and the risk of its occurrence is proportionate to the subarachnoid blood burden. Anesthetic management largely entails *hypertensive euvolemia* (no longer the classic "triple H" therapy). Hypervolemia has no proven benefit and leads to a myriad of complications such as pulmonary edema and heart failure. The endovascular treatment of cerebral vasospasm consists of either balloon angioplasty or intra-arterial injection of vasodilators including calcium channel blockers, milrinone, nitrates, or papaverine [23]. Arterial injection of such vasodilators can dramatically lower the blood pressure, for which the anesthesiologist should be prepared. These patients are at high risk of ischemic stroke due to the vasospasm, and the anesthesiologist must maintain cerebral perfusion pressure. Typical goals are systolic blood pressure (SBP) 160–180 mmHg. These patients frequently have ventriculostomies and require ICP monitoring and occasional cerebrospinal fluid drainage intraoperatively.

22.6.4 Arteriovenous Malformation/ Fistula/Tumor Embolization

Embolization therapy can be used to treat a variety of neurovascular lesions including arteriovenous malformations (AVM), fistulas (dural AV, cavernous-carotid), and tumors. Embolization can be done with a variety of agents including polyvinyl alcohol particles, liquid agents, cyanoacrylate glues (*N*-butyl cyanoacrylate or NBCA), or nonadhesive polymerizing agents (ethylene-vinyl alcohol copolymer in a dimethyl sulfoxide solvent known as Onyx®) [20, 24]. However, with any embolization therapy, there are potential complications including vessel rupture, inadvertent passage of the embolization material into the systemic circulation or vessels supplying normal brain, potential to glue the catheter to the injected polymer, and even injection of particulate matter into the pulmonary vessels leading to a pulmonary embolism [20]. Injection of embolic material into the pulmonary vessels is more likely to occur with embolization of the great vein of Galen or larger fistulas/AVMs [20]. For these reasons, deliberate hypotension may be required to help lower the risk of these events [1].

AVMs are a confluence of several feeding arteries into a tangled nidus that is drained by one or more veins. The goal of INR management of AVMs is to occlude as many of the fistulous arteries as possible. This is usually done adjunctively with surgical resection or radiotherapy (gamma knife). AVMs can vary in size and can have a high propensity to bleed during surgical resection. INR is increasingly being used to treat intracerebral AVMs both as a primary treatment and to embolize feeding vessels in hopes of helping minimize blood loss prior to surgical resection [25]. During AVM embolization in the angiography suite, some degree of induced hypotension may be desirable in order to prevent flow through the AVM. This can be accomplished with anesthetics, short-acting vasodilators (nitroglycerin, nicardipine, clevidipine), or even adenosine. A smooth, hemodynamically controlled emergence is also paramount in these patients as the AVM is usually not fully secured on the first treatment and often requires multiple interventions. This keeps the patient at ongoing risk of intracerebral hemorrhage [1].

Dural arteriovenous fistulas (AVF) are lesions that are typically acquired due to opening of potential arteriovenous shunts or stenosis of the dural sinuses [26]. Symptoms vary depending on the involved vessels. Dural AVFs can increase venous pressure, and it should be noted that this can impact cerebral perfusion pressure when determining the blood pressure goals [1].

Craniofacial venous malformations are often congenital and are typically treated with sclerotherapy either for cosmetic reasons or to ablate lesions which impede on the airway or oropharynx. It should be noted that the vascular deformities can enlarge after the injection, with potential to impact the airway [1].

22.6.5 Strokes

Anesthesiologists are encountering increasing numbers of patients presenting for endovascular treatment of acute ischemic stroke (AIS). In 2015, multiple prospective randomized controlled trials were published, all demonstrating the superiority of endovascular thrombectomy over intravenous alteplase (TPA) for patients with acute anterior circulation large vessel occlusion (LVO), less than 6 h from onset of symptoms [27–30]. This success is largely credited to the implementation of a new "stent retriever" technology (Fig. 22.6).

The choice of anesthetic type (CS/MAC vs. GETA) has been a hotly debated topic. Because of the extreme urgency in achieving recanalization, and need to minimize door-to-groin and groin-to-reperfusion times, the initiation of the anesthetic must be done in a rapid manner regardless of the type. Multiple *retrospective* studies of patients in the interventional stroke trials demonstrated an association between the use of GETA and increased mortality and/or neurological disability [31–33]. However, concern for selection bias was high as the neurologically "sicker" patient often does not meet criteria for CS/MAC. Fortunately, we now have data from three *prospective* trials conducted in Europe (SIESTA, ANSTROKE, and GOLIATH) [34–37]. These trials randomized patients with acute anterior circulation LVO to GETA or CS/MAC and demonstrated *no* difference in neurological outcome at 24 h or 3 months post-stroke. Although there was a slight delay in the time to initiate GETA compared to CS/MAC, there was a shorter procedural time in the GETA group, presumably from providing more optimal procedural conditions, less patient movement, and less motion artifact, thus resulting in no overall time delay.

At present, the anesthetic management of the patient is an individualized decision to be made between the anesthesiologist and the interventionalist. GETA is considered a safe option for the patient presenting for acute stroke intervention. Maintenance of cerebral perfusion pressure (SBP 140–180 mmHg) is of the utmost importance. Intravenous or inhalational anesthetics are acceptable (both were

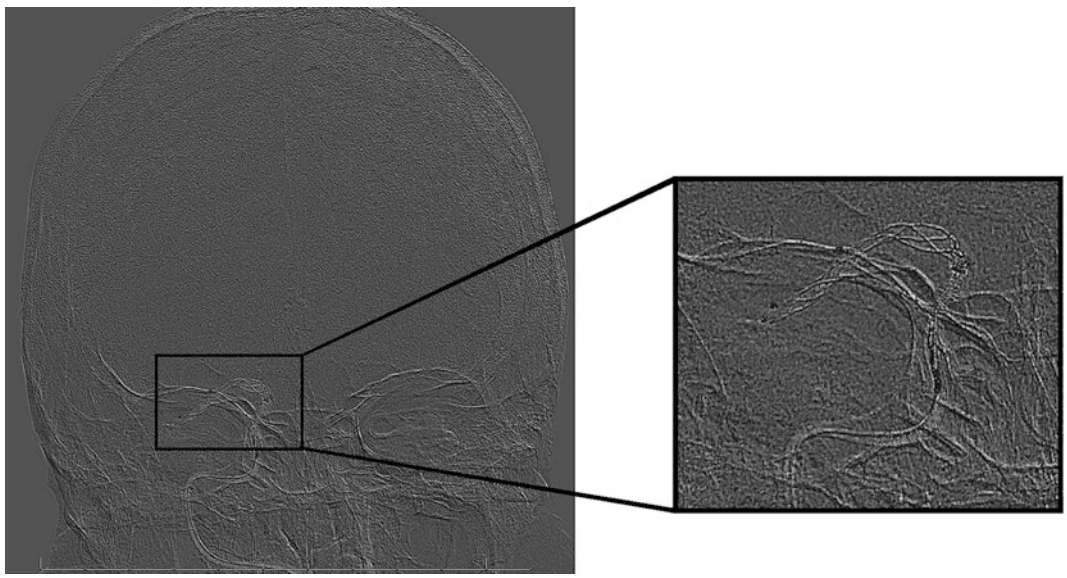

Fig. 22.6 Stent retriever technology at the right internal carotid artery terminus

used in the different prospective trials). Looking ahead, new evidence from the DAWN trial suggests that some patients with small core infarcts and large penumbral regions based on CT or MR perfusion imaging can be treated with endovascular thrombectomy up to 24 h post-ictus [38]. This will continue to increase the number of endovascular stroke thrombectomy patients that anesthesiologists will encounter worldwide as we move into the future.

22.7 INR Complications

The two primary neurologic complications of INR procedures are intracerebral hemorrhage and thromboembolic complications [20], as discussed above.

As with any medication administration, anaphylaxis is possible from medications administered by the anesthesiologist or from contrast given intra-arterially by the interventionalist during the procedure. Epinephrine, inhaled β-2 agonists, steroids, and antihistamines should be available in the INR suite should they become necessary. Pretreatment with corticosteroids and/or antihistamines to prevent such reactions remains controversial [39].

Administration of contrast media can also lead to contrast-induced nephropathy. Patients considered to be at the highest risk include those with pre-existing renal insufficiency (serum creatinine >1.5 mg/dl), diabetes mellitus, volume depletion, myeloma, hypertension, hyperuricemia, advanced age (>70 years), cardiovascular disease, and the use of diuretics. Patients at high risk should be considered for preventative measures such as hydration with 0.9 or 0.45% saline at 100 mL/h for 6–12 h pre-procedure and continuing for 4–12 h afterward. The minimum necessary dose of contrast media should also be utilized in these patients [39].

Groin hematoma, retroperitoneal hematoma, and femoral pseudoaneurysm are also potential complications from arteriotomy. Closure devices, groin pressure, lying flat, and strict hemodynamic control are typically used to help prevent such complications from occurring.

Finally, intra-arterial cerebral air emboli are always a risk. Nitrous oxide should be avoided. Clinically significant air emboli (i.e., large enough to cause neurologic symptoms on emergence) should be treated with 100% inspired oxygen followed by emergent hyperbaric oxygen therapy in a hyperbaric chamber [13, 40, 41].

Ongoing communication with the neurointerventionalist is essential in order to be alerted early to complications, provide timely intervention, and plan for post-procedural care.

22.8 Conclusion

We will continue to see a steady increase in neurointerventional procedures as imaging technology and endovascular devices evolve and improve. Similarly, we will see increasing endovascular stroke interventions as we are able to expand the treatment window using advanced neuroimaging.

Anesthesiologists should keep the following five points in mind when approaching INR cases:

1. Cerebrovascular pathology varies widely between patients. Discuss the specific pathology and planned procedure with the interventionalist.
2. Agree on hemodynamic goals (with the interventionalist) so that everyone shares the same game plan. This is true for both elective and emergent cases.
3. Discuss the degree of urgency of emergent cases and the planned intervention. There is tremendous variability between patients.
4. Discuss the risk for central nervous system injury from *hypotension AND/OR hypertension*. In other words, how fragile is the individual patient's cerebrovascular condition?
5. Finally, plan for the postoperative period in terms of airway management and hemodynamic goals.

Key Points

- Cerebrovascular pathology varies widely between patients. Discuss the specific pathology and planned procedure with the interventionalist.
- Agree on hemodynamic goals (with the interventionalist) so that everyone shares the same game plan. This is true for both elective and emergent cases.
- Discuss the degree of urgency of emergent cases and the planned intervention. There is tremendous variability between patients.
- Discuss the risk for central nervous system injury from hypotension AND/OR hypertension. In other words, how fragile is the individual patient's cerebrovascular condition?
- Finally, plan for the postoperative period in terms of airway management and hemodynamic goals.

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Anesthesia for Gamma Knife Surgery

23

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23.1 Introduction

Henri Becquerel discovered radioactivity, defined as "the ability of some unstable elements to emit certain particles or certain forms of electromagnetic energy while they attain stability and convert into a stable configuration." The particles and radiations that these elements emit have found wide applications in medicine. They have been used as tracers in diagnostic procedures, for example, technetium 99M, phosphorus 32, iodine 131, etc. Others such as cobalt-60 and cesium-137 are widely used to treat cancer, known as *radiation therapy*.

Radiation therapy kills cancer cells by damaging their DNA [1]; however, they can have devastating effects on the normal body cells too. Hence, there is need to administer these radiation elements specifically targeting the tumor cells while protecting the normal body tissue from it.

Gamma knife surgery is a type of radiation therapy, which utilizes highly sophisticated equipment to focus around 200 tiny beams of radiation on a tumor or other target with high accuracy. Although each beam passing through the brain tissue has very little radiation effect individually, a very strong dose of radiation gets delivered to the area where all these beams converge. This precision results in minimal damage to the healthy tissues surrounding the target.

Fig. 23.1 A gamma knife machine (perfexion model)

The first gamma knife device was developed by Leksell, who used cobalt-60 as the energy source. However, it was specifically designed for functional neurological surgery, that is, for movement disorders, pain, and certain behavioral disorders that were not responsive to conventional psychiatric treatment. Leksell termed his new surgical technique as "stereotactic radiosurgery."

Currently, four models of gamma knife machine used around the world are the U, B, C, and the Perfexion model (Fig. 23.1).

23.2 Advantages of Gamma Knife Surgery

Gamma knife surgery scores over traditional surgery in having several advantages. They are listed in Table 23.1.

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Table 23.1 Advantages of gamma knife surgery

1. There is no need of any form of surgical incision on patient's body, and hence there is no pain postoperatively, and no blood loss intraoperatively and no surgical site infection
2. It is an outpatient procedure and gets completed within a day
3. Patients can return to their normal routines the very next day
4. In the majority of adult patients, there is no need to administer anesthesia
5. It is less expensive than the conventional surgery
6. It eliminates lengthy postsurgical hospital stay and disabilities and minimizes rehabilitation costs
7. Gamma knife surgery has been found to be effective in many deep-seated tumors which are difficult to approach by conventional surgery
8. It has a very high precision

Most common side effects of gamma knife surgery are minor swelling of the scalp, skin irritation, hair loss, nausea, headache, brain swelling, and necrosis.

23.3 Indications of Gamma Knife Surgery

The gamma knife is primarily used to treat benign brain tumors, craniopharyngiomas, AV malformations, pituitary adenomas, acoustic neuromas, brain metastases, other tumors of the skull base, and pineal region tumors. Certain specific group of patients with movement disorders and trigeminal neuralgia can also be treated successfully using this procedure.

23.3.1 Gamma Knife Procedure

The patient undergoes placement of a stereotactic frame to the head, which is a mechanical guidance device, after admission to the hospital. During stereotactic frame placement, a mild sedative agent is administered by an anesthesiologist after a thorough pre-anesthetic evaluation, and the location and type of tumor or AVM are evaluated with computed tomography (CT), angiography, or magnetic resonance imaging (MRI). Then the patient's head is placed within a large helmet-like device with small openings called "collimator ports." The beams of radiation are then adjusted through these ports to direct the appropriate amount of energy precisely at the target tissue where the tumor or AVM resides.

Fig. 23.2 Application of stereotactic frame in the patient preparation area

23.4 Parts of a Gamma Knife Suite

A typical gamma knife suite has the following components:

1. *Patient preparation area* – the frame is fixed to the head of the patient in this area before imaging and treatment (Fig. 23.2). The patient is also stabilized and monitored after the radiosurgery procedure.
2. *Treatment room* – where the actual procedure takes place.
3. *Control area* – it contains the instrument control panel and the alarms, the emergency shut-off, and all audio-visual communications with the patient in the treatment room.

4. *Dosimetry* – it is the space where the neurosurgeon and physicist undertake three-dimensional planning of the doses, the dose rate adjustments, and the lesion configuration.
5. *Support spaces* like a nursing station, clean supplies, dressing areas, toilets, soiled utility area, offices, and waiting area.

Most stereotactic radiosurgery procedures in adults are performed without anesthesia. However, general anesthesia is frequently required in the pediatric population and in some of the uncooperative adult patients.

If the procedure is to be undertaken under general anesthesia/sedation, the patient is induced in the patient preparation room, shifted for imaging and then to the treatment room, and finally back to the preparation area where he can be awakened. An anesthetist with an anesthesia technician must always accompany the patient from the beginning to the end of the procedure.

23.5 Anesthesia Considerations

Perhaps the biggest task of an anesthetist attending to these patients is to ensure availability of all anesthesia and resuscitation equipment and to coordinate with the persons of other specialties in ensuring smooth conduct of anesthesia during the gamma knife surgery. It is most imperative to ensure the availability of adequate oxygen supply, suction equipment, difficult airway equipment, and routine and emergency drugs. The whole process must be scheduled and coordinated in advance so that there is no time loss at each of the treatment sites.

There are two types of special considerations in patients undergoing gamma knife surgery. One would be regarding administration of general anesthesia in the nonoperation theatre settings or in an isolated area away from the routine OT settings. The second type of considerations would be regarding the type of patient themselves and their concerns (e.g., pediatric population, uncooperative adults, etc.).

The gamma knife suites may not always be designed to be conducive for administering general anesthesia or sedation with proper monitoring. In addition, the staff working at these suites may not have adequate knowledge of implications of working when general anesthesia or sedation is involved. The golden rule would hence be to take care of all these factors before administering anesthesia rather than having problems cropping up when the patient is anesthetized.

While the adult patients usually undergo the procedure under monitored anesthesia care (MAC) or sedation, children have to be administered general anesthesia.

23.6 Administering Anesthesia in Gamma Knife Suites

Certain physical factors need to be considered before administering anesthesia in gamma knife suites. They are listed in Table 23.2.

23.7 Preanesthetic Checkup (PAC)

A minimum PAC should include a review of patient's clinical history, clinical examination including airway examination, and relevant laboratory examinations. The guidelines regarding pre-anesthetic evaluation and NPO duration apply to these patients as well [3].

Also, extensive discussion and planning with the neurosurgeons and radiologists involved should be done prior to the procedure.

Table 23.2 Physical factors before anesthesia delivery in gamma knife suites that need to be considered

1. Access to patient is simply not possible during the procedure. The patient can be monitored only by means of a closed-circuit camera
2. Absolute immobility of the head is required till the time the stereotactic frame is in place [2]
3. The procedure may require longer duration of anesthesia (even up to 12 h)
4. The anesthetized patient has to be shifted to multiple locations within the hospital

23.8 Monitored Anesthesia Care (MAC)

The American Society of Anesthesiologists (ASA) defines monitored anesthesia care (MAC) as a planned procedure during which the patient undergoes local anesthesia together with mild sedation, and analgesia is provided by an anesthesiologist [4]. Systemic analgesia and sedation is provided by an anesthesiologist, and local anesthesia, including local infiltration or field block, is mainly performed by a surgeon. MAC is provided by an anesthesia care team unlike simple sedation/anesthesia provided by a non-anesthesiologist. The objective of MAC is to provide safe sedation, comfort, pain control, and satisfaction to the patients. Patient's cooperation is imperative for administration of MAC.

Thorough preoperative evaluation, perioperative management, neuromonitoring, and postoperative recovery care of MAC are similar to those patients who receive general or regional anesthesia. Moreover, the attending anesthesiologist should be aware of the various possibilities of airway obstruction, desaturation, or even aspiration due to the deep sedation. Presently, there is scarce literary evidence on the drugs for providing MAC to gamma knife surgery patients. However, opioids like fentanyl and remifentanil and benzodiazepines like midazolam and propofol have been well utilized.

Propofol has long been the most popular agent for sedation and has been used for a variety of procedures. The pharmacokinetic profile of propofol makes it a suitable choice for sedation, even for longer-duration procedures due to its short context-sensitive half-life. This choice should always be weighed, however, against the hemodynamic side effects, tolerance, and rare occurrences of hypertriglyceridemia (and potential pancreatitis) or propofol infusion syndrome. Generally, patients are amnesic at propofol infusion rates of more than 30 μg/kg/min.

Dexmedetomidine is a relatively newer, α2-adrenergic receptor agonist having sedative, anxiolytic, hypnotic, analgesic, and sympatholytic effects. It has been comparable to propofol without its disadvantages or adverse effects [5].

When used for conscious sedation during neurosurgical procedures, patients were able to wake up using verbal stimulation but could not complete neurological testing [6–8].

However, Fahy and Okumura reported that dexmedetomidine proved to be inadequate as a sole sedative drug in a child undergoing stereotactic radiosurgery and required supplementation with other agents [9].

Midazolam, a benzodiazepine, is another agent which has been used for sedation in a wide range of procedures. It also provides anterograde amnesia in patients [10, 11]. Its advantages include water solubility, rapid onset and offset of action, shorter duration, and having an anticonvulsant action. Its metabolites are clinically inactive and have a relatively high margin of safety. Also, a reversal agent, flumazenil, is available in case a rapid reversal of its sedative action is required. Many a times, fentanyl is also administered with midazolam for effective sedation and analgesia.

Whenever a patient is administered sedation, the anesthesiologist should always be prepared adequately to convert it into general anesthesia at any time, concerning about the paramount safety of the patient. Should the need arise, adequate stores of all the necessary drugs and equipment should always be available.

23.9 Application of a Stereotactic Frame

The stereotactic frame is applied in the patient preparatory area usually after infiltration of local anesthetics. Liang and colleagues used a topical application of a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine cream (EMLA) 60 min before frame application and observed that the EMLA group reported significantly lower pain scores 20 and 60 min after frame removal than did the placebo group [12]. However, Duenas et al. assessed the efficacy of EMLA (2.5% lidocaine/2.5% prilocaine) in pain reduction and found it to be ineffective [13]. Harris suggested that adding sodium bicarbonate to local anesthetic while infiltrating the pin sites may have beneficial effects [14]. The patient can be given

some mild IV sedation usually lorazepam or midazolam in a dose of 0.5–1.0 mg before application of frame pins. During application of pins, various complications such as dislodgement of the pins, pin site infections, and skull fracture or penetration followed by subdural and extradural hematomas, arteriovenous fistula, venous air embolism, and pseudoaneurysm formation have been reported [15–19]. The anesthetist must be ready to address these complications and manage them accordingly. Airway emergencies with stereotactic frame in situ may be related to a primary underlying condition or may be secondary to oversedation or due to an intraoperative neurological insult such as seizures [20–22].

Also, managing the airway with the headframe in situ can be quite challenging. Verma et al. observed that general anesthesia for pediatric radiation therapy is quite safe and oxygen delivery via nasal cannula during propofol anesthesia offers the lowest immediate anesthetic complication rates [23].

The headframe limits access to the patient's airway because it covers some or all of the patient's mouth and nose; and in addition, it also restricts neck movements. Removing the headframe can be time-consuming, and after the frame is removed, the patient must return to magnetic resonance imaging (MRI) suite or computed tomography scanner to reestablish the external coordinates before he can proceed for the surgery.

Therefore, ideally, during an emergency scenario, the airway should be secured while the patient remains in the headframe so that the surgery can continue. Since the frame will restrict further access to the patient's airway, it is imperative that the patient is transported with the appropriate tools (screw drivers of appropriate sizes etc.) to quickly remove the frame in case immediate airway access becomes essential (Fig. 23.3).

Fig. 23.3 Screw drivers of all sizes and tools for application and removal of the frame

Table 23.3 Perioperative fasting guidelines

Clear liquids – 2 h
Breast milk – 4 h
Infant formula feed – 6 h
Solid feed – 8 h

23.10 General Anesthesia (GA)

For pediatric population, it is widely stated that they do not have the understanding and capacity to lie still during radiosurgical treatment [24, 25]. Adult claustrophobic patients, uncooperative/mentally retarded, those having movement disorders, or those fearful of frame application may also require general anesthesia.

Pediatric patients need to be administered GA before the frames can be applied, as children do not tolerate frame application under local anesthesia. Also, intubation may become difficult after application of the stereotactic frame. These patients are very susceptible to hypoxia and hypercapnia due to intracranial pathologies.

23.10.1 Fasting Guidelines

The perioperative fasting guidelines (Table 23.3) are the same as for any other operative procedure.

23.11 Premedication

The administration of premedication in pediatric patient population allays anxiety, provides amnesia, and reduces anesthetic drug requirement [26].

A number of drugs (clonidine, midazolam, ketamine, dexmedetomidine, etc.) and modes of administration (oral, intramuscular, intravenous, rectal, sublingual, intranasal, etc.) have been used with varying success [26–28]. The decision to administer premedication should be individualized and strictly done under adequate monitoring of heart rate (HR), breathing, and oxygen saturation (SpO_2), taking into consideration the present status of patient.

23.12 Monitoring

Minimum monitoring standards must include an oxygen saturation probe (SpO_2), electrocardiogram (ECG), noninvasive blood pressure (NIBP) monitoring, and end-tidal carbon dioxide ($EtCO_2$). In addition, there must be provision for additional monitoring which may be required on a case-to-case basis. End-tidal CO_2 monitoring is especially important so as to maintain normocarbia or slight hypocarbia (if needed) in these patients, in addition to ruling out esophageal intubation. Foley's catheter is inserted to monitor urine output keeping into consideration the long duration of procedure. Invasive blood pressure monitoring if done will help prevent problems associated with long-term noninvasive blood pressure measurements [29, 30].

Mobile monitoring systems are required to ensure continuous monitoring of the patients when they are transported from one site to other. Once the patient is in the treatment room receiving radiation therapy, there should be a provision for duplication or demonstration of the patients' vitals on the monitor screen and the ventilator parameters in the control room alongside closed-circuit camera view (CCTV) from where the anesthetist can monitor the patient.

23.13 Induction

Propofol still remains the most commonly used inducing agent. As gamma knife suites may not have vaporizers and scavenging systems, many anesthetists have used only intravenous agents for induction [31, 32]. However, inhalational induction with sevoflurane is an option when the child does not have an IV cannula and vaporizers are available.

A difficult airway cart containing endotracheal tubes of relevant sizes, oral and nasal airways, bougies, laryngoscopes, and supraglottic airway devices must be available. The equipment should be independently set up in different locations where the patient is to be transported during the procedure.

Maintenance of general anesthesia is usually done with TIVA to prevent procedure room pollution. Edler [31] used propofol and remifentanil infusion in their patients, while Bauman et al. [32] used only propofol infusion. Bone and Bristow [33] used TIVA in their patients with propofol infusion, fentanyl, vecuronium, and oxygen in air during stereotactic radiosurgery. Some anesthesiologists have shrugged from using muscle relaxants in these patients and have kept patients spontaneously breathing in addition to supplementation with positive pressure ventilation.

Weninger et al. [34] compared propofol sedation using TCI-system, propofol sedation using manual technique, and sedation using methohexital-sevoflurane in 51 patients undergoing stereotactic brain biopsy and found all 3 techniques to be suitable for general anesthesia in diagnostic neurosurgery. Kamata et al. [35] described a manually controlled regimen of propofol appropriate for gamma knife surgery in a child and suggested that when TCI systems are not available, combination of a small bolus and continuous infusion administered manually might be a good substitute.

If the procedure involves MRI examination of the patient, MRI-compatible instruments and equipment have to be made available (including MRI safe infusion pumps, MRI-compatible anesthesia machines and ventilators). Also, one must be aware of the possibility of development of anaphylactic reaction upon administration of IV contrast agents. During longer-duration scans, staff and patients (awake or anesthetized) must

wear some kind of ear protection devices to protect against loud acoustic noise [36]. During MRI, the airway of patient becomes completely inaccessible.

These patients are predisposed to develop hypothermia because of cool ambient temperatures and impairment of heat-regulating and heat-dissipating mechanisms during general anesthesia [37].

The use of warming devices and adequately covering the patients will help prevent occurrence of hypothermia.

Adequate care must be taken to secure all the pressure points with adequate padding. Eyes should be taped shut, and artificial tears should be administered at regular intervals to ensure adequate lacrimation. Sequential compression devices may be used in view of prolonged immobility.

A very important consideration is ensuring smooth transport of patients from one place to another inside the hospital premises. When the patient is being transported, the anesthetist must make sure that adequate oxygen supply, anesthetic and emergency drugs, and all necessary equipment are available at all times. Also, coordination between all the physicians involved will diminish waiting as well as the transport time.

23.14 Extubation and Recovery

Once the procedure is complete, the patient is assessed for adequacy of extubation on the basis of cerebral pathology, preoperative status, cardiovascular hemodynamics, and core temperature of the patient. It is always advisable to ventilate the patient electively for a few hours if the patient is not adequately warmed, especially infants and smaller children. Routine antiemetics must be administered prior to extubation.

The administration of GA for gamma knife has its own share of complications. Stokes et al. documented 4 potentially serious anesthesia-related events when GA was administered to patients for 68 procedures, including endotracheal obstruction, emesis, lobar collapse, and copious endotracheal secretions [38].

23.15 Sedation

Sedation has been employed in both adult as well as children undergoing gamma knife surgery.

Kondziolka et al. [39] administered 100 adult patients with sublingual lorazepam (1 mg) and IV midazolam (1 mg/ml, with most of the patients receiving 1 mg) and fentanyl (100 μg/2 ml, with most of the patients receiving 50 μg). Only 4 out of the 100 patients were uncomfortable during the procedure.

Harris [14] describe the use of propofol and ketamine while applying frame in pediatric patients; however, in the absence of ability to maintain airway, the consequences of using these drugs can be catastrophic.

Moreover, the concerns with sedation are sudden movement of the patient which can cause pin displacement and head injury, along with respiratory complications like oxygen desaturation, airway obstruction, and aspiration of gastric contents. There may be loss of integrity of the airway requiring emergent intubation.

23.16 Conclusion

Gamma knife surgery involves lots of precision and planning and is a team effort of the neurosurgeon, anesthesiologist, neurologist, and neuroradiologist. It involves shifting of the patient in an anesthetized state to various remote locations inside the hospital. In addition, the total procedure can have long duration of up to 12 h. All necessary equipment should be present at all the locations beforehand to ensure safe administration of anesthesia. Prior preparation and effective coordination between all the concerned specialties involved are the key to make anesthetic management of this procedure a success.

Key Points

- Gamma knife surgery is a type of radiation therapy, which uses specialized equipment to focus about 200 tiny beams of radiation on a tumor or other target with high accuracy after placement of a stereotactic frame on the head of the patient.
- It is used primarily to treat benign brain tumors, craniopharyngiomas, AVMs, pituitary adenomas, acoustic neuromas, brain metastases, other tumors of the skull base, and pineal region tumors. Selected patients with movement disorders and trigeminal neuralgia can also be treated.
- Gamma knife surgery can be done under mild sedation, monitored anesthesia care, and general anesthesia depending upon the patient and surgical characteristics.
- Advantages of gamma knife include early hospital discharge, incisionless tumor shrinkage, noninvasive nature, high precision, and effectiveness against deep-seated lesions in the brain.
- The main problems associated with administering anesthesia to such patients include extremes of age, comorbidities, and administering sedation or anesthesia at remote and unfamiliar locations.

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24 Infection Control in Operating Rooms: Sterilization and Disinfection Practices

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24.1 Introduction

Operation rooms (ORs) are highly critical patient-care areas, where utmost cleanliness and highest levels of sterilization/disinfection practices must be observed. Apart from a robust engineering standard of OR structure, it is essential that staff should be trained and monitored for observing best practices/protocols for in the ORs in order to prevent surgical site infections (SSIs). Prevention of SSIs requires a multipronged approach involving ventilation engineering, appropriate disinfection and sterilization practices, maintenance of OR discipline and protocols, and continuous education of staff [1, 2].

24.2 Cleaning of Operating Rooms

The inanimate theatre environment usually has a negligible contribution to the development of SSIs. However, the surfaces should be kept free of visible dirt and the floors should be dry. For cleaning of ORs, use only vacuum cleaners or wet mopping. The cleaning equipment for the ORs must be dedicated and kept separate from the outer zone [3–6].

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Although in the absence of visible soiling or contamination, it is logical to perform routine decontamination of these surfaces to recreate a clean environment after each operation, there are no evidence to support routine disinfection of environmental surfaces or equipment between operations [3–7]. When there is visible soiling of equipment or surfaces during an operation, an EPA-approved hospital disinfectant should be used to clean the affected areas before the next operation. It should be ensured that medical equipment left in the OR are covered so that solutions used for decontamination do not contact them [3–6].

Cleaning Schedule At the start of the day, clean floors and all horizontal surfaces (examination couches, operating tables, trolley tops or mayo stands, chairs, lamps, sinks, counters, door handles, shelves, office furniture) and other noncritical surfaces with an EPA-approved detergent/low level disinfectant [3–6]. Between patients, clean operating tables, trolley tops, examination couches, counters, lamps, and any other potentially contaminated surfaces in procedure rooms and operating theatres with a cloth dampened with a low level decontaminator solution (used according to manufacturer's recommendations). Immediately clean spills of blood or other body fluids as detailed below. Mop buckets for spillage should be emptied after each use and kept dry until next use. Lint free cloth is recommended for all operating theatre cleaning.

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Empty the waste and sharps disposal containers when they are three-quarters full. Data does not suggest special cleaning measures or closing of an operating theatre after a dirty or contaminated operation has been done. Thorough, routine disinfection is appropriate to provide a safe environment for subsequent operations given the high frequency of air changes in ORs. At the end of session or day, wet vacuuming of the floor with a hospital disinfectant which is EPA-approved should be done. An appropriate floor-scrubbing machine may also be used. Mops should be hot laundered and dried daily. Horizontal surfaces must be damp-dusted with paper cloths or single-use fabric. The sluice should be cleaned with warm water and detergent. The walls with undamaged surfaces acquire very few bacteria even if left unwashed for long durations. However, they should not be allowed to become visibly dirty and should be washed at least every 3–6 months. If parts of paint peel off, the wall should be repainted [3].

Fumigation Routine fumigation is not advocated in current day OT practices. Thorough washing and disinfection of surfaces, if done everyday after the surgeries, is more beneficial than fumigation.

The amount of equipment in operating rooms should be kept minimal. Equipment should be stored under clean conditions and be disinfected or cleaned regularly. Items should be arranged neatly, so that staff movement is minimal. Placing of trolleys in advance of the procedure involves the risk of contamination. Some of the benefits of UCV air will be negated by not unwrapping instruments in the UCV area or not covering them subsequently [8].

24.3 Sterilization and Disinfection

The protocols for sterilization/disinfection should be based on the classification devised by EH Spaulding, as shown in Table 24.1 [9].

In 1991, the CDC proposed an additional category designated as "environmental surfaces" to the Spaulding's original classification [10] to represent surfaces which do not come in contact with patients and thus have minimal risk for transmitting infections [11]. Environmental surfaces are further divided into clinical contact surfaces (healthcare equipment or high-touch surfaces) and housekeeping surfaces. Clinical contact surfaces are those which can act as reservoirs for microbes with the potential for secondary transmission (through the hands of the healthcare workers (HCW) or through equipment that subsequently contacts the patients (e.g., light switches, telephones, countertop, door knobs, etc.)) [11, 12]. These should be disinfected with an EPA-registered low- or intermediate-level disinfectant.

Blood/body fluids spills must be promptly disinfected and cleaned as per the following methods:

All equipment and surfaces contaminated with blood and other potentially infectious material must be disinfected with an appropriate disinfectant. PPE (gloves, face masks, fluid resistant gowns) must be used for cleaning blood spills. Small spills should be cleaned and disinfected using an intermediate level germicide having a tuberculocidal claim. For decontamination of small spills (<10 ml), if sodium hypochlorite solution is selected, use a 1:100 dilution (a 1:100 dilution of 5.25–6.15% sodium hypochlorite provides 525–615 ppm of available chlorine). If

Table 24.1 Spaulding's classification of devices

Item/device	Definition/intended use	Risk of infection	Reprocessing required	Example
Critical	Medical device intended to enter a normally sterile tissue/vasculature	High	Sterilization	Surgical instruments/ implants/needles
Semi-critical	Devices that are intended to come in contact with mucous membrane or non-intact skin	High/ intermediate	Sterilization desirable HLD acceptable	Respiratory therapy equipment, some endoscopes
Noncritical	Devices that come in contact with intact skin	Low	Intermediate or LLD	BP cuff, stethoscope

spills involve large amounts (e.g., >10 ml) of blood or OPIM, or involves a culture spill in the laboratory, a 1:10 dilution of hypochlorite solution for first application (before cleaning) reduces the risk of infection during cleaning. After the first application, remove the visible organic matter with absorbent material (e.g., single-use paper towels discarded into labeled leak-proof container), and then terminal disinfection with 1:100 sodium hypochlorite may be done [13].

24.4 Cleaning of Medical Equipment

Thorough cleaning, done at the point of use, must precede any disinfection or sterilization process. Cleaning is a form of decontamination, which renders the equipment safe to handle and removes the organic and inorganic matter that shield microorganism, rendering the subsequent sterilization/disinfection ineffective. Thus, cleaning alone (physical scrubbing with surfactants and detergents followed by washing with water) effectively removes a large number of microorganisms from contaminated equipment and surfaces. Cleaning should be done using a detergent/soap and water. A neutral/near neutral pH detergent solution is frequently used because such solutions usually have the best material compatibility and good soil removal. Enzymes (usually proteases) are occasionally added to assist in removing organic material. Neutral pH detergent solutions containing enzymes are the preferable method of cleaning sensitive equipment like flexible endoscope [3, 11–17].

The sterilization and disinfection are essential to render a device or equipment free of microbial contamination and safe for reuse.

24.4.1 Sterilization [11, 14–16, 18, 19]

Sterilization can be attained by either physical or chemical methods. Pre-cleaning to remove all the organic matter must be done for all instruments undergoing sterilization. Equipment which can withstand heat and moisture must be sterilized by autoclaving since it affords a wide margin of safety and allows packaging of loads which is important to prevent post-processing contamination. The FDA has approved a few high-level disinfectants which can be used for chemical sterilization if the exposure time is prolonged. These chemicals must be used as per the manufacturer's instructions for use concentration, contact time, temperature, product compatibility, and shelf life. A disadvantage of chemical sterilization is that items cannot be packed and therefore must be used immediately. The disinfectants also need to be rinsed off thoroughly to prevent toxicity. Moreover, there are no reliable biological indicators for monitoring chemical sterilization.

The resistance to disinfection methods varies among microbes. Accordingly, prions, coccidia, spores, mycobacteria, cysts, small non-enveloped viruses, trophozoites, Gram-negative bacteria, fungi, large non-enveloped viruses, Gram-positive bacteria, and lipid-enveloped viruses represent a descending order of resistance to disinfectants [11, 15, 16].

Sterilization can be done by the following methods.

24.4.2 High-Temperature Sterilization

24.4.2.1 Steam Under Pressure (Autoclaves) [3, 11, 14–16, 18]

It is the most efficient and reliable method of sterilization. It is used for sterilization of all critical and semi-critical items that are heat and moisture resistant (surgical instruments, surgical drapes, some respiratory and anesthetic equipment, microbiological waste, and sharps).

Monitoring of Steam Sterilization Process The residual air detection for vacuum sterilizers is to be done daily by the Bowie-Dick test. For this, commercially available Bowie-Dick type test sheet must be placed in the center of the pack. The test pack should be positioned horizontally in the front, bottom segment of sterilizer rack, adjacent to the door, and over the drain in an otherwise empty chamber and run at 134 °C × 3.5 min. If the

sterilizer fails the test, do not use until remedied. Mechanical and chemical monitoring should be done with each cycle. For biological monitoring, *Geobacillus stearothermophilus* spores 10^5 must be used at least weekly (preferably daily) and with each load of implantable devices. Loads containing implantable devices should ideally be quarantined until the results of biological indicators are available.

24.4.2.2 Flash Sterilization [11, 20–22]

This is a high-temperature, rapid, steam sterilization procedure (132 °C at 27–28 lbs × 3–4 min) of unwrapped items for emergency situations. The items are placed in an open tray or specifically designed, covered rigid container for quick penetration of steam.

It is used for sterilization of heat-tolerant, critical medical devices, which are to be used immediately and cannot be packaged and stored. It may be used in emergencies (orthopedic screws). It should not to be used for implants. For its monitoring, mechanical and chemical tests should be done with each cycle. For biological monitoring, there are no suitable timely indicators. A recently developed Attest rapid readout biological indicator detects the presence of a spore-associated enzyme (α-D-glucosidase) in 1 hour. Use biological indicators at least weekly (preferably with each cycle).

24.4.3 Low-Temperature Sterilization [3, 11, 14–16, 18, 23]

24.4.3.1 Ethylene Oxide (EtO) [11, 14–16, 18]

EtO gas must penetrate the entire load. It should be handled according to strict guidelines. Items must undergo aeration to remove residual EtO. It is used for sterilization of heat and moisture labile critical and semi-critical items and for sterilization of devices containing electronic components. The mechanical of EtO should be done with each cycle (time, temperature, pressure). Chemical monitoring should also be done with each cycle. For biological monitoring, *Bacillus atrophaeus* spores (10^6) should be used at least weekly (if possible daily) and with each load of implantable devices. Loads containing implantable devices must ideally be quarantined until the results of biological indicators are available.

24.4.3.2 Hydrogen Peroxide (H_2O_2) Gas Plasma [11, 15, 16, 23–25]

Gas plasmas are the fourth state of matter. They are generated by exciting a chemical precursor (H_2O_2) under a deep vacuum in an enclosed chamber using radiofrequency/microwave energy. This produces highly reactive and biocidal charged particles, many of which are free radicals. The free radicals react and inactivate essential cellular components (enzymes, nucleic acids) of microbes.

24.4.3.3 Sterrad Sterilizers

The Sterrad sterilizers have been the first plasma phase sterilizer, in use since the 1990s. The initial Sterrad 100 systems could sterilize lumened devices with single lumens ≥3 mm in diameter and ≤40 cm in length. The Sterrad 100 was replaced with the 100 S series, which had an added cycle, with resultant reduced sterilization time. It is used for sterilization of devices which are heat and moisture sensitive (plastic, electronic devices, corrosion-sensitive metals), like arthroscope and its instruments, micro instruments, vascular instruments, spine sets, pneumatic drills, dermatomes, micro and mini drill, implants, urethroscope and its instruments, laparoscope and its instruments, thoracoscope and its instruments, laparotomy set, nephrectomy set, microvascular instruments, dental implants, craniotomy sets, tracheostomy set, image-intensifying cover, retractors, bone nibblers, and ophthalmic instruments. The physical and chemical monitoring is inbuilt with each cycle. For biological monitoring, spores of *G. stearothermophilus* (read at 48 hours) should be used. The system has its own monitor in plastic vials, which should be incorporated at least weekly (preferably daily).

24.4.3.4 Chemical/Liquid Sterilization

These should be considered only if single use is not cost-effective and other sterilization methods cannot be used. Any liquid chemical sterilant

approved by FDA may be used in such situations. The choice should be primarily based on material compatibility, time, use conditions, and cost. Strictly follow the manufacturer's instructions of use. Use the items immediately since once the items are unpacked, they are liable to get contaminated. Another disadvantage is that suitable biological indicators are not available to monitor chemical sterilization.

24.4.3.5 Peracetic Acid (STERIS System-1) [11, 15, 16, 23, 24]

An automated machine using PAA (STERIS-1) has been approved by the FDA for chemical sterilization of medical and surgical equipment. It is a low-temperature chemical sterilization process. It works on the principal of oxidizing agent which denatures proteins, disrupts cell walls, and oxidizes sulfhydryl groups. The time to sterilization is 45 min. It is used for sterilization of medical and surgical endoscope. Chemical monitoring strips which detect the active ingredient (at >1500 ppm) are used as process control. Use manufacturer's clip to hold the strip. *G. stearothermophilus* (10^5) spores are used for biological monitoring, at least weekly, although daily monitoring is ideal.

24.4.3.6 Low-Temperature Sterilization with Ozone [11, 16]

A low-temperature sterilization using ozone has been recently cleared by FDA. It uses medical grade oxygen, water, and electricity. O_2 is energized and split into two monoatomic molecules which react with O_2 to form ozone (O_3). One oxygen atom is loose and is readily available to bind and oxidize cellular components. It is used for sterilization of rigid lumened devices with internal diameter (ID) >2 mm, length ≤25 cm, ID >3 mm, L ≤47 cm, and ID >4 mm, L ≤60 cm.

24.4.3.7 Performic Acid [11, 23]

Endoclens is a new, proprietary liquid chemical sterilization method based on performic acid. This is a fast-acting, sporicidal, automated endoscope reprocessing system. The system provides point of use chemical sterilization of flexible endoscopes.

24.4.3.8 Vaporized Hydrogen Peroxide [11]

It is a rapid, low-temperature sterilization technique based on hydrogen peroxide, which is safe, has a good compatibility, and is easy to use. However, it is not FDA cleared.

24.4.3.9 Disinfection

Disinfection is used to kill organisms present on delicate or heat-sensitive instruments which cannot be sterilized or when single-use items are not available. The level of disinfection varies with the intended use and level of risk of infection associated with its use. Disinfection can be achieved by thermal (pasteurization) or chemical means.

24.4.3.10 Thermal Disinfection (Pasteurization) [3, 11, 14–16, 18]

If an instrument is able to withstand heat and moisture and if sterilization is not required, then thermal disinfection is suitable. Pasteurization is a process of hot water disinfection which is attained through the use of washer disinfectors or automated pasteurizers. Semi-critical items suitable for pasteurization include equipment for respiratory therapy and anesthesia. The degree of disinfection depends on the water temperature and duration of exposure. The items to be pasteurized should be thoroughly cleaned with detergent and water prior to disinfection. They must be totally immersed in water throughout the pasteurization cycle. After pasteurization, special care must be taken to dry and prevent recontamination of the equipment during storage and transport.

24.4.3.11 Chemical Disinfection [3, 11, 18, 26]

Numerous disinfectants are used alone or in combination to serve the purpose of rendering an equipment/surface free of microbes. Commercial formulations of these germicides are unique products, which should be registered with EPA or cleared by FDA. The activity of a disinfectant depends on the temperature, contact time, pH, presence of inorganic or organic

matter, and number and resistance of the bioburden on a surface. Thus, while using the product, the users must comply with the manufacturer's label for use/storage and disposal. HCW must exercise precautions and use appropriate PPE while using disinfectants. There is no single perfect disinfectant. Disinfectants must be used taking into consideration the level of disinfection required, the material compatibility, time required to disinfect, and health hazard. Use only instrument grade disinfectants for equipment and instruments. Household/hospital grade chemicals should be used for noncritical surfaces. Pre-cleaning of instruments must be done to ensure appropriate disinfectant activity. The activity of a disinfectant depends on the chemical composition, concentration, temperature, pH, relative humidity, water hardness, and presence of organic/inorganic matter. A rise in pH improves the action of some disinfectants (glutaraldehyde, quaternary ammonium compounds) but reduces the activity of others (hypochlorites, iodine, phenols). Many disinfectants need dilution prior to use. It is mandatory to follow the manufacturer's instructions exactly as per label regarding its use, dilution, and mixing (higher dilution will reduce activity, and high concentration can damage instruments or cause toxic effects to the users). Use diluted preparations only till recommended shelf life. During use, the minimum effective concentration (MEC) must be regularly monitored depending on the frequency of use.

24.4.3.12 Sterilizing Items Potentially Contaminated with CJD Agents [10, 14–16, 27]

CJD is caused by prions, which resist usual inactivation methods. Human infection with CJD has occurred from iatrogenic exposure of the brain or tissues with CJD-contaminated products and devices (brain electrodes, hormones, grafts, etc.). Specific infection control precautions and decontamination procedures are required to prevent CJD transmission.

Items suspected to be contaminated with prions should be steam sterilized for at least 30 min at 132 °C in a gravity displacement sterilizer. If a prevacuum sterilizer is used, 18 min at 134 °C is effective. Semi-critical and noncritical items may be immersed in 1N NaOH for 1 hour at room temperature and then steam sterilized at 121 °C for 30 min. Alternatively, if the instruments do not tolerate this temperature, they can be cleaned twice, treated with various chemicals such as peracetic acid, iodophor, 3% sodium dodecyl sulfate or 6M urea, and 0.5% sodium hypochlorite (at least 2% chlorine free), and autoclaved at 121 °C for 30 min. Table 24.2 provides the details of liquid sterilants and high-level disinfectants approved for disinfection/sterilization of devices.

Key Points

- Prevention of SSIs requires a multifaceted approach involving ventilation engineering, appropriate disinfection and sterilization practices, maintenance of OR discipline and protocols, and continuous education of staff.
- Prevention of intraoperative infections requires a multifaceted approach involving ventilation engineering, appropriate disinfection and sterilization practices, maintenance of OR discipline and protocols, and continuous education of staff.
- Thorough cleaning, done at the point of use, should precede any disinfection or sterilization process. All equipment and surfaces contaminated with blood and other potentially infectious material should be decontaminated with an appropriate disinfectant.
- The amount of equipment in operating rooms should be kept minimal.
- Sterilization can be accomplished by either physical or chemical methods. The protocols for sterilization/disinfection should be based on the Spaulding's classification.

Table 24.2 Liquid sterilants and high-level disinfectants approved by FDA for processing of medical and dental devices (2009) [19]

Disinfectants	Use dilution	Exposure time/comment
Chemical sterilant (sporicidal)		Sterilization claim
Glutaraldehyde	≥2.4%	10 h at 20–25 °C
		7.5 h at 35 °C
Ortho-phthalaldehyde (OPA)	0.55%	Data not available
Gluteraldehyde with phenol/phenate	1.12%/1.93%	12 h at 25 °C
	0.95%/1.64% [7]	
Hydrogen peroxide with peracetic acid	7.35%/0.23%	3 h at 20 °C
	1.0%/0.08%	
	8.3%/7%	5 h at 25 °C
Hydrogen peroxide	7.5%	6 h at 20 °C
Peracetic acid	0.2%	Only cleared for use with STERIS system
		12 min at 50–56 °C
High-level disinfectants		
Glutaraldehyde (different formulations cleared by FDA)	≥2.0%	5 min at 35/37.8 °C to 90 min at 25 °C
Ortho-phthalaldehyde	0.55%	12 min at 20 °C
		5 min at 50 °C in AER
	0.6%	12 min at 20 °C
Hydrogen peroxide	7.5%	30 min at 20 °C
Hydrogen peroxide and peracetic acid	1.0%/0.08%	25 min at 20 °C
	7.35%/0.23%	15 min at 20 °C
	8.3%/7%	5 min at 25 °C
Hypochlorite and hypochlorous acid	650–675 ppm	10 min at 25 °C
	400–450 ppm	10 min at 30 °C
Glutaraldehyde and phenol/phenate	1.121%/1.93%	20 min at 25 °C
Glutaraldehyde + isopropyl alcohol	3.4%/26%	10 min at 20 °C
Intermediate-level disinfectants		
Ethyl/isopropyl alcohol	70–90%	1–10 min
Sodium hypochlorite	100–1000 ppm available chlorine	30 s–5 min
Phenolic germicide	Manufacturer's product label instruction	~10 min
Iodophor germicide	Manufacturer's product label	~10 min
Low-level disinfectants		
Ethyl/isopropyl alcohol	70–90%	
Sodium hypochlorite	100–1000 ppm available chlorine	≥1 min
Phenolic germicide	Manufacturer's product label	≥1 min
Iodophor germicide	Manufacturer's product label	≥1 min
Quaternary ammonium compounds	Manufacturer's product label	≥1 min

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Intravenous Thrombolysis

25

Vasudha Singhal and Jaya Wanchoo

25.1 Introduction

Stroke, or "brain attack," has classically been described as a neurological deficit caused by an acute focal injury of the central nervous system by a vascular cause, either occlusion or hemorrhage [1]. The burden of stroke is overwhelming. It is the second most common cause of deaths worldwide, after ischemic heart disease [2], and the third most common cause of disability.

In ischemic stroke, the focal neurological injury occurs in a defined vascular distribution, either due to occlusion or stenosis of the perfusing artery. Cell death maximally occurs in the ischemic focus and may extend into the surrounding penumbra. The penumbra may thus be "potentially destined to infarction," but "not yet irreversibly injured," and is therefore the target of all acute therapeutic interventions in stroke [3]. Over the last two decades of stroke research, the advent of the intravenous use of thrombolytic agents in hyperacute stroke reperfusion has proved to be the most groundbreaking advancement that has changed the paradigm of ischemic stroke treatment worldwide.

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25.2 History of Intravenous Thrombolytics

Penumbral salvage determines recovery in stroke. Intravenous thrombolysis produces early arterial recanalization by the lysis of the occluding thrombus or embolus, thereby allowing reperfusion of the ischemic penumbral tissue and preventing its progression to infarction [4].

The earliest use of thrombolytics can be dated back to 1958, where intravenous fibrinolysin was used to mitigate cerebral arterial occlusion [5]. Experimental studies conducted in the subsequent years with fibrinolysin, streptokinase, and urokinase raised concerns of an increased frequency and severity of intracerebral hemorrhage. These agents proved unacceptably hazardous in terms of early deaths, with no apparent long-term efficacy [6–8].

The tissue plasminogen activator (tPA) was developed by the recombinant DNA technology in the mid-1980s to be used in myocardial infarction. Renewed interest in thrombolytic therapy in stroke with the advent of tPA prompted dose escalation safety studies of tPA in early onset neurological deficits. Pilot studies estimating the potential efficacy of tPA within 90 min of stroke onset yielded promising results [9, 10] and paved way for larger, randomized controlled trials.

In 1995, the NINDS (National Institute of Neurological Disorders and Stroke) tPA trial was published, and it brought about a revolutionary

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breakthrough in the acute management of ischemic stroke [11]. This randomized, controlled trial demonstrated a clear reduction in disability with 0.9 mg/kg of intravenous (iv) tPA 0–3 h after stroke symptom onset. The subsequent trials published between 1995 and 2002 were European Cooperative Acute Stroke Study (ECASS), ECASSII, and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) A/B [12–15]. These trials also authenticated a robust treatment effect in favor of tPA in the under 3-h time window. In 2008, the ECASS 3 randomized controlled trial demonstrated the clinical efficacy of tPA within the 3–4.5-h time window [16]. The third international stroke trial (IST-3) justified extending treatment to patients older than 80 years of age [17]. In 2014, a Cochrane review evaluating data from 27 trials and 10,187 patients suggested that thrombolytic therapy given up to 6 h after onset of symptoms significantly reduced the likelihood of death or dependency at 3–6 months after stroke. However, the risk of symptomatic intracranial hemorrhage and death at 3–6 months also increased significantly [18]. Extending the time window up to 6 h for benefit with tPA should await results of further trials. The latest 2018 American Heart Association/American Stroke Association (AHA/ASA) guidelines for the early management of patients with acute ischemic stroke [19] advocate administration of iv tPA (with alteplase) to patients who can be treated within 4.5 h of ischemic stroke symptom onset, after reviewing the eligibility criteria.

The thrombolytic drug alteplase (rtPA) is licensed for use within 3 h of stroke in the USA and Canada and up to 4.5 h in most European countries.

25.3 Pharmacology of Intravenous Thrombolytics

An ischemic stroke is caused by a thrombus that blocks the flow of blood in a vessel of the brain. This pathological thrombus forms when there is an imbalance in the blood coagulation system—either due to circulatory stasis (turbulence in stenotic regions, atrial fibrillation), atherosclerosis causing endothelial injury, or a hypercoagulable state. A thrombus is formed by the aggregation of circulating platelets, reinforced by fibrin deposition. Under physiological conditions, the dissolution of these intraluminal thrombi involves activation of the fibrinolytic system to remove the fibrin.

The enzyme that is responsible for the degradation of the fibrin clot into soluble fibrin degradation products (FDPs) is a serine protease—plasmin. Plasmin is generated from plasminogen by the tissue plasminogen activator (tPA) produced by the vascular endothelium. tPA binds to fibrin on the surface of the clot and activates fibrin-bound plasminogen to release plasmin, which in turn dissolves the clot. Any plasmin that leaks from the clot surface is inactivated by the circulating antiplasmins. tPA has a short half-life of around 4–8 min due to the presence of specific inhibitors, such as plasminogen activator inhibitor-1 (PAI-1).

Thrombolytic drugs, commonly referred to as clot buster drugs, lyse intraluminal thrombi by activating precursor plasminogen to active plasmin. Plasmin degrades clots by lysing fibrin into fragments, thereby dissolving the clot. As a result, the occluded artery is recanalized and the ischemic penumbra reperfused, thereby salvaging the at-risk brain tissue. The plasmin, however, also breaks down other circulating proteins, including fibrinogen, causing an undesirable systemic fibrinolytic state and bleeding complications. Normally, circulating α_2-antiplasmin inactivates plasmin, but the therapeutic doses of intravenous thrombolytics produce sufficient plasmin to deluge the limited circulating concentrations of the antiplasmin. The efficacy of thrombolytic drugs depends on the age of the clot—older clots are more compacted with greater fibrin cross-linking and are more difficult to dissolve.

An ideal thrombolytic agent is described as one with a relative fibrin specificity, longer half-life (to enable bolus administration), and low rates of systemic bleeding and reocclusion and is cost-effective.

Fibrinolytic drugs can be classified into three categories depending upon their fibrin specificity and half-life:

1. First-generation fibrinolytics: Streptokinase and urokinase—Non-fibrin specific
2. Second generation: Recombinant tissue plasminogen activator (rtPA)—alteplase
3. Third generation: Tenecteplase, reteplase, monteplase, lanoteplase, pamiteplase

rtPA is relatively selective for clot-bound fibrin and thus has a decreased incidence of systemic bleeding as compared to the first-generation drugs—streptokinase and urokinase.

Alteplase has a short half-life of ~5 min, and is therefore administered as an iv bolus, followed by an infusion. Reteplase has an increased potency and is faster acting. Tenecteplase has a longer half-life (due to its resistance to plasminogen activator inhibitor-1) and a greater binding affinity for fibrin. Both reteplase and tenecteplase are administered as an iv bolus. Among the available fibrinolytic drugs, alteplase is the recombinant form of tPA licensed for use in stroke. In a recent randomized trial involving patients with acute stroke, the incidence of revascularization, as well as the functional outcome, was higher with tenecteplase (0.4 mg/kg single iv bolus) than with alteplase for intravenous thrombolysis before endovascular thrombectomy [20].

25.4 Administration of Intravenous Thrombolytics

25.4.1 Prerequisites

Patients with symptoms suggestive of stroke should be triaged with priority in the emergency department (ED), regardless of the severity of neurological deficits. After an initial stabilization of the airway, breathing, and circulation (ABCs), a quick assessment of the neurological deficits, along with the time of symptom onset (last the patient was known to be normal or symptom-free), is mandatory. At this time, *stroke code activation* (an in-hospital rapid response system) to expedite diagnostic and therapeutic interventions should occur. An organized protocol with a goal of achieving a door-to-needle time (DTN) of ≤60 min (time from arrival in ED to initiation of iv thrombolysis) is recommended.

The use of formal and standardized stroke scales, such as the NIHSS (National Institute of Health Stroke Scale), evaluating the level of consciousness, response to commands, motor palsy, sensory deficits, aphasia, limb ataxia, etc., helps in quantifying the degree of neurological deficits [21]. A brief history about the possible comorbidities helps in establishing the risk factors responsible for the stroke, such as cardiac disease, liver dysfunction, etc. A quick blood glucose level helps in excluding the most common mimic of stroke, i.e., hypoglycemia, and in fact is the only laboratory test necessary prior to initiating iv tPA for an ischemic stroke. All patients admitted with a suspected acute stroke should undergo a non-contrast computed tomography (NCCT) to rule out parenchymal hemorrhage, thereby excluding patients not fit to receive iv thrombolysis. An NCCT brain should be performed within 20 min of arrival in the ED (door-to-imaging time ≤20 min) in order to initiate fibrinolytic therapy in eligible patients at the earliest. The extent and severity of acute CT hypoattenuation are no longer used as a criterion to withhold thrombolytic therapy in patients who otherwise qualify [22–25].

Since time is critical in the management of patients with acute stroke, intravenous thrombolytic administration is initiated soon after obtaining the NCCT brain.

Several diagnostic laboratory tests may be considered immediately in patients with suspected ischemic stroke to assess for comorbid conditions and as an aid in treatment selection, although fibrinolytic therapy should not be delayed while awaiting results of the same. These tests include:

1. *Renal function tests* with *serum electrolytes*.
2. *Complete blood count* (CBC), including platelets.

3. *Coagulation profile*: Prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT).

   While determination of the platelet count and PT/INR may be important in patients with liver dysfunction or bleeding diathesis or those receiving heparin or warfarin, their results should not delay thrombolytic therapy in general population, where the risk of unsuspected abnormal platelet count or coagulation profile is extremely low [26, 27].
4. *Baseline electrocardiography (ECG)*: Atrial fibrillation (AF) or a concurrent acute myocardial infarction (MI) may have precipitated a stroke, which would need optimization.
5. *Markers of cardiac ischemia*: Elevated baseline cardiac troponin-T is associated with increased stroke severity and worse outcomes [28, 29].

Certain laboratory tests that may be considered in selected patients depending upon their availability include:

1. Liver function tests.
2. Thrombin time (TT) or ecarin clotting time (ECT) in patients on direct thrombin inhibitors (such as dabigatran) as oral anticoagulants.
3. Toxicology screen for sympathomimetic use (cocaine, amphetamines, etc.) in young adults as a cause of stroke.
4. Pregnancy test should be performed in women of childbearing age with acute stroke.

   Pregnancy, which was historically regarded as a contraindication to iv tPA treatment, is no longer considered to be one. tPA is a large molecule that does not cross the placenta and has proven to be non-teratogenic. The potential benefits of this therapy in terms of clinical recovery and prevention of disability clearly outweigh the risk of maternal hemorrhagic complications in this subgroup of patients. The current evidence thus supports the use of intravenous thrombolysis, when other clinical and imaging factors are favorable, in a center with an adequate obstetric backup [30].
5. Chest radiography: Usefulness unclear in the setting of hyperacute stroke in the absence of any evidence of acute cardiopulmonary disease [31].
6. Electroencephalogram (EEG): If seizures are suspected.
7. Lumbar puncture: Has a limited role unless there is a strong suspicion of subarachnoid hemorrhage (and the NCCT head is negative) or acute central nervous system infections.

Role of Advanced Imaging in Acute Stroke Multimodal CT and MRI (magnetic resonance imaging), including perfusion imaging (to determine the diffusion-perfusion mismatch and penumbra) or angiography (for intra- and extracranial vessels imaging), should not delay the administration of tPA.

For patients who meet the criteria for endovascular therapy and are suspected to have an intracranial large vessel occlusion, a CT angiography (CTA) is indicated before obtaining a serum creatinine in patients without a prior history of renal impairment, as the risk of contrast-induced nephropathy secondary to CTA is relatively low [32–34].

In patients presenting with symptoms of stroke 6–24 h after onset and have a clinical deficit that is disproportionately severe relative to the infarct volume, obtaining a CT perfusion, diffusion-weighted MRI, or MR perfusion is recommended to aid in patient selection for mechanical thrombectomy (DAWN and DEFUSE 3 trials) [35, 36].

Blood Pressure (BP) Control in Acute Ischemic Stroke (AIS) Blood pressure levels should be maintained in stroke in order to preserve systemic perfusion to the target organs, including the brain. The occurrence of hypotension is rare and should be handled cautiously, as it may point toward a cardiac arrhythmia or ischemia, aortic dissection, or shock [37]. Prompt evaluation and correction of the cause are mandatory to minimize the extent of brain damage. Hypovolemia should be corrected, and vasopressors initiated to normalize blood pressure if required. The usefulness of induced hypertension and volume expansion in otherwise normotensive patients, for the purpose of augmenting cerebral perfusion in AIS, is not recommended.

Patients with grossly elevated BP, who are otherwise eligible for fibrinolytic therapy, should have their BP carefully lowered to <185/110 mmHg prior to the initiation of therapy, with the help of antihypertensives like labetalol, nicardipine, clevidipine, hydralazine, enalaprilat, etc. As a rule, reperfusion therapy, both intravenous thrombolysis and endovascular treatment, is not administered if the BP is not maintained ≤180/110 mmHg, for an increased risk of precipitating intracranial hemorrhage [38–40]. During and after the reperfusion therapy, the target BP is ≤180/105 mmHg, with BP monitoring every 15 min for 2 h, then every 30 min for 6 h, and then every hour for 16 h.

Patients with marked hypertension who are not otherwise candidates for fibrinolysis should receive antihypertensive medication if the systolic blood pressure is >220 mmHg or the diastolic pressure is >120 mmHg. A rational goal is to lower the BP by ~15% in the first 24 h after stroke onset in a well-controlled manner, with the use of labetalol, nicardipine, or clevidipine infusions as per the institutional preference and availability. If the BP is uncontrolled and the diastolic pressures exceed 140 mmHg, intravenous nitroprusside may be considered.

25.4.2 Intravenous Alteplase

Reperfusion therapy using thrombolytic agents within 3–4.5 h of stroke onset is the mainstay of acute stroke management protocols. The thrombolytic drug approved for use is intravenous alteplase. *Alteplase is administered in a dose of 0.9 mg/kg, with a maximum dose of 90 mg, over 60 min. The initial 10% of the dose is given as an iv bolus over 1 min.* The patient is closely monitored in the intensive care or stroke unit after administration of alteplase, and all invasive line placements, such as the nasogastric tube, urinary catheter, arterial line, etc., are postponed if feasible. A close watch on the patient's neurological status during and after iv thrombolytics is important, so that early signs of raised intracranial pressure due to hemorrhage, such as headache, vomiting, acute hypertension, and drop in the level of consciousness, can be promptly recognized and treated. Post-thrombolysis, appropriate antihypertensives with regular BP monitoring, should be administered to maintain the target BP (≤185/105 mmHg). A follow-up CT or MRI brain should be obtained 24 h after iv alteplase and decision regarding the initiation of antiplatelets or anticoagulants taken.

25.5 Eligibility Characteristics of IV tPA

The fundamental principle in the treatment of patients with acute ischemic stroke is to minimize the total ischemic time and restore blood flow to threatened but not yet infarcted tissue as soon as feasible. Healthcare systems should aim for a door-to-needle time of ≤60 min in all their patients. The eligibility criteria of patients who could be treated with iv thrombolysis differ depending upon the time of symptom onset. While a broad spectrum of patients can be treated within 3 h of the last well known time, a relatively more selective spectrum of patients can be treated between 3 and 4.5 h:

For patients presenting with ischemic stroke within 3 h:

1. Duration of symptom onset <3 h
2. Age ≥18 years
3. Both severe as well as mild but disabling stroke symptoms

For patients presenting within 3–4.5 h:

1. Onset of symptoms within 3–4.5 h prior to initiation of iv thrombolysis
2. Age ≥18 years but ≤80 years
3. No history of diabetes and prior stroke
4. Patient not taking an oral anticoagulant (regardless of INR)
5. Stroke severity:
   a. NIHSS ≤25
   b. Without imaging evidence of ischemia involving >1/3rd of the MCA (middle cerebral artery) territory

In recent studies, intravenous alteplase has been found to be safe in patients presenting in the 3–4.5-h window period with age ≥80 years, taking warfarin with an INR <1.7, and those with prior stroke and diabetes [41, 42]. The benefit of fibrinolysis in patients with NIHSS >25 presenting in the 3–4.5 h window is, however, uncertain.

Other factors determining eligibility include:

- *BP*: iv alteplase is recommended in patients whose BP can be safely lowered to ≤185/110 mmHg and stabilized at this level.
- *Blood glucose*: Initial glucose levels >50 mg/dL. Patients with initial glucose levels <50 or >400 mg/dL that are subsequently normalized are eligible for therapy.
- *Prior antiplatelet therapy*: Alteplase is recommended in patients taking antiplatelet drug monotherapy, as well as combination therapy (aspirin + clopidogrel) prior to stroke, as the benefit of therapy outweighs the risk of symptomatic intracranial hemorrhage [43–45].
- *End-stage renal disease*: Thrombolysis is recommended in patients on hemodialysis with a normal aPTT [46]. Patients with elevated aPTT may have a higher risk of bleeding complications.
- *CT findings*: iv alteplase should be given in the setting of mild to moderate ischemic changes on NCCT head. Patients with a frank hypodensity are usually excluded because of a high association with subsequent symptomatic ICH [47]. Also, the presence of an obvious hypodensity on CT would represent an irreversible injury.

25.6 Contraindications to Thrombolytic Therapy [48]

1. Time of onset: Unclear time or unwitnessed symptom onset/wake up stroke/time last known to be normal ≥4.5 h
2. CT: Acute intracranial hemorrhage
3. Ischemic stroke within the last 3 months
4. Severe head trauma within 3 months
5. History of intracranial/intraspinal surgery in the past 3 months
6. History of intracranial hemorrhage
7. Presence of an intracranial lesion:
   a. Intra-axial neoplasm
   b. Arteriovenous malformation
   c. Giant, unruptured aneurysm
   d. Intracranial arterial dissection
8. Symptoms suggestive of subarachnoid hemorrhage
9. Patients with a gastrointestinal (GI) malignancy or a recent GI bleed within 3 weeks
10. Coagulopathy:
    a. Platelet count <100,000/mm^3
    b. PT >15 s or INR >1.7
    c. aPTT >40 s

    In patients without a history of thrombocytopenia or coagulopathy, in whom iv alteplase has been initiated, the thrombolytic infusion should be discontinued if the platelet count is found to be <100,000/mm^3 or the INR >1.7.
11. Arterial puncture at a non-compressible site in the last 7 days
12. Anticoagulant use:
    a. Patients on warfarin with INR >1.7 and/or PT >15 s.
    b. Patients who have received a treatment dose of low molecular weight heparin (LMWH) in the previous 24 h.
    c. Patients on direct thrombin inhibitors or factor-Xa inhibitors—iv alteplase may be considered if laboratory tests such as INR/aPTT/ECT/TT/factor-Xa activity assays are normal, or the patient has not taken the medication for >48 h, assuming a normal renal clearance.
13. Infective endocarditis
14. Aortic arch dissection

25.7 Additional Recommendations

- Patients who have undergone a *major surgery in the past 14 days* may be considered for iv alteplase, after weighing the anticipated benefits of neurological recovery versus the risk of surgical site hemorrhage.

- In patients presenting with AIS with *concurrent acute MI*, iv alteplase (0.9 mg/kg) followed by percutaneous coronary intervention (angioplasty and stenting) is recommended.
- Patients with a *history of MI in the previous 3 months*:
  - Administer iv alteplase if the recent MI is non-ST elevation MI (NSTEMI).
  - Treatment with iv alteplase *is reasonable* if the ST elevation MI (STEMI) involves the right or inferior myocardium.
  - It *may be reasonable* to treat with iv alteplase in case of STEMI involving the left anterior myocardium.

Patients with recent MI may be harboring ventricular thrombi that may embolize post fibrinolysis and hence the concern. Anterior wall location and the size of myocardial damage are the most consistent predictors of thrombus formation. The incidence of left ventricular thrombi after MI however has decreased considerably with the advent of PCI and is reported to be ~2–8%. Similarly, patients with MI may develop pericarditis, more commonly with transmural infarction, anterior wall involvement, and depressed ejection fraction. The incidence is 7–25%. Pericardial hemorrhage may occur post fibrinolysis in these patients with pericarditis. A fibrin clot in the necrotic myocardium may lyse to cause hemopericardium post thrombolysis, which may be fatal.

- In patients with a known *left heart thrombus* or *pericarditis* (from causes other than an acute MI), or *cardiac myxoma* or *papillary fibroelastoma*, treatment with iv alteplase may be reasonable for a major stroke causing severe disability.
  For patients presenting with moderate AIS likely to produce mild disability, fibrinolytic therapy is of uncertain net benefit.
- Patients with a history of *past gastrointestinal/genitourinary bleeding* have a low bleeding risk following iv alteplase administration and thus can undergo fibrinolytic treatment for stroke (recent bleeding within 21 days remains a contraindication).
- It may be reasonable to administer iv alteplase in patients with a small number (1–10) of *cerebral microbleeds* (CMB) on MRI. Patients with a high burden (>10) of CMBs in otherwise eligible patients may have a higher risk of developing symptomatic ICH, and fibrinolysis may be offered only if there is a potential for substantial benefit.
- Intravenous alteplase may be given in patients who present with *seizures* at onset, if residual neurological impairment is evidently due to stroke, and not a postictal phenomenon.
- In patients who have undergone a *lumbar puncture in the preceding 7 days*, iv alteplase may be considered.
- *Menstruating females* without a history of menorrhagia can be administered iv alteplase, with a rider that their menstrual flow might get increased. In patients with an active history of menorrhagia, thrombolysis may be given if there is no clinically significant anemia or hypotension. In females with recent or active vaginal bleeding causing clinically significant anemia, an emergency gynecologist review is mandated prior to initiation of tPA therapy.
- Patients harboring a small- to moderate-sized (<10 mm) unruptured and unsecured *intracranial aneurysm* may undergo iv thrombolysis. Giant, unruptured aneurysms, however, carry a high risk of hemorrhage, and the usefulness and safety of iv alteplase are not established.
- Intravenous alteplase may be given in patients with an *extra-axial intracranial neoplasm*.
- Intravenous alteplase is safe in patients with AIS associated with *extracranial cervical arterial dissection*.
- Patients with *pre-existing dementia* may benefit from iv alteplase, if they have a good life expectancy and premorbid level of function.
- Patients with *active malignancy*, without brain metastases, who have a life expectancy of >6 months, may benefit from iv alteplase, provided other contraindications like coagulation abnormalities, systemic bleeding, and recent surgery do not coexist.

- Administration of intravenous tPA may be reasonable for patients with *pre-existing disability* with a modified Rankin scale (mRS) score ≥2, although it may be associated with less neurological improvement and higher mortality. Social support and quality of life should also be taken into account in these patients.
- Patients with a history of *diabetic hemorrhagic retinopathy* or other hemorrhagic ophthalmic conditions may undergo iv thrombolysis, after weighing the benefits of reduced stroke-related disability against the potential risk of visual loss.
- In *procedural stroke*, such as that occurring during cardiac or cerebral angiographies, iv alteplase is recommended.
- Patients with a known *sickle cell disease* may benefit from thrombolytic therapy in AIS [49].
- In patients presenting with *illicit drug use*-associated strokes with no other exclusions, iv alteplase is a reasonable choice for reperfusion.
- In the *stroke mimic* population, starting iv alteplase, in comparison to waiting for additional diagnostic tests, is recommended, as the risk of symptomatic ICH is low.
- Avoidance of *antiplatelet drugs* (aspirin, intravenous glycoprotein IIb/IIIa inhibitors) for 24 h post thrombolysis is recommended, due to an increased risk of intracranial hemorrhage.

25.7.1 Consent for the Incompetent Patient

An explicit, informed consent conveying the risks and benefits of fibrinolytic therapy is indicated. For an incompetent patient, a substitute decision maker may be needed. In an emergency, if the patient lacks decision making capacity, and there is no attendant or legally authorized representative to provide proxy consent, it is both ethical and legally permissible to proceed with fibrinolysis within the treatment window [50].

25.8 Complications of Thrombolysis

Complications related to intravenous rtPA therapy include [51]:

1. Symptomatic intracranial hemorrhage
2. Major systemic hemorrhage
3. Angioedema

25.8.1 Symptomatic Intracranial Hemorrhage

Symptomatic intracranial hemorrhage (sICH) is defined as a CT- or MRI-documented hemorrhage post thrombolytic treatment, associated with neurological deterioration in the patient. The risk of sICH after iv tPA is ~6% in most studies [52–54] but is associated with ~50% mortality. The risk factors associated with an increased risk of intracranial bleed include age, male sex, obesity, uncontrolled hypertension, diabetes, combination antiplatelet therapy, increased stroke severity, large areas of early ischemic changes, atrial fibrillation, and congestive heart failure [54–57].

Management of sICH occurring during or after (within 24 h) iv alteplase consists of stopping the alteplase infusion if already on flow and seeking an emergent NCCT head. A complete blood count, PT/INR, aPTT, fibrinogen level, and blood for typing and cross matching are sent. Proposed treatments to prevent hematoma expansion and neurologic worsening in sICH include vitamin K, fresh frozen plasma (FFP), cryoprecipitate, prothrombin complex concentrates, platelet transfusions, and antifibrinolytics. Cryoprecipitate (10 units over 10–30 min or more if the fibrinogen levels are low) is typically administered to reverse the thrombolysis. Antifibrinolytic agents such as tranexamic acid (1 g iv over 10 min) or ε-aminocaproic acid (4–5 g over 1 h, followed by 1 g IV until bleeding is controlled) may be given. Patients should be closely monitored in the intensive care for intracranial pressure (ICP), cerebral perfusion pressure (CPP), and mean arterial pressure (MAP) so

as to facilitate early recognition of cases needing surgical decompression. Hematology and neurosurgery consultations should be sought early on [58, 59].

25.8.2 Major Systemic Hemorrhage

Major systemic hemorrhage occurs in ~2% of all patients receiving iv alteplase. A careful review of exclusion criteria, including recent MI within a month, GI or urinary tract hemorrhage within 21 days, major surgery within 14 days, and arterial puncture at a non-compressible site, is important.

25.8.3 Orolingual Angioedema

Orolingual angioedema following alteplase treatment occurs in ~2–5% of all patients. It may be unilateral or bilateral and is usually mild. The risk is increased with the concomitant use of angiotensin-converting enzyme inhibitors (ACE-I) and in frontal and insular strokes [60, 61]. Management of serious angioedema consists of appropriate airway control (intubation if needed). Standard treatment for anaphylaxis is recommended including corticosteroids, diphenhydramine, and subcutaneous epinephrine, if indicated. Icatibant, a selective bradykinin β_2 receptor antagonist (30 mg subcutaneous) and plasma-derived C1 esterase inhibitor (20 IU/kg), has been successfully used in hereditary angioedema and ACE-I-related angioedema [62–64].

25.9 Conclusion

Early treatment with intravenous thrombolysis has resulted in a significant reduction in death and disability following acute ischemic stroke. The use of iv alteplase in the appropriate setting maximizes benefit while reducing risk. Further advancements in endovascular treatment to reduce the clot burden, without delaying iv tPA, has a high potential of reducing morbidity in stroke.

Key Points

- Intravenous thrombolytics target penumbral salvage to reverse the ischemic effects of stroke. The recombinant tissue plasminogen activator (rtPA) can be given up to 3–4.5 h of symptom onset and is administered in a dose of 0.9 mg/kg, with a maximum dose of 90 mg, over 60 min. The initial 10% of the dose is given as an iv bolus over 1 min.
- rtPA is relatively selective for clot-bound fibrin and thus has a decreased incidence of systemic bleeding as compared to the first-generation drugs—streptokinase and urokinase.
- An organized protocol with a goal of achieving a door-to-needle time (DTN) of ≤60 min (time from arrival in ED to initiation of iv thrombolysis) is recommended in patients with ischemic stroke.
- All patients admitted with a suspected acute stroke should undergo a non-contrast computed tomography (NCCT) to rule out parenchymal hemorrhage, thereby excluding patients not fit to receive iv thrombolysis.
- A quick blood glucose level helps in excluding the most common mimic of stroke, i.e., hypoglycemia, and is the only laboratory test necessary prior to initiating ivtPA for an ischemic stroke. Fibrinolytic therapy should not be delayed while awaiting results of other laboratory investigations (e.g., renal function tests, platelet count, or coagulation profile).
- For patients who meet the criteria for endovascular therapy and are suspected to have an intracranial large vessel occlusion, a CT angiography (CTA) is indicated before obtaining a serum creatinine in patients without a prior history of renal impairment, as the risk of contrast-induced nephropathy secondary to CTA is relatively low. Mechanical thrombectomy may be undertaken in patients presenting

up to 6–24 h, with a clinical deficit disproportionately severe relative to the infarct volume (DAWN and DEFUSE 3 trials).

- Patients with grossly elevated BP, who are otherwise eligible for fibrinolytic therapy, should have their BP carefully lowered to <185/110 mmHg prior to the initiation of therapy, with the help of antihypertensives like labetalol, nicardipine, etc.
- Symptomatic intracranial hemorrhage (sICH) post thrombolytic treatment with neurological deterioration in the patient is seen in ~6% of patients and is associated with ~50% mortality. Close neurological monitoring is recommended for early recognition of cases needing surgical decompression.

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Part VII

Transfusion Practice

Fluid Management in Neurosurgical Patients

26

Wojciech Dabrowski, Robert Wise, and Manu L. N. G. Malbrain

26.1 Introduction

Fluid administration in the perioperative management of neurosurgical patients is challenging. Inappropriate intravenous (IV) fluid administration is associated with postoperative complications and increased mortality [1–3]. However, there is little data on how fluid therapy affects neurosurgical patients treated for tumors, cerebral aneurysms, or angiomas. Intravenous fluid therapy is frequently used to correct and maintain adequate cerebral blood flow (CBF) and cerebral perfusion pressure (CPP). Perioperative problems are created by the administration of hypo- or hyperosmotic fluids or by administering too much or too little. Added to this complexity is the risk of causing hypotension on induction of anesthesia in hypovolemic patients, hence creating a situation where intravenous fluids are often administered rapidly. Thus, maintaining euvolemia, without the morbidity associated with hypovolemia or hypervolemia, becomes a challenging exercise.

Available intravenous fluids are generally classified into two main groups: crystalloids and colloids. Fluid constitution differs with respect to ion content, buffer, strong ion difference (SID), tonicity, and oncotic pressure. Intravenous fluids should be considered as drugs, as their administration strongly affects intravenous homeostasis and intra-/extravascular water balance. As with other drugs, as their administration can either correct or disturb end-organ function.

26.2 Crystalloid Fluids

26.2.1 General Principles

Crystalloids are the most popular fluids administered for correction of intravascular volume. Crystalloids are solutions of inorganic ions and organic molecules dissolved in water. An ideal crystalloid solution is described as one similar to interstitial fluid, but not inducing electrolyte or acid-base disturbances [4–6]. Use of crystalloids in neurosurgical patients has been the subject of several studies [7–9]. All isotonic

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balanced solutions consist of water with different Na^+, K^+, Ca^{++}, Mg^{++}, and Cl^- ions which are buffered by anions such as acetate, malate, lactate, or citrate. This differs from plasma containing proteins, organic acids, phosphate, sulfate, and acidic carbonates. Hence, the theoretical osmolality (as indicated on the fluids information package) is calculated by using a multiplication factor of 0.926 to estimate the fluid's "in vivo" osmolality [10]. Based on this principle, many isotonic fluids are actually hypotonic.

Hypotonic solutions should be avoided in neurosurgical patients and patients with traumatic brain injury (TBI) (Grade 1C) [11]. A slight reduction in plasma osmolality by 1 mOsm/L increases the pressure of fluid shifts across the blood-brain barrier (BBB) to 19 mmHg. Furthermore, a decline in plasma osmolality by 3% leads to overt cerebral edema with a 30% reduction in intracranial blood cerebrospinal fluid volume [7, 12, 13].

Some crystalloids are buffered and termed balanced solutions. A buffer is a partially neutralized acid that resists changes in pH. Citrate, a crystalloid buffer, binds intravascular ionized calcium, thus stimulating coagulation disorders. Use of large volumes of such fluids may cause serious problems, particularly when rapidly infused during sudden perioperative bleeding.

Strong ion difference (SID), calculated as the sum of all ions, should be taken into consideration in patients undergoing neurosurgical procedures due to the effect on pH. Administration of fluids with a SID of zero, such as 0.9% sodium chloride (NaCl), induces metabolic acidosis, whereas administration of fluids with SID >40 induces metabolic alkalosis [14].

Also, chloride-rich solutions may induce hyperchloremic acidosis, associated with impaired renal blood flow [15–17]. Again, maintaining euvolemia becomes important as any disorders in renal blood flow may lead to acute kidney injury (AKI), one of the most important postoperative complications following major surgery [16, 18]. A large meta-analysis of 22,851 patients with preoperatively low chloride concentration and normal renal function confirmed the strong correlation between acute postoperative hyperchloremia and the incidence of renal dysfunction. Hyperchloremia was also associated with increased 30-day mortality and length of hospital stay in non-cardiac surgical patients [18]. An association between hyperchloremia and administration of 0.9% NaCl has been widely analyzed in experimental and clinical studies [16, 17, 19–21]. A normal plasma chloride concentration ranges between 95 and110 mEq/L, in contrast to 0.9% NaCl containing 154 mEq/L of chloride. Both animal and clinical studies documented a dose-dependent 0.9% NaCl-induced hyperchloremia [19, 20]. Evidence also suggests that chloride-rich fluids contribute to delayed recovery of gut function and reduced gastric blood flow [21, 22], which may stimulate postoperative vomiting and subsequent increases in intracranial pressure (ICP). Therefore, treatment with balanced isotonic crystalloids is preferred over administration of 0.9% NaCl in patients undergoing neurosurgical procedures.

26.2.2 Saline Solutions

There are two kinds of saline solutions in clinical practice: 0.9% normal saline (NS) and hypertonic saline (HS). Importantly, all saline solutions have a SID of zero. Normal saline has been the mainstay therapy for patients undergoing cerebral surgery, but its effect on the progression of brain injury has not been well documented [23, 24]. Experimental animal studies comparing resuscitation with NS and fresh frozen plasma have documented pronounced cerebral edema and a larger lesion size when using NS. When comparing NS and synthetic colloid solutions in resuscitation, NS was noted to increase cerebral edema but resulted in a lesion size equal to that caused by the synthetic colloid resuscitation [23]. Administration of NS also affects coagulation parameters, increasing activation of natural anticoagulation in the brain that results in activated fibrinolysis in serum and upregulation of vascular adhesion molecule expression in the injured brain [24]. Also, administration of large volumes of NS

may result in extravasation of intravascular fluid, with increased extravascular water accumulation causing tissue edema and gastrointestinal dysfunction [25, 26].

Adverse effects, similar to those seen in patients given NS, have been documented in patients treated with HS [27, 28]. The increased risk of hyperchloremic metabolic acidosis and AKI should prompt physicians to limit the liberal use of NS and HS. Nevertheless, HS is frequently used with good effect to treat elevated ICP. It may be safer to use repeated boluses of HS as opposed to continuous infusions, as infusions are associated with higher rates of hyperchloremia and AKI [28]. It has been suggested to use an infusion of NS or HS in hypovolemic TBI patients with metabolic alkalosis due to massive alcohol-related vomiting [29]. The administration of saline solutions in these situations corrects volume deficit and acid-balance disorders via induction of metabolic acidosis, while HS has the added advantage of potentially reducing ICP.

26.2.3 Balanced Solutions

In recent years buffered (balanced) salt solutions have been the most common choice of resuscitation fluid in clinical practice [30]. Their composition more closely resembles the extracellular (intravascular) fluid and thus is considered a better choice, for many of the reasons already outlined. Balanced crystalloids do not affect acid-base balance to the same degree and have a lower incidence of hyperchloremic acidosis, perioperative AKI, need for blood transfusion, and systemic inflammation [31–36]. Recent large retrospective trials documented beneficial effects in patients treated with balanced crystalloids compared to NS. They demonstrated significantly lower postoperative complications, such as electrolyte disturbances, postoperative occurrence of AKI requiring renal replacement therapy, postoperative infections, and need for blood product transfusions [36].

In traumatic brain injury patients, the administration of balanced solutions did not affect ICP, SID, phosphate, sodium, or chloride levels, whereas saline solutions lowered blood pH, SID, and phosphate and also significantly increased chloride and sodium [37]. Balanced crystalloids have also been presented as a more effective treatment of hypovolemia-induced acidosis [38]. Therefore, the use of balanced isotonic crystalloids appears to be a more attractive choice than saline solutions in perioperative fluid resuscitation of TBI and other neurosurgical patients.

26.2.4 Synthetic Colloid Fluids

Synthetic colloids are frequently used in patients undergoing intracranial surgery. These solutions have large insoluble molecules that increase the intravascular oncotic pressure, thus potentially drawing water from the extravascular space. Their high oncotic pressure decreases cerebral edema and improves mean arterial blood pressure via increased intravascular volume [39]. Gelatin and hydroxyethyl starch (HES) solutions are the most popular colloids used in neurosurgical patients. Gelatins consist of polydispersed polypeptides from degraded bovine collagen with molecular weights between 30 and 35 kDa, while HES is an artificial polymer of amylopectin obtained from potatoes, waxy maze, or sorghum. Unfortunately, both types of fluids can diffuse into the interstitium via an injured glycocalyx following surgery-induced general inflammation, and their administration affects the transendothelial filtration rate (Jv) [40, 41]. Evidence regarding the effects of HES on coagulation are conflicting. Several authors have shown HES to increase coagulation disorders by decreasing the concentration of blood coagulation factors VII, VIII, and von Willebrand and impairing platelet aggregation [42, 43]. Others did not confirm these disorders in patients undergoing neurosurgical procedures; however, they did note increases in thrombin-antithrombin levels postoperatively without plasmin-antiplasmin activation. This may have resulted from the administration of HES [44]. Several studies also documented an increased incidence of AKI following HES

administration in critically ill [16, 45, 46]. Administration of HES potentially corrects intravascular volume deficit but does not necessarily remain intravascularly. According to the revised Starling Principle, unsolved molecules can deposit in the skin, liver, muscle, spleen, endothelial cells, and kidneys leading to organ dysfunction [7, 40, 41, 47]. However, some researchers have suggested that the adverse effects of HES are dependent on dose and molecular weight [48]. Several retrospective studies in patients with subarachnoid hemorrhage (SAH) have not yet confirmed a correlation between high volumes of HES and the incidence of AKI [48, 49]. Therefore, the effect of HES on renal function has remained controversial, and the precise understanding of kidney injury following HES administration requires further investigation in neurosurgical patients.

The effect of gelatin solutions on renal function is not yet well understood. A case report documented AKI following Gelofusine administration in a patient undergoing aortobifemoral grafting [50]. This patient received 2 liters of Gelofusine together with mannitol, which may have impaired renal function per se [51]. Experimental studies seem to confirm an unfavorable effect of infusions of gelatin solutions on renal function [52]. An infusion of 4% Gelafundin, at the dose 1 mL/100 g body weight, resulted in serum creatinine and neutrophil gelatinase-associated lipocalin (NGAL) elevation in septic rats, and histological examination showed significantly increased interstitial edema, loss of brush border in the proximal tubules, and higher defragmentation of cell nuclei in kidneys [52]. Clinical studies also confirmed that only higher cumulative doses (>33 mL/kg body weight) of gelatin were associated with an increased risk of AKI in septic patients [53]. Thus, it seems reasonable to avoid large volumes of gelatin infusions, particularly in patients with impaired renal blood flow, history of renal disease, or combination with other osmotically active fluids such as mannitol.

Recently the Coordination Group for Mutual Recognition and Decentralised Procedures—Human (CMDh) endorsed the recommendation of European Medicine's Agency PRAC (Pharmacovigilance Risk Assessment Committee) to suspend the marketing authorizations of HES solutions for infusion across the European Union. HES solutions are used as plasma volume replacement following acute (sudden) blood loss, where treatment with alternative products known as "crystalloids" alone is not considered sufficient. The suspension was due to the fact that HES solutions have continued to be used in critically ill patients and patients with sepsis, despite the introduction of restrictions on use in these patient populations to reduce the risk of kidney injury and death in 2013.

26.2.5 Mannitol

Current guidelines recommend mannitol at the dose of 0.25–1 g/kg body weight as basic hyperosmotic therapy in patients with intracranial hypertension (ICH) [54]. Mannitol is a six-carbon alcohol of mannose sugar and is frequently used as hyperosmotic therapy to reduce ICH, as well as intraocular hypertension and tissue edema. The mechanism is thought to be via an increase in water drawn from the extravascular space. It should preferably be used in patients with low plasma osmolality, whereas it needs to be avoided when plasma osmolality is above 320 mOsm/kg H_2O. Mannitol is not reabsorbed in the renal tubules, and as such it increases the osmolality of the glomerular filtrate, resulting in a diuresis through inhibition of sodium and chloride reabsorption [55, 56]. Many studies document a close association between mannitol and postoperative AKI in TBI patients [57, 58]. Deng and colleagues demonstrated that the use of mannitol intraoperatively (as compared to preoperatively) was an independent risk factor for postoperative AKI with a 1.97-fold increase in the risk-adjusted odds ratio [57]. Hence, more than 50% of clinicians prefer HS for treatment of ICH [59]. Mannitol-related AKI develops within 1 week of administration, with a more rapid cessation of mannitol resulting in a better AKI prognosis [57].

26.3 Hemodynamic Goals

The main goal of perioperative fluid management is to optimize the circulatory system with adequate CBF during neurosurgery. However, elevated net fluid balance may worsen postoperative outcome [60]. It is difficult to improve CBF without appropriate monitoring. Various authors have suggested continuous blood pressure monitoring via an arterial line in patients undergoing surgery for cerebral aneurysm, brain tumor, angioma, or endovascular mechanical thrombectomy [61–68]. Unfortunately, analysis of continuous blood pressure has been frequently criticized when used as the only method for evaluating volume status in neurosurgical patients [64–66]. Rapid and uncontrolled infusion of fluids immediately after induction of anesthesia may negatively affect local, tumor-related brain edema in fluid-unresponsive patients. Hence, many clinicians recommend the use of dynamic variables, such as pulse pressure variation (PPV), stroke volume variation (SVV), or pleth variability index (PVi®), to identify fluid responsiveness and to guide intraoperative fluid management [66–71]. Stroke volume variation is a sensitive predictor of fluid responsiveness in previously healthy patients before brain surgery [68, 69], especially in patients receiving hyperosmotic therapy in the perioperative period. Goal-directed therapy has been recommended for patients undergoing neurosurgical procedures [65, 68, 72]. Pleth variability index (PVi®) is a noninvasive parameter that may be superior to other dynamic parameters, especially when used in combination with continuous hemoglobin measurements [73]. It has been proposed as a sensitive, noninvasive measurement to optimize fluid treatment in major non-cardiac surgery under general anesthesia [70, 71]. Rapid infusion of crystalloids immediately after anesthesia induction may result in iatrogenic hemodilution in patients receiving hyperosmolar therapy in the preoperative period. Iatrogenic hemodilution may further induce dilutional coagulopathy leading to increased surgical bleeding and increased use of intraoperative blood transfusion. Continuous noninvasive measurement of hemoglobin concentration together with PVi®, in accordance with intravascular volume status, allows real-time detection of iatrogenic hemodilution in non-bleeding patients [73].

26.4 Fluid Management in Specific Neurosurgical Procedures

The multiplicity of neurosurgical procedures calls for fluid diversification. Traumatic brain injury is frequently associated with hypovolemia and hemodynamic instability. Patients undergoing surgery for cerebral aneurysms are frequently hypertensive, while patients undergoing surgery for brain tumors sometimes require preoperative hyperosmotic treatment and forced diuresis which is in contrast to patients undergoing elective spinal surgery who are generally normovolemic. Therefore, fluid treatment should be individualized and tailored in accordance with the patient's clinical condition and needs.

26.4.1 Traumatic Brain Injury

The main goal of fluid therapy related to neurosurgery is to restore and maintain adequate CPP. Fluid management in TBI will be discussed elsewhere (see chapter "Fluid Management in Neurointensive Care"). The perioperative administration of fluids in TBI should be guided by hemodynamic monitoring using dynamic variables such as SVV, PVV, and PVi® [65, 74, 75]. Primary cerebral injury is the main factor determining final outcome, but secondary brain injury following pre- and perioperative cerebral hypoperfusion can contribute to unfavorable outcomes [76]. Perioperative hypotension has been observed in 36–65% of patients undergoing emergency craniotomy following TBI [77–79]. Balanced crystalloids should be the first line choice of fluid to correct hemodynamic instability (in patients who remain fluid responsive), and hypotonic solutions should be avoided. Also, synthetic colloids can be used together with crystalloids, but their administration should be guided

by plasma AKI biomarkers. Inotropic support should be added in all cases with fluid-unresponsive hypotension.

26.4.2 Brain Tumor Surgery

The primary goal of perioperative fluid therapy is to maintain preoperative mean arterial pressure during the intraoperative and early postoperative period. Rapid changes in mean and diastolic blood pressure, fluid balance, and length of surgery are all independently associated with perioperative cerebral infarct size and overall survival after elective brain tumor surgery [80]. Therefore, appropriate fluid therapy is essential to reduce perioperative brain injury and subsequent morbidity and mortality. Treatment options to restore intravascular volume deficiencies include crystalloids and colloids, but an elevated plasma osmolality following preoperative hyperosmotic therapy significantly limits the use of hypertonic crystalloids during the perioperative period. Hypotonic solutions should be avoided. The use of balanced crystalloids seems be the best option for initial fluid resuscitation, since colloids impair coagulation during and after surgery [44]. The occurrence of colloid-related coagulation disorders is a controversial issue in brain tumor surgery. Some pediatric studies did not confirm a relation between colloid administration and coagulopathy suggesting that colloids may be safely used during intracranial tumor resection [81]. However, large amounts of colloids may impair kidney function, especially in patients receiving hyperosmotic therapy with mannitol in the preoperative period.

26.4.3 Cerebral Aneurysm Surgery

Delayed cerebral ischemia (DCI) following intra- or postoperative cerebral vasospasms is the main cause of poor outcome and raised mortality in patients undergoing cerebral vascular surgery [82, 83]. The incidence of vasospasm can be as high as 70% between day 5 and 14 after the onset of subarachnoid hemorrhage (SAH); however, clinical symptoms are only noted in 30% of patients [83, 84]. Both hyper- and hypovolemia increase the risk of vasospasm and DCI [82–86]. A randomized pilot trial showed a fourfold increase in hypervolemia-related adverse effects in patients with SAH [86]. Appropriate management of fluid therapy is crucial for patients with cerebral aneurysm, and balanced crystalloids seem again to be the best choice. The use of colloids in patients with SAH is associated with increased inflammatory responses, more requirements for blood transfusion, and altered cerebral autoregulation when compared to those treated with balanced crystalloids [87]. Interestingly, a study using transpulmonary thermodilution in SAH showed that the magnitude of DCI was related to the global end-diastolic volume index (GEDVI) and cardiac index (CI) [88]. Achieving a mean 822 mL/m² (680–800 mL/m²) was deemed appropriate to prevent DCI. The use of invasive hemodynamic monitoring in combination with goal-directed fluid therapy significantly decreased DCI incidence and improved outcome [74]. Thus, dynamic hemodynamic variables seem be superior to static, but fluid administration have to be closely monitored in patients undergoing cerebral vascular surgery.

26.5 Conclusions

In summary, the choice of fluid during neurosurgical procedures depends largely on the patient's clinical condition, particularly renal function. Balanced, isotonic crystalloids are a good first choice to restore and/or maintain intravascular volume and hemodynamic stability and are superior to normal saline. Generally, normal saline should be avoided; however (hypertonic) saline solutions can be administrated in selected patients, but their infusion has to be guided by plasma electrolyte concentrations and acid-base balance. Hypotonic solutions and colloids (HES) should be avoided. Fluids should be treated as drugs, and the clinician should always consider the dose and duration of fluid administration, moving toward de-escalation when fluids are no longer needed. Fluid administration should be guided by dynamic variables assessing fluid responsiveness.

Key Points

- Inappropriate intravenous (IV) fluid administration is associated with postoperative complications and increased mortality.
- Hypotonic solutions and colloids should be avoided in neurosurgical patients.
- Treatment with balanced isotonic crystalloids is preferred over administration of 0.9% NaCl in patients undergoing neurosurgical procedures.
- The choice of fluid during neurosurgical procedures depends largely on the patient's clinical condition, particularly renal function.
- Fluid administration should be guided by dynamic variables assessing fluid responsiveness.

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Blood Transfusion in Neurosurgery

27

Kavitha Jayaram and Shibani Padhy

27.1 Introduction: Blood and Brain

Anemia, the most common complication arising during neurosurgical practice, plays a major role in influencing outcome. The brain is especially vulnerable to decreased perfusion and hypoxia, and brain oxygenation is highly reliant on cerebral blood flow. In recent years, transfusion practice across the world has generally witnessed a shift toward adopting a more restrictive strategy for red blood cell administration. The serious risks of transfusion might dwarf the putative benefits of increased oxygen-carrying capacity. The neurosurgical patients, who belong to a different spectrum, are further complicated by lack of evidence-based guidelines. This has resulted in highly variable transfusion thresholds across different institutions worldwide. The ideal strategy between restrictive and liberal transfusion therefore remains in clinical equipoise.

27.2 Physiopathology of Anemia in Neurosurgical Population

The adult human brain represents about 2% of total body weight and receives 12–15% of the cardiac output to maintain its high metabolic rate.

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Cerebral O_2 delivery (DO_2) is dependent on cerebral blood flow (CBF) and the total O_2 content of the blood (CaO_2).

$$DO_2 = CaO_2 \times CBF \quad (27.1)$$

$$CaO_2 = 1.39 \times Hb \times SaO_2 + 0.003 \times PaO_2 \quad (27.2)$$

where DO_2 is oxygen delivery to the brain, [Hb] is the concentration of hemoglobin, SaO_2 is the oxygen saturation of hemoglobin, PaO_2 is the oxygen partial pressure, and CBF is the cerebral blood flow.

Any condition affecting either of the factors is subsequently managed to some extent by the changes in the other factor to maintain the cerebral physiology. Cerebral perfusion pressure (CPP) is the difference between mean arterial pressure and cerebral venous pressure or intracranial pressure whichever is higher. CBF is normally autoregulated over a cerebral perfusion pressure range of 60–160 mm of Hg, outside which it is linearly dependent on mean arterial pressure. Autoregulation is often impaired in neurocritical care patients so that CBF becomes directly dependent on CPP, thus making the brain more vulnerable to extremes of blood flow. CBF is dependent on other factors like cerebral metabolic rate of oxygen consumption ($CMRO_2$) and variations in partial pressure of carbon dioxide (CO_2 reactivity).

Oxygen delivery during anemia (reduced CaO_2) is compensated by an increase in cardiac output, preferential distribution to cerebral circulation,

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cerebral vasodilatation, and increased brain tissue oxygen extraction. Upregulation of nitric oxide production by perivascular neurons is the mechanism underlying anemia-induced increase in cerebral vasodilatation. Multiple biochemical mediators like vascular endothelial growth factor, hypoxia inducible factor 1α, and erythropoietin also play a role in the cerebrovascular response to anemia. These compensatory mechanisms are however limited up to a critical cerebral DO_2 value beyond which brain ischemia ensues. Many neurocritical care patients like those with aneurysmal SAH have concomitant cardiac disease or neurologically mediated cardiac dysfunction which prevents an appropriate increase in cardiac output in response to anemia. Thus, maintaining adequate Hb levels, which primarily determine DO_2, is imperative to avoid hypoxic insult to the injured brain (Fig. 27.1) [1].

In the healthy brain, anemia-induced cerebral hypoxia has been shown to occur at a Hb concentration of 6–7 g/dL [2]. However, in the setting of acute brain injury, such an insult may manifest at higher Hb threshold. Coexistence of physiological stressors like cardiac dysfunction, hypotension, and anemia imposed on a central nervous system pathology with deranged regulation of CBF raises concerns regarding restrictive transfusion threshold of 7 gm/dl in neurocritical care.

27.2.1 Transfusion in Neurosurgery

Neurosurgical procedures are associated with higher incidence of bleeding requiring multiple transfusions. The optimal Hb concentration for transfusion in neurosurgical population is highly variable and still under a significant debate. When surveyed, neurosurgeons recommend higher threshold of Hb for transfusion as compared with the trauma surgeons and intensivists [3]. The decision to transfuse must be a balance between its presumed benefits on cerebral oxygenation and the potential complications (Fig. 27.2).

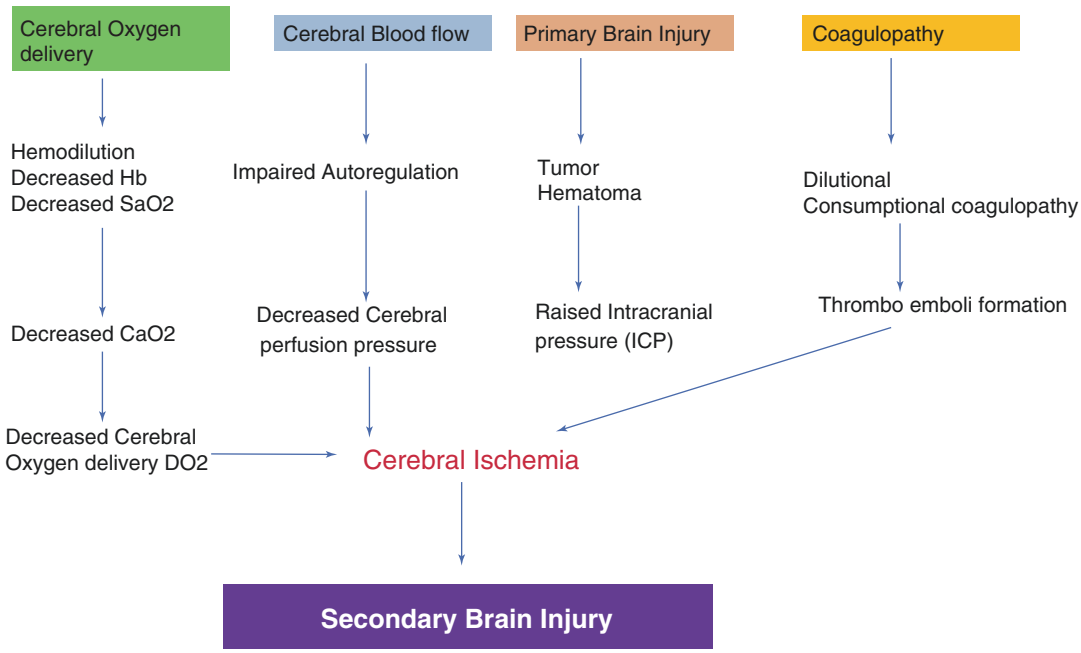

Fig. 27.1 Pathophysiology of secondary brain injury

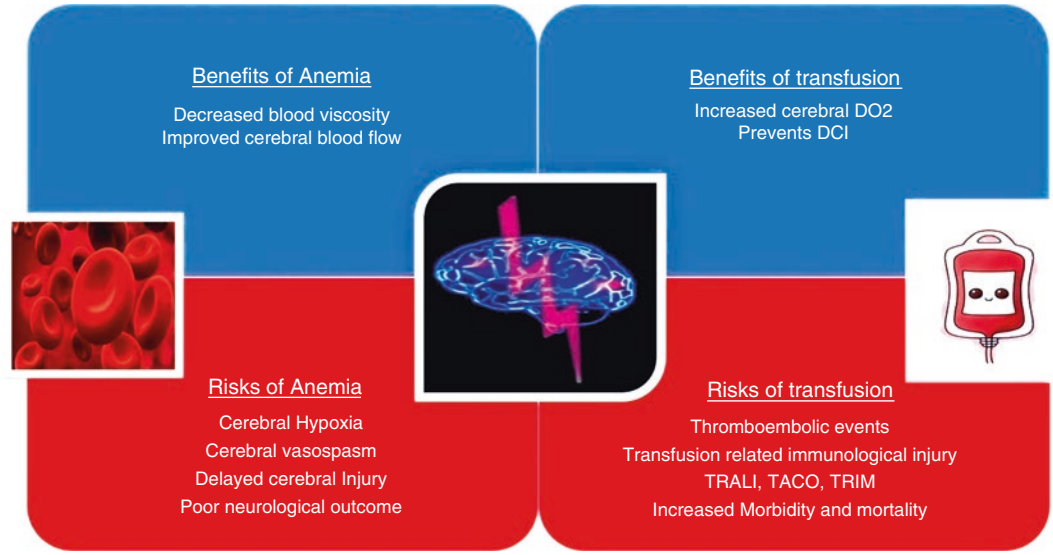

Fig. 27.2 Risks and benefits of perioperative anemia and transfusion

Table 27.1 Predictors for allogenic red blood cell transfusion in neurosurgeries

Surgeries	Predictors	References
Pediatric craniosynostosis	Craniofacial syndromes Pansynostosis Duration of surgery >5 h Age ≤ 18 months	White et al. [6]
TBI	Acute traumatic coagulopathy Associated major injuries	Epstein et al. and Boutin et al. [7, 8]
SAH	Intraoperative aneurysm rupture, poor grade SAH	Mc Ewen et al. [9], Luostarinen et al. [10]
Spine	Duration of surgery, multiple levels of fusion, Cobb's angle	Oetgen et al. [11]

27.2.2 Incidence and Predictors of Transfusion

The overall rate of allogenic transfusion in neurosurgical population is 1.7–5.4% (Table 27.1) [4, 5]. The range is much wider in specific surgeries like craniosynostosis (45%) and cranial vault reconstruction (95%) in pediatric population followed by traumatic brain injury (TBI) (36%) and aneurysmal subarachnoid hemorrhage (SAH) (25%). The predictors for allogenic red blood cell transfusion in specific neurosurgeries are represented in Table 27.1.

27.2.3 Complications

The benefits of red blood cell transfusion to improve oxygenation are achieved only when transfused blood efficiently stores and offloads oxygen, which should be properly utilized by the compromised tissue. Numerous studies have shown that these purposes are not achieved with transfusion of stored blood due to biochemical and mechanical changes in the RBCs (termed as "storage lesion"). Depletion of 2,3-diphosphoglycerate levels shifts the oxygen hemoglobin dissociation curve to the left, reducing the amount of oxygen available for tissue consumption. Mechanical changes in the RBCs (transformed to sphero-echinocytes) result in loss of deformability and compromise the microcirculation. There is an increase in RBC aggregability and endothelial cell adhesion resulting in microvascular obstruction.

Blood transfusion has been associated with increased risk of thromboembolic events, pro-

gressive hemorrhagic injury as evidenced by clinical trials in TBI and SAH [12, 13]. A high Hb concentration results in increase in blood viscosity and reduced cerebral blood flow further exacerbating the neurological damage.

Malone et al. had identified blood transfusion as an independent risk factor for mortality and ICU stay in his study of 15,534 patients over a 3-year period at a level 1 trauma center [14]. There is enough evidence to establish that transfusion of red cells itself is associated with an increased risk of morbidity and mortality [15, 16]. The mechanism is multifactorial, including transfusion-related immunomodulation (TRIM), infectious and allergic complications, transfusion-related lung injury (TRALI), and circulatory overload (TACO). These are often translated into consequences like ARDS, respiratory failure, prolonged intubation, sepsis, adverse cardiac events, and increased length of ICU and hospital stay [17, 18].

The immunological reactions are primarily mediated by donor leucocytes which do undergo structural changes following storage. Intuitively, the use of fresh and leuco-depleted blood might minimize the transfusion risks while maximizing the physiological benefits. However, specific effects of stored blood in neurocritical care patients need trial-based evaluations.

27.2.4 Blood Conservation Strategies in Neurosurgery

The conflicting evidences toward allogenic blood transfusion in neurosurgical procedures emphasize the application of blood conservation strategies (Fig. 27.3). *Preoperative measures* include identification and correction of coagulopathy and antithrombotic reversal especially in the setting of intracranial hemorrhages (has been described below in ICH) and erythropoiesis-stimulating agents. The role of erythropoietin (EPO) as transfusion-sparing agent has been established in critically ill patients by two large randomized

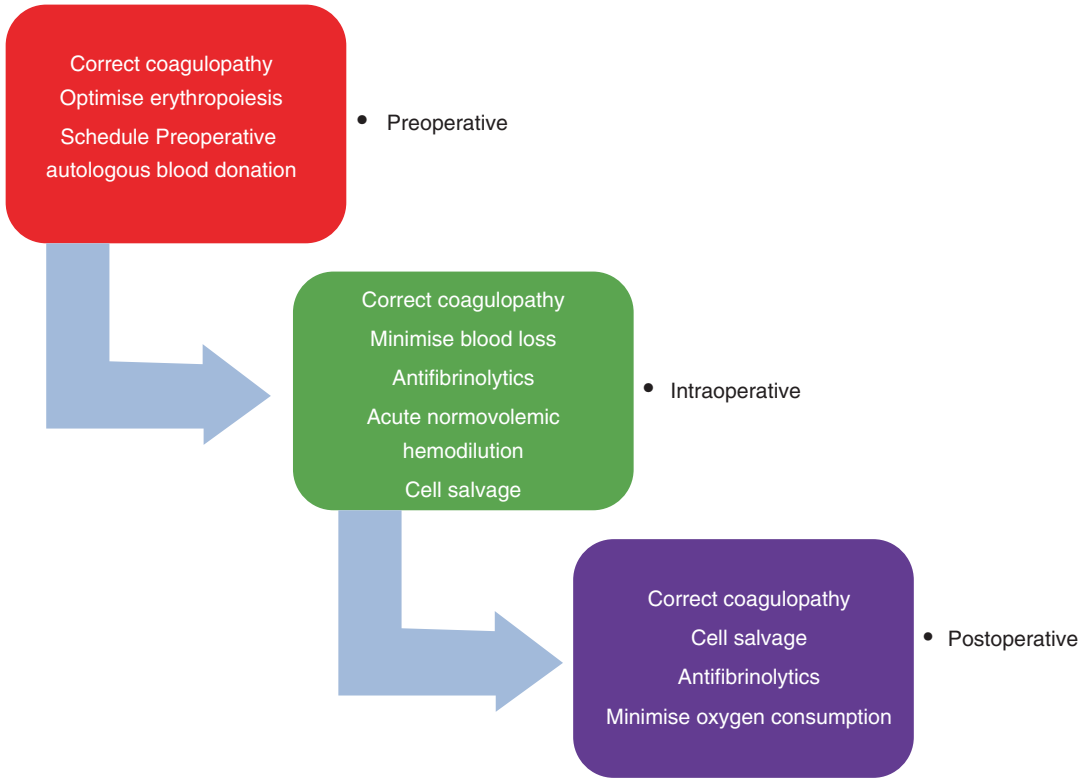

Fig. 27.3 Perioperative blood conservation strategies

controlled trials. The potential benefits of erythropoietin beyond anemia include cerebral protection after ischemic injury (stroke, TBI, vasospasm) via effects on preconditioning, reducing inflammatory responses, and restoring vascular autoregulation [19]. However, caution should be exercised in patients at risk of DVT and pulmonary embolism before administration of erythropoiesis-stimulating agents. Preoperative autologous donation (PAD) has been shown to reduce allogenic transfusion in many elective surgeries, but evidence for its beneficial role in neurosurgery is limited. As per the retrospective cohort by McGirr et al., PAD does not reduce the risk of allogenic blood transfusion in neurosurgery and hence cannot be recommended as a blood conservation strategy.

Intraoperative blood conservation strategies include avoidance of NSAIDS and starch solutions, administration of antifibrinolytic agents, acute normovolemic hemodilution (ANH), and cell salvage. NSAIDS and synthetic starch solutions are known to inhibit platelet function and are associated with an increased risk of hematoma formation following intracranial procedures [20].

Antifibrinolytics are a common group of drugs which are used for blood conservation in both intraoperative and postoperative periods. Antifibrinolytic therapy prevents lysis of existing clots along the traumatized edges of the bone resulting in reduced microvascular bleeding. There are two categories of antifibrinolytics in use for blood conservation. These include the lysine analogs—tranexamic acid and epsilon-amino caproic acid (EACA)—and the serine protease inhibitor, aprotinin.

The benefits of tranexamic acid, a synthetic lysine analog which acts as a competitive inhibitor of plasmin and plasminogen, have been proven in diverse surgical procedures. In the neurosurgical population, it significantly decreases blood loss in pediatric craniosynostosis [21] surgery, spine [22] and skull base surgery [23], and intracranial brain tumors [24]. For elective intracranial meningioma surgery, use of tranexamic acid has reduced blood loss by 27% [24]. The data from CRASH-2 trial [25] (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage) in trauma patients has shown a reduction in ICH size and mortality in patients who received tranexamic acid. In SAH it is associated with a reduction in re-bleeding albeit with an increased risk of cerebral ischemia [26]. The complications of tranexamic acid include increased risk of thromboembolism and seizures. The structural homology of tranexamic acid with GABA could be the reason for its competitive inhibition of the inhibitory receptors resulting in seizures.

The efficacy of epsilon-aminocaproic acid in reducing perioperative blood transfusion has been established in major spinal surgeries in both adult and pediatric age groups. EACA has been found to increase the levels of fibrinogen in the postoperative period predominantly [27]. A loading dose of EACA of 50 mg/kg followed by an infusion of 25 mg/kg/h is found to be associated with decreased blood loss and transfusion requirements during cranial vault reconstruction surgeries [27, 28].

Aprotinin, apart from inhibiting clot breakdown, also possesses anti-inflammatory properties. Other measures which have been tried for this purpose with little success include recombinant factor VII and aprotinin.

The evidence on the safety and efficacy of ANH as a blood conservation strategy in neurosurgery is limited. Although ANH has reduced the risk of allogenic transfusion in a small group of patients undergoing meningioma resection [29], it has failed to be of benefit in ruptured cerebral aneurysm [30]. Currently ANH can be recommended for elective neurosurgery with expected massive blood loss, in patients who are otherwise healthy. The technique may be considered if baseline hemoglobin concentration allows adequate hemodilution without hampering tissue oxygenation. Patients with poor cardiac and respiratory function are considered unsafe for this method of blood conservation.

The only study which evaluated the benefit of cell salvage in intracranial surgeries demonstrated that it was safe and decreased the amount of allogenic transfusion [31]. Cell salvage techniques are predominantly used in spine surgeries, particularly spine instrumentation and fusion, to

reduce the need for intraoperative transfusion [32]. But from the health economic viewpoint, cell saver is a costly alternative. Also, reservation exists due to their concerns over tumor dissemination and infection. With the development of newer cell salvage techniques and leucocyte depletion filters, its use has been extended to metastatic spine tumors [33]. Cell salvage technique can be considered as a reasonable choice in surgeries involving massive blood loss such as spinal deformity corrections and cerebral aneurysm rupture. Firm recommendations for its use in neuro-oncological surgeries cannot be formed at present due to paucity of data.

Nonpharmacologic approaches [27] include several different surgical techniques, patient positioning, ventilatory strategies, maintenance of normothermia, and controlled hypotension in major spine surgeries. Surgical techniques for improved hemostasis include spray on collagen-thrombin, fibrin sealant, kaolin-soaked sponges, and local vasoconstrictors [34]. The various considerations during patient positioning to decrease intraoperative bleeding include avoidance of extreme rotation of the neck (leading to jugular venous engorgement) and elevation of the operative site above the right atrium (to facilitate venous drainage). In prone position excess intraabdominal pressure can increase epidural venous pressure, thereby exacerbating blood loss. Use of prone positioning devices such as Relton-Hall frame reduces the inferior vena cava pressure to one-third as compared to conventional paddings [35]. Ventilatory strategies to reduce blood loss include maintenance of low intrathoracic pressures during controlled ventilation with minimal use of positive end-expiratory pressure and low tidal volumes [36]. Controlled hypotension for reducing blood loss in elective spine surgery can be achieved with intravenous anesthetics, inhaled agents, and direct vasodilators.

27.3 Monitoring Blood Loss

Continuous monitoring of vital signs and estimated blood loss are commonly used to guide transfusion decisions in the intraoperative period.

27.3.1 Systemic Monitoring

Systemic indicators to guide transfusion include inadequate oxygen delivery, indicated by mixed (SvO_2) or central venous oxygen saturation ($ScvO_2$) and lactate. Venous oxygen saturation is a clinical measure of the relationship between whole body oxygen uptake and delivery (VO_2–DO_2). Central venous oxygen saturation ($ScvO_2$) is often used as a surrogate to mixed venous oxygen saturation (SvO_2) in the absence of a pulmonary artery catheter. The normal SvO_2 value is in the range of 65–75% with $ScVO_2$ being considered to be 5% above these values. When DO_2 decreases, VO_2 is initially maintained by an increase in oxygen extraction up to a critical DO_2 value (DO_2 crit) beyond which there is a state of VO_2–DO_2 dependency. Such a state is usually found when SvO_2 falls below a critical value of 40% (SvO_2 crit).

Low SvO_2 or $ScvO_2$ is predictive of bad outcome in neurosurgical practices [37]. Surve et al. in their study on acutely ill neurological patients have established that baseline $ScvO_2$ value of <70% was a useful physiological trigger for blood transfusion in brain-injured patients [37]. However, the trend rather than absolute values of $ScvO_2$ correlates with SvO_2 during varying hemodynamic conditions [38].

Lactate is another important systemic biomarker which suggests inadequate oxygen delivery. Blood transfusion is shown to improve $ScvO_2$ and decrease lactate levels in critically ill patients [39]. However, no specific data are available evaluating the effects of transfusion on lactate levels in neurosurgical patients.

Intraoperative coagulation abnormalities are detected by viscoelastic tests such as rotational thromboelastometry (ROTEM) and thromboelastography (TEG). Both of them have been used to guide management of perioperative coagulopathy in adults and children [40]. Early detection of coagulation disorders reduces the exposure to fresh frozen plasma (FFP) and other allogenic blood products in the pediatric population.

More accurate method to guide RBC transfusion includes continuous and noninvasive Hb monitoring (SpHb) [41]. It provides real-time trends in Hb values and has been shown to reduce blood transfusion frequency. SpHb monitoring incorporates pulse cardiac output-oximetry tech-

nology and multiwavelength sensors thus providing continuous measurements in Hb and traditional pulse oximetry [41]. SpHb monitor provides earlier detection of attainment of threshold Hb, as assessed by real-time microcirculatory value, thereby reducing unwarranted transfusion.

27.3.2 Regional Cerebral Monitoring

Monitoring modalities such as near-infrared spectroscopy (NIRS), brain tissue oxygen tension ($PbtO_2$), and jugular bulb catheter sampling can be used to monitor the cerebral oxygenation and determine transfusion needs.

Near-infrared spectroscopy is an optical imaging technique used to monitor the variation of hemoglobin saturation in the tissues. It is used for continuous monitoring of regional cerebral oxygen saturation (rSO_2) during various surgical procedures. A desaturation of >20% from the baseline or an absolute saturation value of <50% is associated with an increased risk of neurological damage. The usefulness of this device has been demonstrated in patients undergoing elective heart [42] and major abdominal surgeries [43] who have an otherwise healthy brain. Use of NIRS in neurosurgery is limited due to practical difficulties of maintaining probe position for longer time period, contamination from extracranial blood and the validity is questionable [44].

Jugular venous oximetry is achieved by passing a cannula into the jugular bulb allowing continuous measures of oxygen saturation in the jugular bulb ($SjvO_2$). It is used as an indirect estimate of cerebral oxygen consumption as oxygen levels in the cerebral venous effluent correlates inversely with global brain oxygen consumption. This provides relevant information on adequacy of CBF in patients with TBI or SAH [45]. The major disadvantages of $SjvO_2$ are question regarding side of jugular venous cannulation and poor representation of regional brain hypoxia [45].

Brain tissue oxygen monitoring involves measurement of partial pressure of oxygen at tissue level directly by insertion of catheter probes in the region of interest. In TBI patients, Hb level of less than 9 gm/dl and $PbtO_2$ value of <20 mm of Hg were associated with poor outcome. Hence such patients should be considered as candidates for transfusion [46]. Limitations to the use of $PbtO_2$ include relative unavailability in many centers and the information being limited to particular area of brain. Thus, $PbtO_2$ in combination with $SjvO_2$ better identifies all episodes of cerebral ischemia (Fig. 27.4).

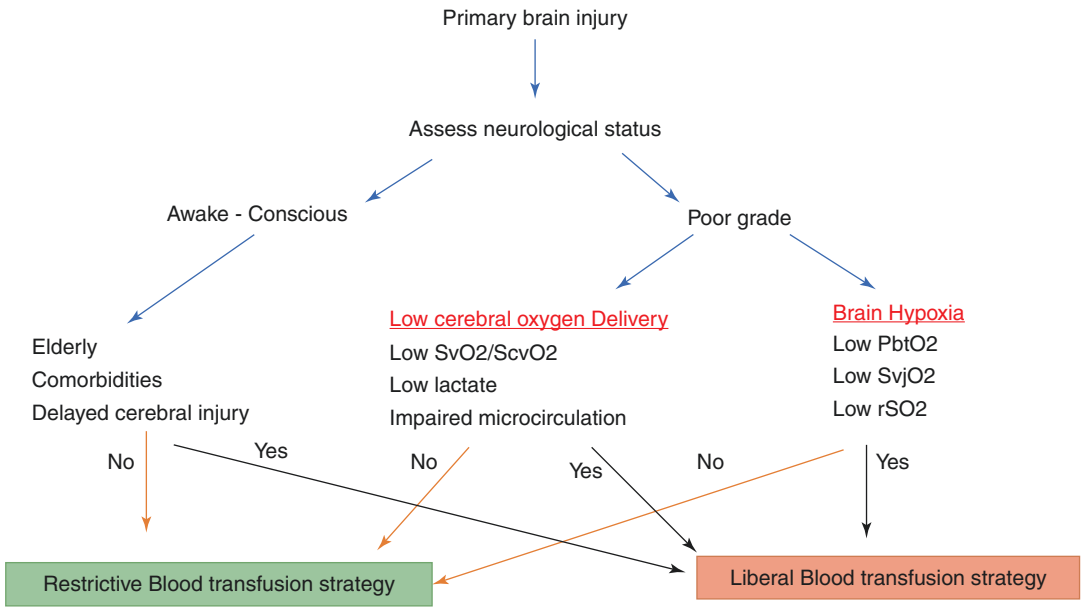

Fig. 27.4 Suggested management based on monitoring. SvO_2, mixed venous oxygen saturation; $ScvO_2$, central venous oxygen saturation; $PbtO_2$, brain tissue oxygen tension; rSO_2, regional cerebral oxygen saturation

27.4 Specific Situations

27.4.1 Traumatic Brain Injury

TBI is a common cause for emergency surgeries and mortality in most of the trauma centers in people less than 45 years. Traumatic brain injury is associated with almost 40–50% incidence of anemia, with patient presentation ranging from closed head injury to multiple injuries. The management of TBI patients focuses on avoiding secondary neurologic insult from reduced oxygen delivery as a result of hypoperfusion, hypoxemia, and anemia. The adaptive mechanisms to ensure an adequate cerebral oxygen delivery during anemia like cerebral vasodilation, decreased viscosity, increased cardiac output, and oxygen extraction are altered and may result in cerebral hypoxia at higher hemoglobin thresholds than in other populations [47]. But recent literature has failed to show any benefit from liberal transfusion therapy in this group of population [48].

To add upon to this complication, a scenario of coagulation disorder may coexist in TBI patients. Acute traumatic coagulopathy (ATC) is an acquired coagulation disorder that has been described in the context of isolated TBI and increases the possibility that a patient will require an RBC transfusion. In a recent meta-analysis, Epstein et al. [8] reported that ATC was uniformly associated with worse outcomes and high mortality that ranged from 17 to 86%. ATC was also associated with transfusion rates of 41%, as well as longer ICU stays, decreased ventilator-free days, and multiple organ failure.

Brain parenchyma is a rich source of tissue factor, which activates coagulation when released in TBI [9]. It has been postulated that hypoperfusion also has a role to play in coagulopathy of TBI. Brain injury has some detrimental effects on platelet function for unknown reasons. Usually patients may have associated injuries which predisposes to massive transfusion of various blood products. All these factors together contribute to the complex clinical state of coagulopathy and anemia in TBI.

It appears logical that maintaining higher hemoglobin levels might enhance cerebral oxygen delivery thereby improving outcomes in patients with TBI. But in reality, its complex decision to have a threshold hemoglobin for transfusion, as literature is lacking. Both in mild and severe TBI, transfusion is associated with poor functional outcomes. Transfusions do more harm than good in patients on both ends of the head injury severity spectrum. Carlson et al. [49] followed by Salim et al. [50] have proved that increasing transfusions have a negative impact on the Glasgow coma scale (GCS) and Glasgow outcome scale (GOS). Recent study by Warner et al. [48] concluded that in moderately anemic patients with TBI, RBC transfusions are associated with poor long-term functional outcomes. It is therefore essential to reassess transfusion recommendations in this population which have to be framed on the basis of randomized controlled trials.

Studies have shown significant variability in the response of brain tissue O_2 tension to transfusions, with some patients showing improved oxygenation and others having minimal or even decreased change in brain tissue O_2 tension [51]. It is unclear whether increasing brain tissue O_2 tension by transfusion has translated into improved clinical outcomes [52]. The relationship between hemoglobin and brain tissue oxygenation (before and after transfusion) is not well-defined and needs further studies. Brain tissue O_2 monitoring is also limited to only a few specialized trauma centers.

Preclinical and clinical data suggested erythropoietin, a glycoprotein hormone, as a promising candidate in place of transfusions in TBI. Erythropoietin has pleiotropic cytokine-like effects which ameliorated secondary brain injury after TBI [53]. But EPO TBI trial (erythropoietin in traumatic brain injury) has stated that erythropoietin did not reduce the incidence of severe neurological dysfunction at 6 months after moderate to severe TBI.

Current recommendations to maintain hematocrit levels >30% in otherwise hematologically stable patients should be reconsidered. Specific interventions aimed at reducing the demands and increasing the oxygen supply should be maximized before transfusion. Transfusion strategies

should be directed toward patients with symptomatic anemia or obvious signs of physiological compromise, such as decreased brain tissue O_2 tension, and transfusion volume should be minimized whenever possible. Other useful indicators like low venous hemoglobin, high lactate levels for inadequate systemic oxygen delivery and low regional hemoglobin saturation, and brain tissue oxygen tension for cerebral hypoxia can be helpful to guide transfusion [1].

27.4.2 Subarachnoid Hemorrhage

Anemia in SAH patients is caused by various factors like hemodilution induced as a part of the therapy for vasospasm, occult hemorrhage, surgical blood loss, aneurysm rupture and re-bleeding [54]. A growing body of evidence suggests anemia to be independently associated with poor neurological outcome and increased mortality [52] regardless of the SAH severity. Unlike other critically ill patients, those with SAH are of special concern, due to their well-defined risk of vasospasm and cerebral ischemia [55]. This makes them less tolerant to anemia and increases their likelihood to benefit from blood transfusion.

Risk factors for anemia after SAH include female sex, advanced age, worse clinical grade, lower admission Hb, and surgery. Intraoperatively, large blood loss may occur during clip reapplication or with aneurysm rupture. Even a short period of uncontrolled bleeding as during intraoperative rupture may be associated with excessive bleeding. Patients with anterior communicating artery aneurysms are most likely to receive transfusion, while those with internal carotid artery aneurysms are least prone. Other surgical factors contributing to excess blood loss include large aneurysms (>10 mm), multiple aneurysm obliteration, and intracerebral hematoma evacuation [55].

An important preventable factor associated with poor neurological outcome after SAH is delayed cerebral ischemia (DCI) [56]. DCI occurs in about 30% of patients and is often associated with arterial vasospasm which impairs CBF and cerebral DO_2. Anemia may exacerbate DCI by further reducing cerebral oxygen delivery. As the risk of vasospasm continues predictably for several weeks after aneurysmal rupture (greatest risk period between days 6 and 11), anemia may be most detrimental during this period. The optimal Hb threshold for transfusion in SAH patients remains unclear although Hb > 10 g/dL is associated improved outcome [57]. Prevention of vasospasm has seldom shown to improve clinical outcome, despite reduced vessel narrowing. This lack of association between clinical outcome and vasospasm has renewed interest in intensive care strategies to prevent DCI.

A liberal use of transfusion at Hb > 10 gm/dl may offset the benefits of increased oxygen-carrying capacity by increase in blood viscosity and reduced CBF. It has also been linked with medical complications, infection, vasospasm, poor cognitive performance, and poor outcome [52, 56]. The deleterious effects of transfusion (storage lesion) like altered nitric oxide metabolism, red blood cell adhesiveness, and aggregability appear integral to vasospasm [58]. Consequently, a restrictive transfusion policy (Hb −7 g/dl) has been suggested at least in patients with normal cardiac and cerebrovascular reserves. However many SAH patients, unlike traumatic injury patients, often have associated cardiac dysfunction [59], thus posing a relative contraindication to restrictive transfusion.

Lacking concrete guidelines, presently transfusion decisions for SAH patients should focus on an individualized assessment of anemia tolerance, risk of DCI, presence of cardiac dysfunction, feasibility of blood conservation strategies, and awareness of the potential risks and benefits of blood transfusion. The results of the ongoing Aneurysmal Subarachnoid Hemorrhage: Red Blood Cell Transfusion and Outcome (SAHaRA Pilot) [60], which aims to compare RBC transfusion triggers from 10 g/dL down to 8 g/dL, will probably give us firmer guidelines in this context. Awaiting its results, the Neurocritical Care Society guidelines [61] suggest a transfusion threshold of 8 g/L in SAH patients without DCI, with a more aggressive transfusion trigger of 9–10 g/L as a tier one rescue therapy in cases of DCI unresponsive to first-line therapy.

27.4.3 Intracranial Tumors

Surgery for intracranial tumors is associated with higher incidence of bleeding and transfusion as compared to other neurosurgical conditions. This excessive blood loss has led to several adverse clinical outcomes including increased duration of ventilator and ICU stay. Morbidity and mortality are directly related to intraoperative blood loss especially in those who lose >500 ml [62]. Blood transfusion is usually not required in astrocytomas, low-grade gliomas, and transsphenoidal pituitary tumor excisions. Cerebellopontine tumors and meningiomas in particular are notorious for bleeding due to high vascularity from carotid and vertebral arteries and from the site of dural attachment. Recent retrospective study stated that skull base meningiomas of size greater than 4.64 cm and operative time greater than 10 h are independent factors related to excess risk of blood loss and transfusion [63]. Endovascular embolization of the tumor, particularly when complete, reduces bleeding, thereby decreasing the transfusion demand.

Tissue plasminogen activator (t-PA) is present in larger quantities in glioblastoma compared to other tumors. The t-PA-induced hyperfibrinolysis adds upon to stress-induced consumption and dilutional coagulopathy associated with protracted intracranial surgeries. This may aggravate blood loss during intracranial tumor surgeries necessitating transfusion.

Blood transfusion, however, may be an independent risk factor for cancer progression owing to its immunomodulatory effects. Aged RBCs in stored blood and allogenic leucocytes have been implicated as the possible culprits for cancer progression, favoring the use of fresh leuco-depleted blood whenever feasible [64]. A restrictive threshold of Hb as compared to liberal strategy does not appear to prolong the length of hospital stay or the risk of morbidity and mortality in intracranial tumor surgery [65].

27.4.4 Spine Surgeries

The incidence of blood transfusion in spine surgery is about 20–35% and is aimed at improving tissue oxygenation. Reconstructive trauma, tumor, and multilevel spine surgeries are complicated by significant intraoperative blood loss. The surgical reasons for blood loss are exposure of the spine, stripping of the muscle off the bone, and leaving exposed surfaces of the muscle and bone. In elderly patients, the periosteum is thinner, and the osteoporotic bones have wider vascular channels [66]. There is an increased bleeding from the exposed bone in osteotomies and from the epidural plexus in laminectomies. Adult deformity correction surgeries are likely to involve multiple segments as their compensatory curves become structural and may require inclusion in the surgery. They also have a higher rate of revision surgery which are associated with greater blood loss [67]. Tumors of the vertebral column tend to be highly vascular in nature and carry a risk of allogenic blood transfusion.

Intraoperative blood loss and transfusion are among the factors influencing the outcome of patients in major spine surgeries. The number of units transfused perioperatively is associated with age, comorbidities, number of levels instrumented, magnitude of arthrodesis, preoperative Hb, duration of surgery, and complexity of the operation [11]. Congenital and neuromuscular scolioses are more likely to have clinical comorbidities than in idiopathic scoliosis reflecting a lower functional reserve and hence a greater need for transfusion [68]. Patient positioning plays an important role in reducing blood loss during spinal surgeries. The benefit of controlled hypotension in spine surgery is due to decreased blood extravasation and local wound blood flow with the lowering of arterial blood pressure. However epidural venous plexus pressure and intraosseous pressure which are important determinants of blood loss are independent of arterial blood pressure. The worrisome complications of controlled hypotension in spine surgery are postoperative visual loss and decreased perfusion to end organs including the spinal cord.

Antifibrinolytics like tranexamic acid effectively decrease transfusion requirements in this population [27]. There is an increased risk of venous thromboembolism after spinal surgery, but the role of antifibrinolytics as causative is questionable [69]. Autologous blood transfusion

and intraoperative cell salvage are the commonly used blood conservative method in elective spine surgery, which reduces the homologous blood exposure. Patients receiving blood transfusion in major spine surgeries have been found to have higher rates of surgical site infections and urinary tract infections [70].

Neuraxial opioids along with general anesthesia decrease intraoperative blood loss and need for transfusion in spine surgeries [71]. Unlike local anesthetics, intrathecal morphine when given alone neither causes hypotension nor interferes with neurological assessment, in addition to providing adequate pain relief. Though randomized controlled trials have proved this benefit, the mechanism still remains unknown.

27.4.5 Pediatric Neurosurgery

Though there have been multiple evolutions in anesthesia and surgical techniques in pediatric neurosurgery, yet there is no decrease in bleeding and allogenic blood transfusion. In intracranial surgeries the incidence of coagulation disorder is higher as compared to general pediatric surgeries. There has been reported evidence of hypercoagulable state in pediatric neurosurgery [72]. This phenomenon coupled with surgical blood loss and dilutional and consumptional coagulopathy may further amplify blood loss in this subpopulation. Children undergoing major craniofacial reconstructions, spine reconstructions, resection of vascular malformations, and tumors area at great risk for massive blood loss. Despite diligent efforts, assessment of blood loss in pediatric neurosurgery is difficult. There is an increased incidence of morbidity and mortality following transfusion in pediatric patients.

In children undergoing oncologic neurosurgeries, duration of surgery poses high risk of transfusion [72]. This is specifically attributed to the presence of large, highly vascular, inaccessible deep-seated lesions which are close to functional areas of the brain. Hemostasis disturbances are due to hyperfibrinolysis and loss of coagulation factors along with blood loss in craniotomies [72].

Craniofacial reconstructions need a special mention as they have a potential for excess blood loss ranging from 20 to 500% of patient's circulating blood volume even in the best centers [73, 74]. In these cases, the issue continues in the postoperative period as well in the form of blood loss in the drains. The patient factors which influence transfusion in pediatric spine surgeries include neuromuscular etiology, Cobb's angle of >50°, and a greater number of levels fused [11]. The presence of any one of these risk factors doubles the risk of transfusion as per Vitale et al. [75]. Protocol-based transfusion algorithms and blood-sparing surgical techniques have proved to reduce the transfusion of blood and products to some extent [73]. Acute normovolemic hemodilution, erythropoietin injection, acceptance of lower Hb levels, cell salvage techniques, use of antifibrinolytics like tranexamic acid, controlled hypotension, and factor administration (activated factor VII A, prothrombin complex concentrate) have been attempted with success in many studies [11].

Studies have demonstrated that lower hemoglobin levels are well tolerated by pediatric patients without adverse effects [76]. Blood conservation modalities can be safely used in pediatric neurosurgery with combined technique being more effective than any single modality.

27.4.6 Intracranial Hemorrhage (ICH)

Intracranial hemorrhage is a life-threatening condition, resulting from spontaneous bleed, vascular malformations, trauma, or anticoagulant therapy. An expanding intracerebral hematoma may have a rim of hypoperfusion due to mechanical compression and vasoconstriction of the surrounding vasculature producing the so-called perihematomal penumbra. However, oxygen extraction fraction is not increased in this region suggesting the hypoperfusion to be due to reduced cerebral metabolism. Thus, it remains uncertain whether transfusions help salvage the penumbral region and contribute to improve neurological recovery.

In patients with ICH, anemia is associated with larger hematoma volumes and is an independent predictor of unfavorable functional outcome [77]. Due to conflicting evidence from various studies, it still remains unclear whether treatment of anemia can improve outcomes after ICH [78, 79].

ICH related to anticoagulant use accounts for >15% of all cases. Prevention of hematoma expansion by blood pressure management and reversal of coagulopathy is an important consideration in the management of these patients. The newer oral anticoagulant drugs, which are being used in the setting of stroke, have no antagonists except for dabigatran. Hence it is very challenging for anesthesiologists to manage ICH which develop in the course of treatment with these anticoagulants. Specific recommendations have been drawn down by the Neurocritical Care Society for the reversal of these agents and they are given in Table 27.2 [80].

Table 27.2 Recommendations for reversal of antithrombotic agents

Antithrombotic agents	Reversal
Vit K antagonists (warfarin)	INR >1.4: Vit K 10 mg IV + 3 or 4 PCC IV If PCC unavailable FFP 10–15 ml/kg
Direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban)	Activated charcoal 50 mg within 2 h of ingestion, activated PCC 50 U/kg IV, or 4 factor PCC 50 U/kg IV
Direct thrombin inhibitors (argatroban, bivalirudin, dabigatran)	Activated PCC 50 U/kg IV or 4 factor PCC 50 U/kg IV For dabigatran reversal: activated charcoal 50 mg within 2 h of ingestion, idarucizumab 5 gm IV, hemodialysis
Unfractionated heparin	Protamine 1 mg IV for every 100 units of heparin administered
Low molecular weight heparin (enoxaparin, dalteparin, tinzaparin, nadroparin)	If <3–5 half lives since LMWH: protamine 1 mg/100 anti Xa units of LMWH If contraindicated rFVIIa 90 mcg/kg IV Enoxaparin reversal: protamine if <12 h since LMWH (0.5–1 mg IV/1 mg enoxaparin)
Danaparoid	rFVIIa 90 mcg/kg IV
Indirect factor Xa inhibitors (fondaparinux)	Activated PCC 20 U/kg or rFVIIa 90 mcg/kg IV
Thrombolytic agents (plasminogen activators)	Cryoprecipitate 10 units iv, if cryo contraindicated tranexamic acid 10–15 mg/kg or EACA 4–5 gm IV
Antiplatelet agents (NSAIDs, GPIIb/IIIa inhibitors)	DDAVP 0.4 mcg/kg IV If neurosurgical intervention: platelet transfusion

Adapted/translated by permission from Springer Nature: Neurocritical Care: Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine Frontera et al. [80]

27.4.7 Neurocritical Care

The most important goal in the management of patients in the neurosurgical ICU is avoidance of secondary brain injury. Delayed cerebral injury in the ICU is the result of conglomeration of several factors which impair cerebral DO_2 and include anemia, hypovolemia, hypoxemia, raised ICP, vasospasm, autoregulatory failure, and uncoupling of cerebral flow metabolism.

Anemia, common in patients admitted to ICU, and is further accelerated by frequent phlebotomy, reduced RBC survival, occasional hemorrhage, and dilution by large volume fluid resuscitation. Systemic inflammation interferes with the erythropoietin production and ability of erythroblast to incorporate iron. However, the manipulation of anemia to maintain cerebral DO_2 remains debatable. The significance of anemia and optimal transfusion thresholds may not be universally applied to all neurocritical care patients.

The Stroke: RelevAnt Impact of hemoglobin, Hematocrit and Transfusion (STRAIGHT) [81] trial conducted on critical care patients with severe ischemic stroke has concluded that both low hemoglobin and red blood transfusion are

associated with prolonged ICU stay. In ischemic stroke patients, the effect of hematocrit on outcome is therefore u-shaped [52] with both high and low Hb associated with poor outcome.

Presently there are no large randomized trials to guide transfusion practice in critically ill TBI and SAH patients. A recent survey conducted across 66 European trauma centers as part of the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI study [82]) found that 41% of the centers maintained target Hb of 7–9 gm/dl and 59% >9 gm/dl. Overall there was a lack of consensus across the European ICUs on blood transfusion management. In SAH patients, the consensus panel of the neurocritical care society strongly recommends blood transfusion to maintain a Hb concentration more than 8–10 gm/dl based on moderate-quality data.

27.5 Role of Hemoglobin-Based Oxygen Carriers (HBOC)

A lot of effort has gone into developing formulations to substitute red blood cell transfusion. Most of these formulations are Hb-based oxygen carriers (HBOCs). Blood substitutes present a promising strategy for resuscitation in patients of TBI when complicated with hemorrhagic shock. Substantial benefits on intracranial pressure, brain tissue oxygenation, and neuropathology have been suggested with the use of polymerized hemoglobin in TBI patients [69]. HBOCs possess a theoretical advantage over other fluids in neurocritical care by hemodilution-induced enhanced cerebral blood flow while simultaneously maintaining CaO_2. This concept has been validated in several preclinical studies in the setting of experimental ischemic stroke, TBI, and SAH. However, reports of myocardial infarction and mortality with the use of HBOC resulted in decrease in enthusiasm and its use. Hence it is important to develop recombinant hemoglobins which would maximize the benefits of oxygen affinity targeted to specific indications and minimize the inherent toxicities. This should be followed by preclinical studies in experimental models which closely mimic complex clinical scenario in the neurologic ICU.

27.6 Current Consensus

Concerns regarding the safety and efficacy of blood products have led to a paradigm shift in transfusion practices. In the Transfusion Requirements in Critical Care (TRICC) trial [83], a Hb trigger of 7 gm/dl was generally agreed upon, and liberal transfusion therapy was found to be associated with poor outcome. However, in this trial, patients with primary neurological injury were excluded.

In TBI patients, there is a clear agreement that Hb < 7 gm/dl requires transfusion. However, transfusion practices between thresholds of 7 and 10 gm/dl vary widely between studies [7]. Interestingly the recently updated Brain Trauma Foundation guidelines do not mention any threshold for transfusion in severe TBI [84]. A recently conducted international survey found that most of the clinicians initiated blood transfusion at a Hb threshold of 7–8 gm/dl in their ICU for brain-injured patients. Presence of associated noncerebral factors like coronary artery disease, active bleeding, and low mixed venous oxygen saturation would shift the Hb threshold to higher limits. In geriatric population, liberal transfusion strategies produce better outcomes with a decreased risk of 30-day and 90-day mortalities [85].

In SAH, patients should receive transfusion to maintain hemoglobin concentration above 8–10 gm/dl. Higher hemoglobin concentrations might be appropriate for those who have or at high risk for DCI. Current aneurysmal SAH management guidelines recommend transfusion in anemic patients at risk for cerebral ischemia but do not suggest any particular transfusion threshold. Restrictive transfusion therapy in this group of patients, who are at risk of vasospasm and DCI, is questionable. The results of ongoing Subarachnoid Hemorrhage: Red Blood Cell Transfusion and Outcome (SAHaRA) trial [60] in adult patients with aneurysmal SAH may

probably aid clinicians to arrive at a guideline for transfusion.

The common strategies employed in neurosurgical population to minimize the rate of allogenic blood transfusion include:

1. Acceptance of a low transfusion trigger of Hb (<7 gm/dl)
2. Initiation of EPO/iron therapy prior to surgery to improve preoperative Hb levels
3. Utilization of intraoperative blood salvage techniques
4. Blood and product transfusion based on standard laboratory tests for platelets, fibrinogen, TEG, ROTEM, etc.
5. Recommendations for transfusion of products include:
   (a) Arterial blood gas, TEG, complete blood count, and fibrinogen samples must be sent with the onset of microvascular bleeding or loss of 1 estimated blood volume.
   (b) Initiate packed red cell transfusion (10–15 ml/kg) with PCV <27% or Hb <9 gm/dl in the presence of ongoing blood loss.
   (c) Initiate fresh frozen plasma (10–15 ml/kg) at a reaction time (R) >10 min in TEG.
   (d) Platelet transfusion (5–10 ml/kg) is indicated with platelet count of less than 1 lakh/microL.
   (e) Cryoprecipitate infusion (10–15 ml/kg) should be started at fibrinogen <100 mg/dl.
   (f) With persistent bleeding after 30 min, TEG and fibrinogen levels should be resend and managed accordingly.

27.7 Future Directions

The TRansfusion Strategies in Acute Brain Injured Patients (TRAIN) trial (ClinicalTrials.gov NCT02968654)—endorsed by European society of Intensive Care Medicine—compares liberal and restrictive transfusion strategy in TBI, SAH, and ICH patients. The HEMOglobin Transfusion Threshold in TBI OptimizatioN (HEMOTION) trial (NCT03260478) being conducted in Canada is evaluating the effects of RBC transfusion thresholds on neurological outcome in TBI patients. These along with the SAHARA study [60] should provide reliable evidence to guide transfusion therapy in most of the neurosurgical patients.

An individualized approach, intended to target physiological end points like cerebral tissue hypoxia rather than a hemoglobin cutoff, guided by multimodal neuromonitoring, has to be validated through large randomized clinical trials. Development of future guidelines based on trials in this direction would help improve outcome in most of the neurocritically ill patients.

Key Points

- Anemia-induced cerebral hypoxia is manifested at higher threshold of hemoglobin in a setting of acute brain injury than compared with normal brain.
- The risks of transfusion as weighed against the benefits have rewritten the transfusion threshold in neurosurgical population. The ideal strategy between restrictive and liberal transfusions therefore remains a clinical equipoise.
- Blood conservative strategies during the perioperative period along with advanced technologies in monitoring cerebral oxygenation have reduced unwarranted transfusion to a major extent.
- In TBI patients, there is a clear agreement that Hb < 7 gm/dl requires transfusion. However, transfusion practices between thresholds of 7–10 gm/dl vary widely between studies.
- In SAH, patients should receive transfusion to maintain hemoglobin concentration above 8–10 gm/dl. Higher hemoglobin concentrations might be appropriate for those who have or at high risk for DCI.

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Part VIII

Near Misses

Near Misses in Neuroanesthesia

28

Zakir Hajat and Zoe Unger

28.1 Introduction

A near miss in healthcare is defined as an unplanned, preventable event that can potentially cause physical or psychological harm to a patient and/or physician. Preventable errors have significant human and financial costs [1]. These adverse events offer unique learning opportunities—understanding the causes of preventable errors is crucial to preventing them from happening again [2]. It is important to recognize that near misses differ from recognized patient complications; patients are counselled about potential complications as part of the consent to treatment. In this chapter, we approach the subject of near misses using the airway-breathing-circulation (ABC) method familiar to healthcare professionals worldwide and suggest management strategies to avoid these preventable errors.

28.2 Airway Events

28.2.1 Accidental Extubation

28.2.1.1 Background

Deviation from the familiar supine position adds complexity to neurosurgical procedures. Posterior approach spinal surgery is ordinarily performed in the prone position, and cranial procedures can be performed in a variety of nonstandard positions, such as park bench, lateral, and sitting. Moving the anesthetized patient post-induction is a potentially hazardous process in which a poorly secured endotracheal tube (ETT) can be advanced into a bronchus, dislodged, or extubated completely. In the prone and lateral positions, restoring oxygenation and ventilation can be exceptionally difficult without a secured airway and in an anesthetized or paralyzed patient can result in catastrophic hypoxia.

28.2.1.2 Recommendations

Waterproof adhesive tape adheres well to clean dry skin. Oily and/or bearded faces can pose challenges because tape and dressings do not adhere well to them; however, a topical adhesive, such as benzoin tincture, can improve their adhesiveness. Another near miss with taping can occur if the application of alcohol- or betadine-based surgical sterilizing solutions seeps into the tape adhesive, reducing its effectiveness. Clear film dressings applied over the tape can minimize this problem. To prevent the ETT from being dislodged while moving a patient, disconnecting the airway tubing prior to the patient turn (and pausing gas flow to minimize theater pollution) is good practice and reduces the possibility of inadvertent tension on the ETT. Preoxygenation with high FiO_2 concentration before any positioning maneuvers may prove beneficial in the event of an accidental extubation because it provides a

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marked delay before developing cyanosis. The benefit of this should be balanced against the risk of absorption atelectasis caused by high oxygen concentrations [3].

In the event of accidental extubation, call for help early. Bag-mask ventilation is not ideal in the prone position, and a supraglottic airway device is a satisfactory temporizing measure; it may provide an invaluable means of ventilation while the patient is repositioned for re-intubation [4]. The patient may require a turn on the Jackson table and removal of Mayfield pins, or the patient may need to be turned back onto an inpatient bed from a Wilson frame or similar device; during prone cases, therefore, a patient bed should be available immediately outside the operating room. Re-intubation can be achieved through a variety of methods as long as oxygenation is maintained; examples include fiber-optic intubation, indirect video laryngoscopy, or intubating via a supraglottic device. The experience and competence of the operator in the chosen method are more important than the method itself; attempting rarely practiced airway skills in a stressful situation is not recommended.

28.2.2 Extubation Timing and Management

28.2.2.1 Background

The timing of extubation is particularly important after neurosurgical procedures. Acutely brain-injured patients and elective neurosurgical patients may have postoperative neurological deficits. Airway protective reflexes are impaired by anesthesia, and an added neurological insult can impair them further. Assessments of neurological and airway reflexes recovery must be undertaken to assess the timing of extubation. Posterior fossa craniotomy is especially associated with impaired upper airway reflexes, and patients having undergone this procedure are most frequently re-intubated and readmitted to ICU [5]. Unnecessarily delayed extubation is associated with the added risks of ventilator acquired pneumonia, prolonged ICU and hospital stay, and economic burden [6].

28.2.2.2 Recommendations

Short-acting anesthetic and analgesic agents facilitate rapid recovery and extubation; recommended methods to achieve these goals include target-controlled infusions (TCI) of remifentanil and propofol titrated to processed EEG depth of anesthesia monitoring or vapor-based anesthesia. A rapid recovery is desirable to allow for an early diagnosis of intraoperative complications, which may improve outcome [7]. The value of rapid recovery must, however, be balanced against the risk of rapid awakening, which can result in emergence hypertension leading to intracerebral bleeding or cerebral edema. Emergence hypertension should be anticipated and controlled with short-acting intravenous alpha- and/or beta-blockers; infusions are rarely necessary in the anesthetic recovery period.

An assessment of neurological recovery should include motor function, the ability to follow commands, and the presence of adequate upper airway reflexes to support extubation. If a gross neurological deficit is identified, it should be investigated with a radiological assessment. Extubation in this scenario is unadvisable; cerebral hemodynamics should be optimized and gas exchange tightly controlled during the patient's transfer to the radiology department for imaging.

Cervical spine cases should be extubated at the end of the case unless there is a concern regarding airway edema. During prolonged prone surgeries it is possible, though rare, for significant airway edema to occur; direct and indirect visualization and assessment of the airway as well as an ETT cuff leak test (described in the following section) can help determine suitability for extubation.

28.2.3 Tongue Damage and Airway Edema

28.2.3.1 Background

Macroglossia in neurosurgery is a potentially serious complication, and the cause is often unclear. Prolonged prone positioning results in dependent edema affecting the face and oropharynx; however,

this is usually self-limiting. Sustained tongue protrusion, inadvertent tongue biting during motor-evoked potential (MEP) testing, venous engorgement from oral crowding, and flexed surgical positioning (prone, park bench, and sitting) resulting in impaired venous and lymphatic drainage are recognized risk factors [8–10]. Posterior fossa disease has also been linked to neuroendocrine-mediated macroglossia [11]. Serious hypoxic injury may occur from extubation in the setting of unrecognized macroglossia, and re-intubation of the trachea via the oral route may not be possible, thus leading to emergency surgical airway management.

28.2.3.2 Recommendations

Unfortunately, there is no proven method for eliminating the risk of macroglossia; therefore, preventative measures must be employed. Recognition of the complication and knowledge of the appropriate actions to avoid the loss of a secured airway are extremely important. Oropharyngeal airways, extreme flexion, and oral overcrowding should be avoided because they may impair venous drainage of the tongue [12, 13]. The use of a bite block between the incisors pushes the tongue back into the oropharynx assisting venous drainage; however, when the tongue protrudes laterally, it can be lacerated by molar teeth during MEP testing, and care must be taken to avoid this. Proprietary bite blocks (BB) are available to purchase, or a roll of cotton gauze wrapped in tape will suffice. Care must be taken to fix the BB appropriately so that it does not advance into the airway unnoticed and be retained leading to complete airway obstruction.

The assessment for extubation after surgery can include an oropharyngeal examination with either direct or indirect (video) laryngoscopy to assess the degree of supraglottic edema and/or an ETT cuff leak test. This test was originally designed to detect the probability of post-extubation stridor, which is suggestive of glottic edema and the increased likelihood of re-intubation [14, 15]. An ETT cuff leak test is a useful assessment tool to determine the timing of extubation, but it does not provide reliable information on supraglottic structures or degree of supraglottic edema because the oropharyngeal airway remains stented open with the presence of an ETT. The cuff leak test is performed by deflating the ETT cuff and calculating the difference in inspiratory and expiratory tidal volume on a ventilator, which quantifies the volume of air leak [16]. In the cuff leak test, a leak of >10% of the tidal volume or 110 mL is considered a negative cuff leak (high value). A negative test implies leakage of air around the ETT at the level of the glottic opening; a patency must exist between the ETT and trachea for a leak to be present. The absence of air leak or a positive test suggests edema surrounding the ETT at the level of the glottic opening [15, 17].

28.2.4 Vocal Cord Injury (VCI)

28.2.4.1 Background

VCI can occur during anterior cervical decompression and fusion (ACDF) surgery and carotid endarterectomy [18–22]. The incidence is unclear, although studies have suggested a rate of approximately 1–11% [23]. Revision surgery is associated with higher risk of VCI, but single-level versus multilevel ACDF surgery has not been shown to significantly affect the risk [24]. The recurrent laryngeal nerve (RLN) lies between the trachea and esophagus, and RLN injury may result from direct damage or sustained retraction during surgery [25]. The over-inflation of the ETT cuff has been attributed to VCI, especially when tissue retraction is applied externally [26]. Although VCI is a recognized complication of surgery, some anesthesia strategies are recommended to mitigate its risk.

28.2.4.2 Recommendations

Interventions relevant to anesthesia for the prevention of VCI are limited because VCI is primarily a surgical complication. While there is little data available about its efficacy, deflating and reinflating the ETT cuff to the point of minimal leak has been suggested as a method of minimizing cuff pressure and so minimizing one potential risk of VCI; this technique should be used in conjunction with a cuff pressure gauge to

maintain cuff pressures <20 cm H_2O [27]. A balance needs to be achieved between minimizing the cuff pressure and maintaining sufficient pressure to form an adequate seal to effectively ventilate the patient.

In thyroid surgery, intraoperative monitoring of recurrent laryngeal nerve provides an early warning of changes in RLN function secondary to retraction [28]. ETT's with incorporated recurrent laryngeal nerve monitoring are readily available, although most studies demonstrating their efficacy are in thyroid surgeries. Dimopoulous et al. investigated intraoperative laryngeal EMG during ACDF surgery in 298 patients and found a sensitivity of 100% and specificity of 87% for vocal cord palsy.

Before extubation, an ETT cuff leak test should be performed to assess the suitability of extubation, because significant tissue edema may develop from surgical retraction. While bilateral cord paralysis is extremely uncommon during ACDF surgery, it can result in complete airway obstruction—the few case reports that are available are in the setting of a previous injury to one of the RLN's. In two case reports, the patients had pre-existing unrecognized unilateral RLN palsy from a previous surgery, and an ACDF procedure resulted in damage to the remaining healthy RLN, leading to bilateral vocal cord dysfunction [19, 29].

28.3 Cardiac Events

28.3.1 Cardiovascular Collapse

28.3.1.1 Background

Hypovolemia is poorly tolerated in the prone position. Compression of the inferior vena cava results in reduced venous return to the heart, deleteriously affecting cardiac output [30]. This reduced venous return is not usually clinically significant in a well-hydrated patient presenting for elective surgery; however, acutely unwell patients presenting with mass effect cranial pathology may have cerebral edema causing significant nausea, vomiting, and dehydration. These patients may precipitously decompensate in the prone position.

Prone positioning systems have varying effects on hemodynamic physiology. A study tracking transesophageal echocardiographic changes on five different systems (Andrews, Wilson, Jackson, Siemens, and Bolster) found that prone positioning caused reductions in cardiac output, stroke volume, and the left ventricular end systolic/diastolic area. Restoration of fluid deficit prior to induction of anesthesia was found to blunt hemodynamic changes. The Jackson table produced the least effect on cardiac function compared with Andrews, Wilson, and Siemens, although the differences were not clinically significant in healthy patients undergoing elective surgery [31].

Severe bradycardia may present during neurosurgery. The trigemino-cardiac reflex (TCR) is a well-established phenomenon most commonly associated with sudden bradycardia and fall in cardiac output. The dura is innervated by the maxillary (v2) and mandibular (v3) branches of the trigeminal nerve [32]. Dural stretch caused by raised intracranial pressure or direct trigeminal nerve manipulation during microvascular decompression surgery can lead to activation of a reflex mechanism. Trigeminal afferent pathways connect with the vagal efferent pathways via the Gasserian ganglion in the reticular formation, thus potentially resulting in bradycardia or asystole and falls in mean arterial pressure [33–35]. Similar events may also occur both during cerebellar and upper thoracic spinal cord surgeries and because of autonomic dysreflexia in spinal cord injury patients [34].

28.3.1.2 Recommendations

Accurate volume status is difficult to assess without a pulmonary artery flotation catheter, but its use is becoming increasingly rare, marking a movement away from direct measurement of intravascular volume status toward noninvasive methods of measurements. Pulse pressure variability and stroke volume variability are surrogate measures of intravascular fluid volume responsiveness, and their use is well recognized in supine ventilated patients in the operating room and intensive care [36]. The literature also finds their use relevant in prone position surgeries [37]; their

use requires invasive arterial monitoring that is often already indicated in cranial and spinal procedures. Arterial lines are sited in the supine position, allowing the physician to track changes in pressure/volume variability from supine to prone position and to address hemodynamic changes appropriately. Transesophageal echocardiography is an excellent resource available in unique circumstances, such as with critically ill patients, but its wider availability is limited without a cardiac anesthetist present.

Severe bradycardia is often difficult to avoid. Preemptive treatment with anticholinergic drugs, such as atropine and glycopyrrolate, has been demonstrated to be effective [35]. Topical lidocaine has also been used with success in some cases [38], and a combination of both therapies can eliminate TCR effects altogether [39]; however, simple measures, such as avoidance of hypoxia, hypercarbia, acidosis, and careful surgical manipulation, should be considered first-line management strategies [39].

28.3.2 Paradoxical Air Embolus (PAE)

28.3.2.1 Background

Venous air embolism (VAE) is a relatively common phenomenon in neurosurgery. Small VAE are often missed, and these benign events are usually clinically insignificant. VAE can be particularly dangerous when they cross over to the arterial circulation, resulting in paradoxical air emboli (PAE) which can in-turn result in cryptogenic stroke. During neurosurgery the operative site is frequently above the level of the heart, especially in the sitting, lateral, park-bench, and prone positions; this poses the risk of VAE entrainment. Sitting position incurs the highest risk of VAE, recent studies on sitting position craniotomy have shown an incidence of up to 20% [40], and 2.7% of these have clinically significant sequela [41]. A volume of approximately 3–5 mL/kg can lead to fatal VAE; however, this figure is based on animal studies [42].

PAE results from a patent foramen ovale (PFO), and PFO has an overall incidence of 27%. Cadaveric studies of normal hearts have reported a higher incidence (34%) in the first three decades of life and a decrease in incidence during the fourth to eighth decades (25%) [43]. Sitting position neurosurgery is contraindicated in patients with known PFO due to the dangers of VAE leading to a PAE [44].

28.3.2.2 Recommendations

Craniotomy in the sitting position is still used in many centers. Though risk of VAE is relatively high, sitting position offers good surgical exposure due to better venous drainage from the operative site. This position is typically used for posterior fossa surgery as well as for surgery in the cranio-cervical junction. Central venous cannulation (CVC) is often recommended for procedures in sitting position. Monitoring of the central venous pressure is useful for determining if there is negative pressure at the surgical site, which causes entrainment of air from the open venous sinuses. In addition, a multi-orifice central venous catheter can be useful for aspiration of air in the event of VAE; however, in order for this to be successful, the tip of the CVC has to be in close proximity to the right atrium.

Patients undergoing elective sitting surgery should have echocardiogram to rule out the presence of PFO because of the risk of PAE. Though the presence of PFO is a contraindication for sitting position, there are reports of percutaneous closure of the PFO prior to the sitting position surgery [45].

28.4 Miscellaneous Events

28.4.1 Medications

28.4.1.1 Background

Phenytoin and mannitol are often used in neurosurgery; these medications must be administered appropriately as careless administration can result in significant side effects.

Phenytoin is an older-generation anti-seizure and anti-arrhythmic medication which has fallen out of favor in the management of epilepsy due to its significant side effect profile, pharmacokinetic variability, and potent enzyme induction

properties. Ironically, as with many anti-arrhythmic drugs, it has the potential to cause arrhythmias despite its use in treating them. Other side effects include hypotension, respiratory arrest, and phenytoin toxicity leading to bradycardia and death [46]. It has a narrow therapeutic range, and small dose increases can result in large increases in plasma concentration in patients who have saturated the enzyme systems responsible for its metabolism [47]. It is still used in acute seizure control in the neurosurgical setting, although preemptive use for post-craniotomy seizure prophylaxis is controversial, and a recent Cochrane systematic review did not find evidence to support this indication [48].

Mannitol is an osmotic diuretic used to achieve brain relaxation and to reduce cerebral water content in a "tight brain" or as a rescue measure in critically high ICP. The latest Brain Trauma Foundation Guidelines [49] advocate hyperosmolar therapy for temporary control of raised ICP. Mannitol has significant side effects, such as hypovolemia, renal injury, and electrolyte disturbance; for this reason, hypertonic saline use is increasing over and above mannitol, and recent systematic reviews suggest it is a superior agent; however, the same precautions apply [50–52].

28.4.1.2 Recommendations

The recommended loading dose of phenytoin is 10–15 mg/kg, at a rate no greater than 50 mg/min. Phenytoin is an irritant and should be infused into a large vein.

Mannitol is administered at a dose of 0.25–1 g/kg and infused over 30–60 min. Under- and overdosing errors are common in Mannitol's administration [53]. Underdosing results in insufficient brain relaxation and failure to lower ICP; overdosing causes hypotension and electrolyte disturbance, leading to lower cerebral perfusion pressure and worsening brain injury. Rapid dosing can cause sudden volume expansion, which can precipitate cardiac failure in those at risk.

Free flowing intravenous fluids with added drugs can be hazardous if managed inappropriately. In an emergency or trauma setting, the presence of medications in intravenous bags can be overlooked and administered as boluses inadvertently. Therefore, a volumetric pump programmed with a drug library for drug preparation is safer practice.

28.4.2 Perioperative Vision Loss (POVL)

28.4.2.1 Background

Perioperative vision loss in non-ocular surgery has an incidence of 0.01–0.1% [54–56]. Although extremely rare, POVL is a devastating outcome. Depending on the nature of the injury, the causes of POVL are multifactorial [54, 57, 58]:

- Anterior or posterior ischemic optic neuropathy (painless, unilateral, or bilateral)
- Vascular injuries, such as central or branch retinal artery occlusion, and orbital compartment syndrome impeding ophthalmic venous flow (painless, unilateral)
- Corneal abrasions, lacerations, and chemical irritation (painful, unilateral)
- Cortical blindness
- Acute angle glaucoma (painful, unilateral, or bilateral)

Surgical and anesthesia-related factors that have been associated with POVL include prolonged surgery in the prone position (>6 h), large blood loss, anemia, low hematocrit, hypotension, and administration of large quantities of crystalloids [59]. Patient-specific factors that predispose the patient to small-vessel disease, such as hypertension, diabetes, and vascular disease, confer a higher risk of POVL.

28.4.2.2 Recommendations

The American Society of Anesthesiologists Task Force on Perioperative Visual Loss [60] has published guidance on strategies to minimize POVL.

- Direct pressure on the eye must be stringently avoided. This alone will not prevent all vision loss complications; however, inadvertent pressure on the globe for a prolonged surgery is preventable. Care must be taken during prone positioning of the head to ensure that the eyes

are free of pressure and that padding does not cover the eyes. A reflective mirror can help ensure that the eyes are safe. Additionally, positioning the head above the level of the heart improves dependent edema.

- Hemodynamic management must be tailored appropriately to the patient. Large volumes of crystalloid are inadvisable; however, strong evidence for synthetic colloids does not exist in the literature either [60].
- Anemia and hematocrit must be monitored periodically. Lower cutoff limits of 9.4 g/dL and 28%, respectively, have been suggested [61], but no strong evidence exists in the literature to support the use of these cutoff values.
- The duration of surgery is an important risk factor, and staging lengthy surgeries may be beneficial to avoid prolonged prone position.
- Protection of the eyes with film dressings and tape can usefully prevent ingress of skin sterilizing solutions.

28.4.3 Limb Ischemia and Nerve Injuries

28.4.3.1 Background

Prone and lateral position surgery is associated with a variety of nerve injuries due to a combination of direct pressure and impaired intraneural venous drainage. Examples of nerves that can be injured during this surgery include the lateral femoral cutaneous nerve [62] and the brachial plexus [63], among others. Patients with preexisting neuropathy or conditions that predispose patients to neuropathy, such as diabetes, hypertension, and malnutrition, are particularly at risk for nerve palsies [57]. Critical limb ischemia may occur due to impaired blood supply to a badly positioned limb, resulting in significant muscle necrosis and edema, which may require fasciotomies postoperatively.

28.4.3.2 Recommendations

Continuous monitoring of somatosensory evoked potentials (SSEP) is increasingly employed in neurosurgery for early detection and prevention of nerve injury [64]. It can also be used to detect changes in amplitude and latency of upper limb SSEP's. Case reports identify instances where changes have been detected and subsequently resolved after a corrective adjustment in limb position. Usual precautions should be taken to ensure neutral positioning of the limbs. The humerus should be positioned anterior to the thoracic cage in the prone position [65] and padding used to protect against direct pressure on the limbs from the bed frame and arm supports.

Key Points

- In the prone and lateral positions, restoring oxygenation and ventilation can be exceptionally difficult without a secured airway and in an anesthetized or paralyzed patient can result in catastrophic hypoxia.
- The timing of extubation is particularly important after neurosurgical procedures.
- Macroglossia in neurosurgery is a potentially serious complication, and the cause is often unclear.
- Vocal cord injury can occur during anterior cervical decompression and fusion (ACDF) surgery and carotid endarterectomy.
- Hypovolemia is poorly tolerated in the prone position.
- Venous air embolism and postoperative vision loss are serious neurosurgical complications.

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29 Near Misses in the Intraoperative Brain Suite

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29.1 Background

Errors occur across all industries including the medical field. In the context of medicine, an error can be defined as any mistake that harms or could cause harm to a patient [1, 2]. Medical errors range from the most severe, wrong-patient and wrong-site surgery, to the most miniscule, such as dropping a syringe to the floor. When analyzing errors in medicine, it is important to realize the difference between a near miss and medical negligence. Near misses are a subset of errors that had potential to cause harm to the patient but are discovered and corrected before harm can be caused to a patient or an adverse event occurs [1, 2]. Negligence occurs when a physician or other healthcare professional, directly involved in patient care, does something outside of the acceptable standard of care leading to foreseeable harm to the patient [3]. If negligence is involved, malpractice claims usually proceed.

Preventable errors and near misses are widespread throughout medicine. In primary care literature, preventable errors and near misses can be divided into three categories: misdiagnosis, mistreatment, and inappropriate or complicated preventive services [4]. A study on adverse drug events published by Bates et al. found that near misses in drug administration were more likely to be caused by an ordering error (56%) than an administration error (24%). In two Boston, Massachusetts hospitals, 7.3% of admissions had a preventable adverse drug event or near miss during their stay [5, 6]. Preventable errors and near misses are twice as more likely to occur due to omission (i.e., misdiagnosis or a delay in treatment/drug administration) than commission (incorrect drug use) [6].

Surgical errors are prevalent due to the multispecialty and complex nature of the perioperative setup. Preventable errors occur during all phases of perioperative care. Rogers et al. conducted an analysis of 444 malpractice claims involving various surgeries. It was determined that the vast majority of surgical errors occur intraoperatively (75%), 25% occurred preoperatively, 35% postoperatively, while 31% of cases had errors in multiple phases of surgical care [7].

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Preventable mistakes across all fields of surgery include wrong-site surgery and retained foreign bodies/surgical items after surgical closure. Although these events are rare, they still occur and are easily prevented by effective communication and following proper sign-in and sign-out procedures. Gibbs et al. and Mahran et al. reported that foreign objects are left inside patients after surgery in 1 case per every 8000–18,000 surgeries, the most common retained foreign object being surgical sponges [8, 9]. Wrong-site surgery is defined as any surgery that is on the wrong patient, on the wrong side, or when the wrong procedure is conducted. Devine et al. estimates that the rate of wrong-site surgery is anywhere from 0.09 to 4.5 cases per 10,000 surgeries [10]. The rate of errors and near misses is also dependent on the type of surgery, the highest incidence being reported with gastrointestinal, spine, non-spine orthopedic, and cardiothoracic surgeries [7].

In laparoscopic surgery, there are a different set of common preventable errors, such as minor bleeding, thermal injury to tissue outside the intended surgical area, and serosal tears. Typically, these errors are caused by misuse or the increased force of the laparoscopic surgical equipment/tools [11]. Perioperative anesthesia care could be confronted with multiple near miss errors as well. Difficult intubation, hard to extubate patients, medication error, and allergic reaction are examples [12].

29.2 Near Misses in the Intraoperative Suite: Published Literature

29.2.1 Case Scenario #1: Anesthesia-Related Near Misses

Common anesthesia errors and near misses are those involving intubation, difficult emergence from anesthesia, allergic reaction to anesthetics, hypotension, and arrhythmia. An analysis of 83,844 surgical cases found that preventable errors from anesthesia occurred in a total of 82 cases (0.1%), with intubation and emergence problems being the most common [12].

Anesthesia-related complications during airway approach occurred in 0.2% of all anesthesia cases requiring tracheal intubation. Almost half of these problems were deemed to be preventable and included failed recognition of anatomy that caused difficult intubation, the use of the wrong primary airway approach in patients with known difficult airway, and accidental extubation followed by difficult reintubation. Additionally, 85% of the complications reported during emergence from general anesthesia involved severe airway or oxygen saturation problems. The underlying errors in these cases were misjudgment of residual anesthetic effect and premature extubation attempts. All errors were considered preventable [12].

A study published in 2016 by Nanji et al. described the nature of perioperative medication errors. They found that 5% of all medication administrations involved a medication error or adverse event, 79.3% of these incorrect administrations being preventable. The most common errors were inappropriate dosage (47.1%) and failure to administer a medication (31.4%). Propofol (25.6%), phenylephrine (10.3%), and fentanyl (9.4%) administration encountered the highest rate of errors [13]. The Mayo Clinic reported that perioperative drug-induced allergic reaction was triggered most likely by antibiotics (50.0% of cases). In one case of allergic reaction, a patient was administered ampicillin even though they had a known allergy to penicillin [14]. In order to prevent drug administration errors, it is important to recheck the patient chart and the drug being administered to ensure that the correct drug has been selected for administration. Preventive measures already in place to prevent administration errors range from bar code documentation systems to dosage calculators [13]. Ensuring that providers are properly trained and reducing the ability to work around these systems will increase effectiveness.

29.2.2 Case Scenario #2: Wrong-Level Spinal Surgery

Spinal surgery literature reported the second highest incidence of errors with a relatively high rate of preventable errors and near misses (wrong patient, wrong side, wrong level).

A survey completed by 415 neurosurgeons concluded that 207 (50%) neurosurgeons had performed at least one wrong-level surgery during their career [15]. Different studies estimated that wrong-level lumbar surgery and wrong side cranial surgery occurred approximately 4.5 and 2.2 times out of every 10,000 of these surgeries, respectively, with a relatively high rate of wrong-level spinal surgery [16, 17]. The actual scientific evidence on this topic emphasizes the importance of following the Universal Protocol, which includes a pre-procedure verification process, marking the surgical site, and a time-out, prior to spinal surgery [18]. A retrospective analysis of wrong-site craniotomies concluded that almost all of the cases could have been prevented by adhering to pre-surgical verifications and time-outs, as recommended by the Universal Protocol [19]. A 2007 study emphasized the importance of following the entire protocol, especially stressing the importance of not skipping the verification process, due to wrong-site surgeries still occurring after proper time-out was performed [20].

29.2.3 Case Scenario #3: Intraoperative Macroglossia

Reports of intraoperative and postoperative macroglossia seem to be one of the most prevalent near miss scenarios in neurosurgical literature.

A case report published in 1999 referred to a 17-year-old patient who suffered severe postoperative macroglossia after undergoing a suboccipital craniectomy with C1–C2 laminectomy. His past medical history was positive for Crouzon syndrome, a Chiari malformation with extensive syringohydromyelia, hydrocephalus with shunt placement, and severe gastroesophageal reflux. Anesthesia induction and maintenance were uneventful, except for an episode of hives that broke out on the patient's neck and trunk. The rash was treated and resolved with the intravenous administration of diphenhydramine (50 mg). Surgery was performed in the sitting position. No further complications were noted until the patient was emerging from anesthesia, and a 10 mm diameter transesophageal echo (TEE) probe and esophageal stethoscope were removed. At this time, mild glossal edema was noted. Mild stridor developed during extubation and improved before the patient left the operating room (OR). The patient's glossal edema increased 30 min after extubation and was initially treated intravenously with dexamethasone (10 mg). The glossal edema persisted and further stridor was noted. The patient required reintubation in the recovery unit. Macroglossia was diagnosed and continued to worsen for the next 24 h and remained for 2 weeks. Extensive evaluation to clarify the etiology of this adverse event was unsuccessful. A bite block was used to prevent further dental pressure to the tongue and to reduce tongue swelling. On postoperative day 14, minimal swelling at the base of the tongue was noted by direct laryngoscopy, and thus the patient was again extubated. After extubation the tongue returned to normal size within 1 day, and all sensory and motor function were recovered before discharge on post-extubation day 3. Although the exact etiology of the macroglossia in this case was unclear, cervical flexion during surgery or pressure from the endotracheal tube, TEE probe, or the esophageal stethoscope was the suspected cause. However, the bite block seemed to be beneficial during postoperative evolution. Since reextubation resulted in the quick resolution of the macroglossia, earlier extubation is recommended in cases where the tongue has mild or no swelling at the base of the tongue [21].

A second case of macroglossia reported in 2000 occurred in a 50-year-old woman undergoing a suboccipital craniectomy for the resection of a posterior fossa arteriovenous malformation. The patient underwent an uneventful induction of anesthesia, but 30 s after her head was placed in a Mayfield head-holder with her neck flexed, she began to turn blue above the neck. Her lips turned blue and her tongue swelled and protruded from her mouth. Neck flexion was reduced, and the discoloration and macroglossia quickly resolved, and the rest of the operation and recovery was unremarkable [22]. This case illustrates the importance of diagnosing glossal edema, while a patient's neck was in a flexed position and acting immediately to prevent macroglossia.

Similarly, another near miss occurred during an asleep/awake craniotomy in a 70-year-old female patient diagnosed with a right parietal lesion. Anesthesia induction was performed without complication, and the patient was prepared for surgery with the head flexed in a way that caused a slight chin on chest position. During the awake phase of the surgery, the patient's voice was altered, and the tongue was protruding from her mouth. Stridor was later noted as a snoring-like sound. IV hydrocortisone and adrenaline were administered, and a jaw thrust was performed to improve the airway. After these interventions the macroglossia still persisted and worsened. Surgery was paused as an endotracheal tube was placed. This provided immediate resolution, however, 30 min later the macroglossia began to worsen during surgical closure. Adrenaline was administered again, but this time the neck was extended. The macroglossia immediately improved, and within minutes the airway became clear, and breathing and speech became easier. No further tongue swelling occurred intraoperatively or postoperatively. This case again exemplifies the importance of patients' neck positioning during neurosurgery [23].

29.2.4 Case Scenario #4: Foreign Bodies

Foreign bodies are a relatively common near miss in neurosurgery. An intrathecal lumbar catheter is frequently used in neurosurgical operations, and catheter shearing is one of the most common complications resulting in foreign bodies [24]. The next few cases will involve compromised foreign bodies, including some involving lumbar catheters placed for treatment.

The first case involving foreign bodies referred to an adult patient requiring a lumbar-peritoneal shunting catheter for hydrocephalus developed secondary to meningitis. Due to the recurrence of the meningitis, the catheter was planned to be removed. However, during the removal process, the catheter sheared subcutaneously. Imaging showed the catheter remains in paraspinal tissue between L2 and L3 spinous processes. General anesthesia was used to remove the sheared catheter from outside the catheter tract using fluoroscopic guidance and microvascular forceps under the microscope. In the prone position, an incision was made in order to withdraw the paraspinal tissue from the L2 process. With the L2 lamina viewable, the tiny opening of the catheter tract was found with the microscope. The fractured catheter was still found to be inside the tract, but it was slipping further and further into the spinal canal with the flow of the cerebral spinal fluid. Therefore, the neurosurgeon clasped the fractured catheter with the microvascular forceps in order to prevent the catheter from further entering the spinal canal. Once the catheter was stabilized, the surrounding tissue was retracted in order to remove the entire fragment. In this case, the typical direct approach may have not prevented the catheter from slipping all the way out of the catheter tract. By taking an approach from outside of the tract, this allowed the neurosurgeon to stabilize the catheter before the fragment was lost in the spinal canal [25].

A second case of a near miss of a sheared lumbar catheter involved a 65-year-old female undergoing a right posterior communicating artery aneurysm clipping. A lumbar drain was placed in the L3–L4 intervertebral space to provide for improved exposure during surgery. There was some difficulty while advancing the catheter further into the subarachnoid space. In order to advance the catheter, some gentle manipulation and pulling occurred. Besides this slight difficulty, the catheter was successfully placed. After an unremarkable surgery during removal, the catheter was found to be sheared at multiple places, but all fragments were retrieved still intact [24]. This case illustrates the importance of careful and gentle lumbar catheter placement.

A near miss scenario involving a 72-year-old male patient who was at risk for pulmonary embolism following lumbar spinal surgery was reported in 2014 by Naito et al. During surgery, the neurosurgeons discovered that a rubber covering from the surgical equipment was missing. An X-ray and CT performed in the OR identified a foreign body anterior to the lumbar spine within a branch of the left pulmonary artery. Though there was no indication of complete blockage of the artery and the patient's vital

signs were stable, a pulmonary arteriotomy was conducted in order to remove the foreign body and prevent pulmonary embolism [26]. This case exemplifies the importance of careful observation and action even in highly technical and advanced fields like neurosurgery.

Retained foreign/surgical bodies are preventable by counting surgical items: all soft items, instruments, and sharps before the procedure, when new items/tools are added, before closure of a cavity, when incision closure begins and ends, and at sign off of the scrub person/nurse. However, with the increasing complexity of surgical procedures, this method has become less effective, and innovative solutions are being explored in order to improve this technique [27].

29.3 Recommendations and Future Perspectives

Analysis of 1108 neurosurgical cases performed by Stone and Bernstein uncovered 2684 errors in 87.1% of all operations. The most common errors were classified as procedural errors, contamination, equipment failure, and delay in treatment/care [28]. Near misses offer a rich source of education for healthcare professionals. However, without a system that encourages near miss reporting, near misses will continue to go unreported, and preventable errors will continue to happen. Grant et al. designed an anonymous reporting system, the Patient Safety Report (PSR), to collect events of errors, near misses, and patient harm in their pediatric intensive care unit (PICU). This system was designed based on past PICU-incident reports and from the expert opinions of PICU providers. Compared with their traditional reporting system, the PSR was far superior in collecting near misses; PSR obtained 698 near miss events out of 1119 reports, while the traditional system obtained 0 near misses out of 590 reports [29]. Based on the effectiveness of the PSR, it is clear that the neurosurgical field needs to develop a similar system that allows and encourages near miss reporting. Accurate and consistent near miss reporting can surely lead to a lower incidence and lessen the negative impact of preventable errors, which account for over 2/3 of all medical errors and are involved in approximately 100,000 deaths per year in the United States [28, 30].

29.4 Conclusion

Near miss scenarios are scarce in the literature, yet errors continue to occur in the neurosurgical setting. In order to mitigate the effects of errors on our medical system, comprehensive error prevention and reporting programs should be initiated. Sustained reporting of near misses will provide the evidence essential to design these programs.

Key Points

- The current neurosurgical literature provides near miss scenarios involving difficult intubation and extubation, incorrect drug administration, wrong-level spinal surgery, intraoperative macroglossia, and retained foreign bodies.
- Spinal neurosurgery had the second highest incidence of errors, outnumbered only by gastrointestinal surgery.
- Reports of intraoperative and postoperative macroglossia seem to be one of the most prevalent near miss scenarios in neurosurgical literature.
- The most common errors were classified as procedural errors, contamination, equipment failure, and delay in treatment/care.

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Complications of Neuroanesthesia

30

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30.1 Introduction

Complications may occur during neurologic surgery. Anesthesiologists need to be aware of the various issues that can arise, potential approaches to prevention, and effective management strategies. This chapter is intended to describe the most common complications encountered by neuroanesthesiologists in the neurosurgical operating room and the neurological ICU.

30.2 Venous Air Embolism

A venous air embolism (VAE) occurs when atmospheric air is entrained into the vascular system. Subatmospheric venous pressure occurs when a venous opening or wound is elevated above the heart. The pressure differential can pull air into the venous system. The incidence increases with the height of the surgical field as compared to the heart. Air entry is increased by the presence of noncollapsable veins such as in the dural sinuses. VAE is most common during posterior fossa operations in the sitting position (Fig. 30.1). Fathi et al. demonstrated a 39% incidence (range 7–76%) in a pooled analysis of posterior fossa surgery. VAE occurred in 11% (range 2–35%) of cervical spine surgeries [1]. Other neurosurgical procedures with an increased risk of VAE include craniosynostosis repair, spinal fusion, and deep brain stimulator placement [2].

Classically, air enters the right ventricle and pulmonary arteries via the superior vena cava. This leads to elevated pulmonary artery pressures due to direct obstruction of pulmonary arterioles as well as reflex pulmonary vasoconstriction [3]. Air embolism increases alveolar dead space resulting in decreased end-tidal CO_2 and increased $PaCO_2$. As the air diffuses across the alveolar-capillary membrane, the nitrogen is exhaled.

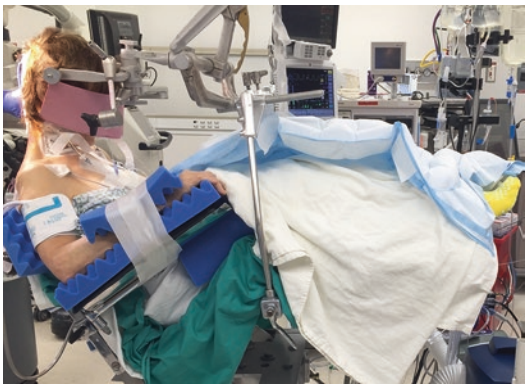

Fig. 30.1 Neurosurgical patient in the sitting position for a posterior fossa craniotomy

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Alternatively, air may cross a patent foramen ovale resulting in a paradoxical air embolism. In this setting, air enters the arterial system and may result in mesenteric, myocardial, extremity, or cerebral ischemia. Probe patent foramen ovale is estimated to occur in 20–30% of adults, and in many centers, a PFO is a contraindication to neurosurgery in the sitting position [3].

Multiple monitors function to detect VAE. The most sensitive monitor, transesophageal echocardiography (TEE), can detect volumes as small as 0.02 mL/kg. However, due to clinical inexperience and the invasiveness of this monitoring technique, TEE is not utilized routinely in the neurosurgical suite. Precordial Doppler ultrasound is the second most sensitive monitor after TEE. The device is placed over the SVC-RA junction just right of the sternum at the third or fourth intercostal space. Correct positioning is confirmed with the injection of aerated saline [3]. Proper positioning may be difficult in obese patients, and interference can occur with sound artifacts and electrocautery. End-tidal CO_2 and nitrogen are not as sensitive as precordial Doppler, and the majority of institutions lack the capabilities to monitor end-tidal nitrogen. Pulmonary artery catheters are no more sensitive than end-tidal CO_2 and introduce the dangers inherent in pulmonary artery catheter placement [3].

Clinical presentation depends on the volume of air and the rate of air entrainment. Small volumes (<0.5 mL/kg) may cause decreased end-tidal carbon dioxide, increased end-tidal nitrogen, and mild oxygen desaturations. Moderate volumes (0.5–2.0 mL/kg) may lead to pulmonary hypertension, right heart strain, arrhythmias, hypotension, myocardial ischemia, and bronchoconstriction. Large volumes (>2.0 mL/kg) can cause an airlock with complete right ventricular outflow tract obstruction leading to cardiopulmonary collapse [2]. Lethal volumes of air have been reported to be 200–300 mL or 3–5 mL/kg.

The mainstay of treatment is to stop the entrainment of air. The neurosurgeon should immediately be notified to flood the field with saline and apply bone wax. Air and nitrous oxide (if used) should be discontinued and 100% oxygen instituted. Jugular venous compression has been shown to raise the pressure in the dural sinus which can reduce entrainment of air; however, this technique may cause increased intracranial pressure and cerebral edema [4]. Also, activation of carotid baroreceptors may produce bradycardia. Positive end-expiratory pressure (PEEP) should not be used to decrease the rate of air entry. PEEP can increase right atrial pressure and may theoretically increase the risk of paradoxical air embolism. In addition, the PEEP required to reduce venous return from the head would considerably impede venous return from the SVC and therefore decrease cardiac output [5]. If present, immediate aspiration of a multi-orifice right atrial catheter can be attempted. This maneuver has been shown to reduce morbidity from VAE [6]. Additional maneuvers include lowering the head, fluid administration, and vasopressor initiation. Changing position to left lateral decubitus with Trendelenburg may help reposition air to the right ventricle but is not helpful with continuous entrainment of air. Complete cardiovascular collapse requires advanced cardiac life support.

30.3 Intracranial Hypertension

The cranial vault is a rigid structure containing three main components: brain tissue (1400 mL), cerebrospinal fluid (CSF, 150 mL), and blood (150 mL). The Monro-Kellie doctrine describes the relationship between intracranial pressure (ICP) and volume of these three components; the total volume of these components must remain constant due to the constraint of the cranium, such that an increase in volume of any one component must be accompanied by a decrease in the volume of another component or an increase in ICP. The ICP elastance curve, a plot of intracranial pressure over volume, is a biphasic, exponential curve. In the lower-volume portion of the curve, the slope is relatively flat (meaning changes in pressure are minimal with changes in volume) due to compensatory mechanisms including displacement of CSF into the spinal compartment. After this phase of compensation, small increases in the volume of intracranial components lead to large

increases in ICP, steepening the slope of the elastance curve.

Normal adult ICP is between 5 and 15 mmHg. Intracranial hypertension is defined as an ICP at or above 20 mmHg, at which pressure neurologic changes such as decreased level of consciousness, nausea, and vomiting will be observed. Methods of monitoring ICP include ventriculostomies/external ventricular drains (EVDs), which can be used for therapeutic CSF removal in addition to ICP monitoring, parenchymal manometers ("subarachnoid bolts") placed directly into brain tissue, and epidural manometers. The most recent guidelines from the Brain Trauma Foundation recommend ICP monitoring in all salvageable patients with severe TBI (GCS 3–8) and an abnormal CT brain [7].

Treatment of elevated ICP consists of reducing the volume of intracranial contents while maintaining cerebral blood flow and reducing cerebral oxygen consumption. Excessive CSF can be removed via extraventricular drainage (or, in chronic conditions, ventriculoperitoneal or ventriculoatrial shunting). Brain parenchyma may be removed in the case of brain tumor or abscess, but more commonly treatment is targeted at reduction of cerebral edema using hyperosmotic therapy with mannitol or hypertonic saline. Hyperventilation-induced hypocapnia results in cerebral alkalosis and vasoconstriction which decreases ICP. However, this effect dissipates over a period of hours as the CSF pH returns to normal. Due to the fleeting effect and potential for vasoconstriction-induced ischemia, this technique is particularly useful in the emergent treatment of intracranial hypertension [8]. Finally, cerebral blood volume reduction is achieved by evacuation of hematoma, avoidance of venous congestion (elevation of the head, avoidance of neck compression by excessive flexion or rotation, endotracheal tube ties, monitoring cables, or internal jugular central venous catheters, and avoidance of excessive positive intrathoracic pressure or PEEP), and careful regulation of cerebral blood flow with avoidance of cerebral vasodilating stimuli including hypoxia, hypercarbia, hyperthermia, and systemic hypertension in the setting of failed autoregulation [9]. With treatment to reduce cerebral blood volume, cerebral perfusion pressure, defined as the difference between mean arterial pressure and ICP (or CVP, if this value exceeds ICP), should be maintained over 60 mmHg, as reduction below this is associated with decreased brain tissue oxygenation [10].

With failure to treat elevated ICP, end-stage intracranial hypertension manifests as brain herniation. Impending herniation is classically heralded by Cushing's triad of hypertension with wide pulse pressure, bradycardia, and irregular Cheyne-Stokes respirations. If medical therapy has been exhausted, decompressive craniectomy to relieve near terminal intracranial pressure may be attempted.

30.4 Pneumocephalus

Pneumocephalus represents air trapped in the cranial vault (Fig. 30.2). During neurosurgical procedures, air can enter the cranium in a similar mechanism as an inverted soda bottle. This phenomenon occurs most frequently after craniotomy or craniectomy but may also occur with endoscopic sinus or transsphenoidal surgery, burr hole decompression, or shunt placement. In addition,

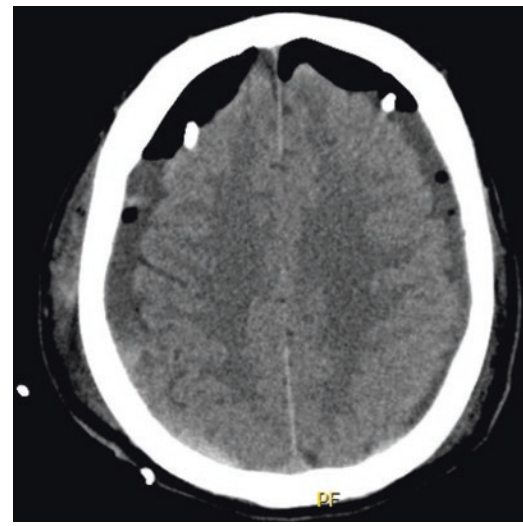

Fig. 30.2 CT scan demonstrating pneumocephalus following craniotomy evacuation of chronic subdural hematoma

pneumocephalus may occur following trauma, infection, barotrauma, or spontaneously [11]. Risk factors for the development of pneumocephalus include head position, duration of surgery, use of nitrous oxide, hydrocephalus, intraoperative osmotic diuresis, hyperventilation, spinal anesthesia, barotrauma, continuous CSF drainage, epidural anesthesia, infections, and neoplasms [11].

The majority of cases are asymptomatic; however, symptoms can include headache, nausea and vomiting, dizziness, seizures, and altered mental status [12]. Pneumocephalus may present as delayed emergence following neurologic surgery. Postoperative CT scans have demonstrated that almost 100% of patients have some degree of pneumocephalus in the first 2 days following surgery, which may persist for over a week. A retrospective study of 240 patients revealed a 26.3% incidence of pneumocephalus 3 weeks following craniotomy [13].

Tension pneumocephalus is an accumulation of air that behaves as a mass lesion in the brain requiring immediate decompression. Air can enter the cranium when hyperventilation, osmolar therapy, CSF loss, and venous drainage have reduced the volume of the intracranial contents. Following dural closure and resumption of normocapnia and normovolemia, the air can become compressed and result in a mass effect. Nitrous oxide can produce a tension pneumocephalus if used in the presence of trapped air and closed dura. Two CT signs have been described which suggest tension pneumocephalus. The Mount Fuji sign occurs when subdural air separates the frontal lobes resulting in a distribution of air resembling Mount Fuji. The air bubble sign demonstrates multiple small air bubbles inside the subarachnoid cisterns [14].

There is little in the anesthesiologist's armamentarium capable of preventing pneumocephalus. Normovolemia and normocapnia should be established toward the end of the procedure before dural closure. Nitrous oxide use is controversial; however, discontinuation of nitrous oxide prior to dural closure is recommended [15]. BiPAP or CPAP should not be used following transsphenoidal surgery due to the risk of dural suture disruption resulting in asymptomatic or tension pneumocephalus [16].

30.5 Delayed Emergence

Delayed emergence or delayed awakening occurs when a patient fails to regain an appropriate level of consciousness within an expected period (20–60 min) following cessation of a general anesthetic [17, 18]. Multiple risk factors exist which may predict delayed emergence including the extremes of age (geriatrics, neonates), obesity, obstructive sleep apnea, and preoperative cognitive dysfunction, seizures, or stroke [17]. The type of procedure may contribute as well. Patients undergoing spinal surgery or craniotomy with small mass excision have been shown to awaken faster than those with large mass excisions [19].

The primary causes of delayed emergence are due to residual drug effect, metabolic factors, and neurological disorders, among others. Residual sedation is the most common mechanism of delayed emergence. Volatile and intravenous anesthetics can take time to eliminate, particularly following prolonged operations. Benzodiazepines can produce prolonged sedation, especially when combined with opioids, which are known to reduce the respiratory rate and the ventilatory response to carbon dioxide. Opioid overdose demonstrates pinpoint pupils on neurological exam. Rarely, liberal use of local anesthetics can cause toxicity which may manifest as delayed emergence. Central anticholinergic syndrome can be caused by the use of antihistamines, anticholinergics, and even anesthetic medications such as volatile anesthetic and can present with seizure, tachycardia, mydriasis, coma, and respiratory depression [20]. In addition to sedative medications, neuromuscular blocking agents can result in delayed emergence if significant blockade persists or if the blockade has not been reversed. Succinylcholine and mivacurium use in a patient with undiagnosed pseudocholinesterase deficiency maintains neuromuscular blockade for 4–8 h [21]. Train-of-four monitoring is

instrumental in evaluating the neuromuscular blockade. Drug-drug interactions may contribute, and serotonin syndrome has been reported as a cause of delayed emergence [22].

On the other hand, non-pharmacologic causes of delayed emergence can result in serious morbidity and should be excluded. Metabolic factors such as hyper- and hypoglycemia should be ruled out, particularly in the diabetic patient. Hyperglycemia in the diabetic patient can result in diabetic ketoacidosis or hyperosmolar coma which can result in profound sedation and require urgent management. Hypothyroidism or myxedema coma may contribute as well as other metabolic factors such as hypercarbia or acidosis. Electrolyte abnormalities such as hyper- or hyponatremia should also be excluded. Hypothermia frequently occurs in the operating room and has been shown to contribute to prolonged recovery from anesthesia [23].

Neurologic disorders can result in catastrophic morbidity and mortality if left undiagnosed. Intraoperative hemorrhagic or an ischemic cerebral vascular accident can present as delayed emergence. The neurologic exam will be limited and may or may not demonstrate signs of stroke. Seizures and status epilepticus can delay emergence and occur in up to 4.3% of neurosurgical patients in the first 24 h following surgery [24]. Local anesthetic infiltration with accidental introduction into the cerebral spinal fluid may result in a total spinal with brainstem anesthesia.

Delayed emergence has many etiologies. Thus, it is essential to develop a stepwise approach to rule out each potential cause (Table 30.1). Airway, breathing, and circulation should take precedence with evaluation of airway, oxygenation, ventilation, and vital signs [18]. A review of the patient's medical and medication history as well as intraoperative medication administration may reveal potential causes. Considering residual drug effect represents the most common cause of delayed emergence, it is appropriate to continue evaluation by ensuring all anesthetic agents have been discontinued and allowed adequate time for elimination. If the patient is unresponsive, residual muscle paralysis can be evaluated with train-of-four monitoring and reversed if required. If the patient is following commands but appears profoundly weak, sugammadex administration should be considered. Opioid reversal with 40 mcg of naloxone can be initiated and repeated every 2 min up to a dose of 200 mcg [18]. Benzodiazepine reversal with 0.2 mg of flumazenil can be administered every minute up to a total dose of 1 mg [18]. The acetylcholinesterase inhibitor physostigmine (up to 2 mg) can be used to treat anticholinergic syndrome and may be useful for the reversal of postoperative somnolence [25]. After eliminating pharmacologic mechanisms, metabolic causes should be evaluated. Finger-stick glucose testing can assess for hypo- or hyperglycemia. Capnography should demonstrate normocapnia. An arterial blood gas will reveal any electrolyte or acid-base abnormalities, and the patient should be rewarmed if hypothermic. Following evaluation of metabolic causes, neurologic disorders should be immediately assessed with a neurologic exam, computed tomography scan, and electroencephalography. If no cause is uncovered, the patient should be monitored in an intensive care setting with neurology consultation and frequent neurologic exams.

Table 30.1 Checklist for delayed emergence

Residual drug effect
– Evaluate neuromuscular blockade with train-of-four
– Reverse neuromuscular blockade if present
– Consider naloxone (40 mcg, up to 400 mcg) for opioid reversal
– Consider flumazenil (0.2 mg up to 1 mg) for benzodiazepine reversal
– Consider physostigmine (up to 2 mg) to aid arousal
Metabolic
– Check finger-stick glucose
– Ensure normocapnia
– Evaluate patient temperature and rewarm if required
– Arterial blood gas
Neurologic causes
– Neurologic physical examination
– CT scan
– EEG
If patient fails to emerge, he/she may need to be monitored in ICU setting for 24–48 h

30.6 Postoperative Seizures

There is an increased risk of seizure activity following neurosurgical procedures. Kvam et al. reported a 4% incidence of seizures in the first 24 h following neurologic surgery, and up to 20% may experience seizures in the first postoperative week [26, 27]. Intraoperative hypoxia, electrolyte derangements, acid-base abnormalities, neurologic insults, vascular abnormalities, tumors, and epilepsy may contribute to postoperative seizures. Intraoperatively, hematoma formation, extensive retractor use, edema, and manipulation of brain tissue can lead to seizures as well [27]. Any intracranial mass lesions such as abscesses, hematomas, tumors, arteriovenous malformations, and aneurysms can act as epileptogenic foci. Skardelly et al. demonstrated an age greater than 60 years, a total tumor/edema volume ≤ 0.64 cm^3, and the size of resection as risk factors for postoperative seizures following tumor resection. The extent of resection was the primary determinant in the development of seizures [28]. Zheng et al. found a new neurologic deficit postoperatively to be a risk factor for seizure development following meningioma resection [22].

Pharmacologic prophylaxis of perioperative seizure following neurologic surgery is controversial. A 2015 Cochrane review evaluated the use of prophylactic antiepileptic drug (AED) treatment with non-trauma neurosurgical patients. Eight randomized controlled trials were evaluated, and only one trial showed a statistically significant advantage of prophylactic AED treatment in the prevention of postoperative seizures. Regarding head-to-head AED comparisons, one trial demonstrated a reduction in seizures with levetiracetam when compared to phenytoin. Other head-to-head trials failed to show significance. In their conclusions, the authors found insufficient evidence to recommend either strategy over the other [29]. On the other hand, patients with preoperative epilepsy should continue their AEDs throughout the perioperative period. When AEDs are used perioperatively, it is essential to monitor the neuromuscular blockade as these medications are known to decrease the duration of action of commonly used paralytics.

Postoperative seizures are typically easy to diagnose in awake, unanesthetized patients. Patients under general anesthesia with neuromuscular blockade will not demonstrate classic signs of seizure activity and will need electroencephalography for diagnosis. Upon recognition, the clinician should assess the patient's airway, breathing, and circulation. Oxygen should be applied, and benzodiazepines should be administered. Refractory status epilepticus may require endotracheal intubation and general anesthesia or barbiturate coma. Following resolution of seizure activity, the patient's electrolytes and acid-base balance should be assessed and corrected. AED serum drug levels should be evaluated in patients with a history of epilepsy to confirm therapeutic dosing. Dosages may need to be altered. Seizures in the immediate postoperative period may indicate a severe neurologic insult, and computed tomography scanning may be required to rule out a new or evolving intracranial process.

30.7 Cardiac Dysfunction Following Neurologic Insult

The heart-brain connection was first described in the medical literature in 1903 by Cushing, who noted a hypertensive response in cases of intracranial hemorrhage with acute cerebral compression. The phenomenon of reversible, nonobstructive cardiac dysfunction after neurologic injury, known as neurogenic stunned myocardium, is best studied in the current literature in subarachnoid hemorrhage (SAH), although this phenomenon has been observed in other central nervous system insults including status epilepticus, meningitis/encephalitis, traumatic brain injury, ischemic stroke, intracranial mass lesions, and brain death. In a literature review by Sakr, the incidence of EKG abnormalities, predominantly ST-segment changes (Fig. 30.3), ranged from 40 to 100% in patients with SAH and was associated with an elevation in cardiac troponin levels in 20–40% and regional wall motion abnormalities (RWMAs) in 9–31% [30]. In an observational

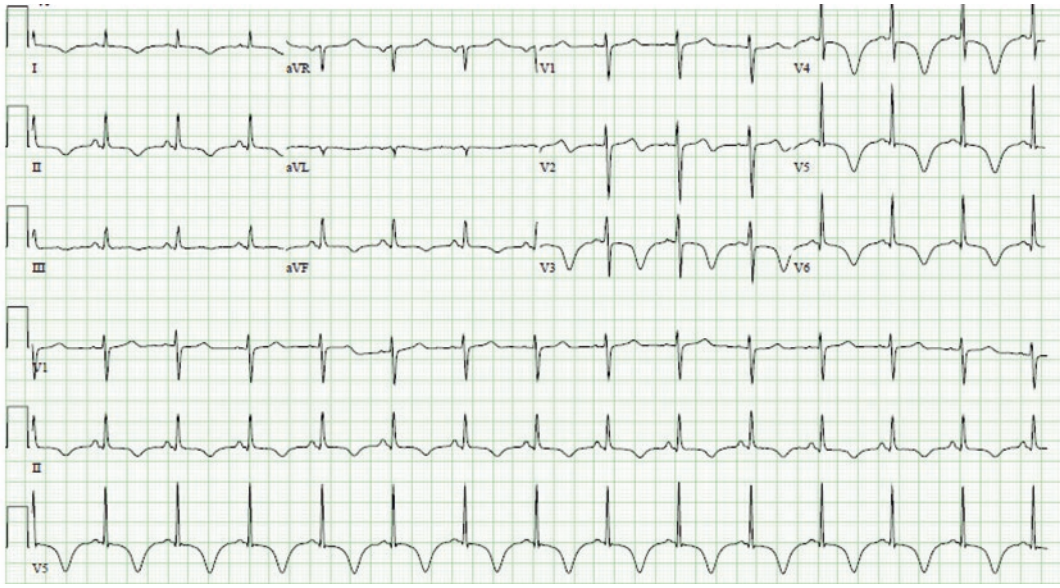

Fig. 30.3 EKG demonstrating the electrical changes of stress cardiomyopathy in a patient with subarachnoid hemorrhage. This patient had an elevated troponin (0.268 ng/mL)

study by Kuroiwa of 23 patients presenting with ST-segment elevation after cerebral aneurysm rupture, all had RWMAs; subsequent cardiac catheterization of 8 of these patients revealed no obstructive coronary artery disease [31]. In a case study by Naidech, 69% of patients presenting with SAH had abnormal EKG findings, prompting cardiac enzyme evaluation [32]. Troponin elevation above normal lab values was present in 98% of patients tested or 68% of the cohort, and abnormal left ventricular function was noted on echocardiography in 55%. Interestingly, increased peak cardiac troponin (cTnI) levels were related to higher Hunt-Hess clinical grade, intraventricular hemorrhage or global cerebral edema on neuroimaging, and loss of consciousness at ictus after an associated seizure, all features associated with inferior neurologic outcomes. In this study, higher peak troponin levels were associated with increased risk of left ventricular dysfunction, pulmonary edema, hypotension requiring vasopressor treatment, and delayed cerebral ischemia from vasospasm or cerebral infarction from any cause. Elevated peak troponin was also associated with increased all-cause mortality and increased disability on the modified Rankin score at 3-month follow-up, highlighting the potential prognostic significance of cTnI measurements after SAH [32]. This potential was reiterated by Tanabe in a case series of 103 patients with SAH. In this series, 52% of patients had a positive cTnI, with 23% having a "highly positive" cTnI of over 1.0 ng/ml. This subset of patients had a higher mean Hunt-Hess grade and a higher incidence of relatively depressed left ventricular function, ventricular diastolic dysfunction, left ventricular wall motion abnormalities, and pulmonary congestion on chest radiography than patients with no troponemia or with "mildly positive" cTnI. The degree of myocardial dysfunction in this subset of patients was mild and transient, with no incidence of cardiogenic shock and 71% improvement of ventricular function on repeat echocardiogram 5–10 days after SAH; however, a highly positive cTnI had an association with both clinical severity of SAH and significantly longer ICU length of stay [33].

The mechanism of injury proposed in neurogenic stunned myocardium is that of catecholamine excess, in which a sympathetic surge initiates a cascade of cellular events ultimately leading to myocardial damage. Anatomically, the heart is innervated by noradrenergic fibers

from the sympathetic nervous system traveling in the intermediolateral gray column of the spinal cord in the cervical and upper thoracic (T1–T4) levels and by cholinergic fibers from the parasympathetic nervous system via the vagus nerve. After brain injury, an increase in both systemic and local catecholamine release at the myocardium from sympathetic nerve terminals is observed. This leads to prolonged opening of beta-1 receptor-controlled calcium channels on myocardial cells with rapid ATP depletion and contraction band necrosis, in which myocardiocytes die in a contracted state following excessive calcium influx. This is histologically distinct from the coagulation necrosis seen in myocardiocytes after ischemic cell death. In a histopathological study by Greenhoot, autopsy examination of myocardium from three patients who expired after intracranial hemorrhage revealed areas of subendocardial hemorrhage, cytoplasmic banding of myocardial cells, and acute inflammatory response interspersed with large numbers of unremarkable myocardial cells. In the same study using a cat model of neurologic injury, histologic examination of feline myocardium revealed a similar pattern of injury, and electron microscopy detailed areas with the most injury immediately adjacent to intracardiac nerves, with changes less apparent at a distance from the nerve [34]. This pattern of injury, which does not correspond to coronary artery distributions, suggests direct neural insult to the heart.

30.8 Cardiopulmonary Resuscitation in the Prone Position

In the neurosurgical operating suite, both cranial and spinal procedures are frequently performed in the prone position, for surgical access to posterior anatomic structures, which can pose significant challenges to the anesthesiologist. Physiologic changes associated with the prone position include increased intrathoracic pressure, decreased respiratory compliance, increased peak airway pressures, and decreased ventricular compliance with a resultant decrease in venous return and preload and an increase in central venous pressure. The accompanying reduction in stroke volume combined with peripheral vasodilation in the anesthetized patient can result in severe hypotension. Paired with increased intrathoracic pressure, increased intra-abdominal and pelvic pressure causes venous pooling which contributes to surgical bleeding from vertebral and epidural veins; estimated blood loss exceeding a liter is not uncommon in multilevel complex spine surgery. Additionally, patients undergoing posterior fossa or prone spinal operations are at risk of air embolism causing cardiovascular collapse as the operative site is above the level of the heart and the veins encountered with decompression of the spinal column and cranium are scaffolded in bone matrix and non-compressible. Laceration of the aorta, vena cava, or iliac vessels during lumbar discectomy can result in complete cardiovascular collapse [35]. Unstable cardiac arrhythmias can be provoked by brainstem manipulation in posterior fossa surgery. Respiratory arrest is also a risk in the prone patient due to the hazard of endotracheal tube kinking or dislodgement with poor access to the airway, in addition to aforementioned alterations in respiratory compliance that can compromise adequate ventilation and oxygenation. These cardiovascular and respiratory changes associated with the prone position elevate the risk of intraoperative cardiac arrest.

Repositioning the prone patient into the supine position for classical CPR requires additional time, personnel, and equipment (stretcher) and risks loss of the airway, intravenous access, and invasive monitors vital to the resuscitation effort. Furthermore, supine positioning obscures surgical access to the posterior anatomic structures and prevents securement in the event of surgical bleeding contributing to arrest. Supinating the intraoperative patient with an unstable spinal column also carries the risk of devastating neurologic injury as well as contamination of the surgical site and potential infection. Prone ACLS is not currently taught in BLS or ACLS courses, and the AHA 2015 guidelines only recommend that ACLS in the prone position may be reasonable when the patient cannot be safely placed in the supine position.

Although no guidelines exist for optimal performance of prone CPR, it has been described in case reports and small trials addressing feasibility in the ICU setting. Prone CPR was first described as the "modified Schafer method" in 1989. Schaefer's method was initially proposed in the 1940s as a mechanism of providing artificial respiration to the near-drowning victim via lower thoracic compressions in the prone position. McNeil suggested that this method also provided circulatory assistance while protecting against aspiration of vomitus and encouraging lay bystanders to perform resuscitation without fear of infectious disease transmission via mouth to mouth [36]. In the hospital setting, a successful case of prone defibrillation during a thoracolumbar decompression was described by Brown, with paddle placement at the right axilla and left apex; no compressions were administered, but the author's experience prompted a systematic review of the literature which identified 22 case reports of CPR on prone patients. Several techniques were described depending on patient characteristics and the surgical site [37]. These include two patients described by W. Sun who suffered cardiac arrest in the prone position and were successfully resuscitated using the "reverse precordial compression maneuver." The first patient arrested during a posterior fossa craniotomy for occipital fracture, after surgical brain retraction to address a dural venous sinus tear, led to severe bradycardia. The patient's head was fixed in the Mayfield head clamp whose safe removal for repositioning would have delayed initiation of chest compressions, and the surgeon had yet to secure the bleeding dural sinus and required continued posterior access. Compressions were performed by a single provider, the staff anesthesiologist, who placed the left hand in a fist against the lower third of the sternum for counter-pressure while compressing the mid-thoracic spine with the right hand. The second case arrested after airway obstruction during cervical laminectomy and fusion for fracture with spinal cord compression. As the spine was not yet stabilized, compressions were carried out in the prone position with a two-provider technique in which the surgeon compressed the thoracic spine with both hands at the level of T7, while the anesthesiologist provided counter-pressure on the lower third of the sternum with a clenched fist [38]. A case of successful prone CPR on a pediatric patient who arrested during thoracic spinal fusion for scoliosis was reported by Tobias. Using a technique in which the surgeon placed both hands at the mid-thoracic level on either side of the incision for compressions, with the thoracic support of the Gardener frame providing counter-pressure, the patient achieved return of spontaneous circulation (ROSC) in 7 min. Effective cardiac output was confirmed throughout CPR via both invasive and noninvasive blood pressure monitoring, and postoperative examination revealed unchanged neurologic status from baseline as well as no evidence of end-organ hypoperfusion injury (Fig. 30.4) [39].

In addition to case reports, two small trials have demonstrated the physiologic adequacy of prone CPR in generating cardiac output. Mazer investigated the utility of "reverse CPR" in a crossover design study on six ICU patients who sustained cardiac arrest and failed to achieve ROSC after 30 min of ACLS. Enrolled patients received an additional 15 min of supine CPR, were repositioned prone with a sandbag on the CPR underbody board as a sternal counter-pressure device, and received another 15 min of CPR. All patients had the airway secured with an endotracheal tube prior to prone positioning. ACLS protocol guided medication administration and defibrillation in both positions. During both supine and prone CPR, systolic and diastolic arterial blood pressures were recorded. The authors found a statistically

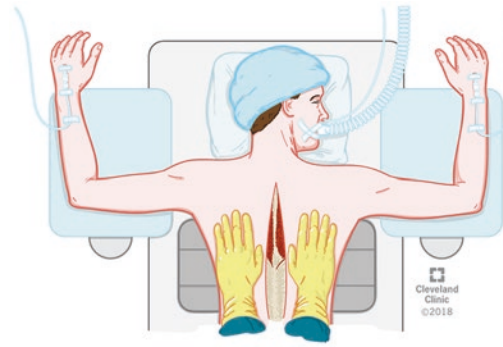

Fig. 30.4 Illustration depicting technique of prone CPR

significant improvement in systolic arterial pressures and calculated mean arterial pressures during prone CPR [40]. A similar study by Wei enrolled five patients who had a cardiac arrest in the ICU and failed to achieve ROSC with ACLS. After a decision by the staff physician to abandon the resuscitation attempt, the patients were turned prone, and compressions continued with the recording of arterial blood pressure. Prone CPR generated a mean systolic pressure of 95 mmHg and diastolic pressure of 25 mmHg [41]. Though small, these studies corroborate operating room case reports that prone CPR can be hemodynamically effective, and, importantly, neither found inferior hemodynamic parameters to supine CPR. As it is established that early continuous CPR improves outcomes in cardiac arrest, and current ACLS guidelines do note the reasonable nature of prone compressions in specialized settings, the anesthesia team should be aware of the feasibility and techniques of prone CPR when providing care to the prone neurosurgical patient.

30.9 Airway Management Pitfalls in the Unstable or Postoperative Cervical Spine Patient

Cervical spine injuries are the most common spinal injuries and occur in 2–4% of adult blunt trauma patients, with an increased incidence in the presence of head trauma with GCS < 8 [42]. Not only should the anesthesiologist be concerned regarding airway securement of the trauma victim due to mental status, hemodynamic instability, or planned operative intervention but must also consider protection of neural structures from secondary injury. As cervical spine injuries at or above C5 can lead to diaphragmatic weakness and respiratory dysfunction, securement of the airway with mechanical ventilation prevents hypoxia which itself can exacerbate neurologic injury by decreased oxygen delivery to the spinal cord. However, airway maneuvers including chin lift, bag-mask ventilation, LMA placement, both direct and indirect laryngoscopy, and flexible fiber-optic techniques have been shown to cause movement of the cervical spine, and the optimal manner of securing the airway in the potentially cervical spine-injured patient remains controversial [43].

Many anesthesiologists prefer awake flexible fiber-optic intubation in trauma patients, although the awake patient who is inadequately topicalized can displace an unstable cervical spine by coughing, and uncooperative or unconscious trauma patients are not candidates for awake intubation. Asleep flexible fiber-optic intubation is an option, provided the anesthesiologist is cognizant of the forces associated with bag-mask ventilation if the patient is not adequately preoxygenated prior to the intubation attempt. In the event of airway bleeding, fiber-optic techniques may not be possible. In a randomized, controlled crossover trial, Houde et al. fluoroscopically compared occiput –C5 segmental motion during flexible fiber-optic intubation with luminous stylette intubation and found no significant difference in mean maximum motion (11° with the flexible fiber-optic scope versus 12° with the luminous intubating stylette, both values including necessary jaw-lift maneuvers) and significantly less time to secure the airway with the luminous intubating stylette [44]. A similarly designed randomized crossover trial by Robitaille compared maximum segmental cervical spine motion during intubation using indirect videolaryngoscopy and direct laryngoscopy with a Macintosh blade, both with manual in-line stabilization. Not only did this trial find no significant difference in cervical motion between direct and indirect laryngoscopy, but the mean maximum cervical motion was between 8° and 11°, slightly less than motion observed in the aforementioned trial of the flexible fiber-optic scope and the luminous intubating stylette [45].

Using more standard intubating equipment, a cadaver model of injury at C5–C6 compared relative safety, based on fluoroscopic degree of axial distraction, anteroposterior (AP) displacement, and angular rotation, of two immobilization techniques as well as three laryngoscope blades, and concluded that manual in-line stabilization (MILS) resulted in less AP displacement than rigid cervical collar immobilization during laryngoscopy.

The Cormack-Lehane grade obtained was superior with MILS, and all intubations were endotracheal on the first attempt with no esophageal intubations; the Miller laryngoscope blade was noted to allow less axial distraction than the Macintosh or McCoy blades [46]. Manual in-line stabilization, a two-person technique in which the non-intubating provider places one hand on either side of the patient's head with the index finger on the mastoid process and the thumb just anterior to the external auditory meatus, with remaining digits posteriorly supporting the neck and maintaining cervical alignment without axial traction, is recommended by ATLS for orotracheal intubation attempts on any patient suspected of having a cervical spine injury, regardless of the method chosen for intubation [47].

The routinely scheduled case of anterior cervical discectomy and fusion (ACDF) can likewise present an anesthetic challenge. As ACDF is performed for the indication of painful, symptomatic herniated cervical disk, the preoperative examination should assess for associated cervical myelopathy that may be exacerbated by airway maneuvers including bag-mask ventilation and laryngoscopy. Postoperative airway obstruction due to wound hematoma, though rare with a reported incidence from 0.2% to 1.9%, can lead to devastating consequences if not quickly and effectively acted upon. The surgical exposure for ACDF is carried out through a plane between the carotid sheath laterally and the midline viscera (esophagus and trachea) medially to expose the ventral surface of the cervical vertebrae. This dissection creates a potential space posterolaterally on one side of the trachea, and hematoma development in this space can cause airway compression both extrinsically from the hematoma itself distorting the trachea and from occlusion of venous and lymphatic drainage of the neck at even lower pressures leading to venous congestion and laryngeal edema. In vitro studies of external pressure applied to the pig trachea up to 257 mmHg (well above systolic blood pressure, the maximum possible pressure achieved due to a hematoma as blood flows down a pressure gradient) resulted in only 20% compression of the trachea, suggesting that the latter mechanism of airway edema due to impaired venous outflow contributes most to the loss of the airway in the setting of postoperative neck hematoma. Therefore, the anesthesiologist should be aware that a distorted airway can still be encountered even if surgical hematoma evacuation is performed [48].

Rapid diagnosis is paramount and should be considered when respiratory distress—heralded with subtle voice changes and restlessness, followed by dyspnea, tachypnea, poor management of secretions, hypoxia, and inspiratory stridor—is noted in the immediate postoperative period, generally within the first 12 h of surgery. Delayed airway obstruction beyond this time is also observed, but more commonly due to prevertebral edema possibly due to spinal construct failure (Fig. 30.5) or the development of CSF leak or retropharyngeal abscess; regardless, the goal is to secure the

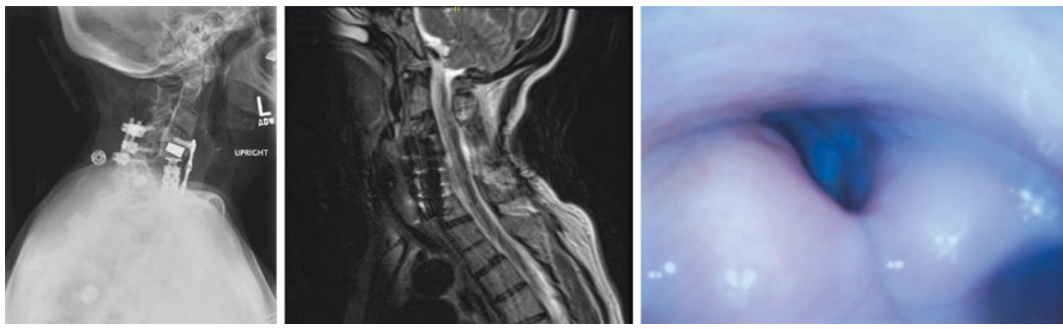

Fig. 30.5 (**a**) Lateral C-spine X-ray demonstrating construct failure in a patient presenting with delayed stridor after ACDF. Note widened prevertebral space and laryngeal edema suggested by soft tissue shadowing in the airway. (**b**) MRI C-spine in the same patient demonstrating airway narrowing and laryngeal edema. (**c**) Fiber-optic bronchoscope image of patient's airway with edema of the epiglottis, arytenoids, and vocal cords

airway via placement of an endotracheal tube. Palumbo et al. suggest a multidisciplinary management approach involving a spine surgeon, anesthesiologist, and ENT surgeon, as follows. If the airway is not severely compromised and the patient is stable for transfer, the optimal setting for securing the airway is in the operating room, via an awake technique. If anatomy is too distorted by an apparent space-occupying hematoma, it is suggested that the spine surgeon open the incision under local anesthesia prior to the subsequent intubation attempt [49]. It is worthwhile to note again that laryngeal edema will likely still be present after hematoma decompression and the airway should still be treated as "difficult" after opening the surgical incision. If the awake intubation attempt fails despite hematoma decompression, a surgical airway should be established via cricothyroidotomy, which can be performed with midline extension of the neck incision. With any postoperative ACDF patient, a plan such as that outlined above should be preemptively considered, so it can be rapidly executed in the event of postoperative airway compromise.

30.10 Sodium Disorders

Hyponatremia, defined as serum sodium less than 135 mmol/L, is reported in up to 50% of neurosurgical patients and has been demonstrated to be an independent risk factor for all-cause morbidity and mortality [50]. In SAH patients, hyponatremia has been associated with a twofold increase in the incidence of cerebral ischemia, even if fluid restriction is avoided [51]. As correction of serum sodium may improve mortality, expeditious diagnosis and treatment of hyponatremia are key. The two most common etiologies of hyponatremia in the neurosurgical population are the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting (CSW). These pathologies are both characterized by hyponatremia and low serum osmolarity (<285 mOsm/L) with high urine osmolarity (>200 mOsm/L) and elevated urine sodium levels (>25 mmol/L) but can be distinguished based on the evaluation of the extracellular fluid status. This distinction has significant treatment implications. In SIADH, excessive ADH from the posterior pituitary leads to increased free water reabsorption from the collecting ducts of the nephron with a resultant euvolemic or hypervolemic dilutional hyponatremia; the perturbation is one of excessive water retention and should be treated with fluid restriction. A notable exception to this is in SAH patients at risk of vasospasm in which euvolemia should be maintained. In CSW, excessive renal sodium losses, thought to be due to natriuretic peptide release from the injured brain, are accompanied osmotically by water loss leading to a hypovolemic hyponatremia. Treatment is based on fluid replacement therapy and sodium supplementation.

While hyponatremia can lead to cerebral edema, vasospasm after SAH, and increased mortality, overly rapid correction of hyponatremia can also have deleterious results. Osmotic demyelination syndrome or central pontine myelinolysis describes the neurologic sequelae of encephalopathy or coma, spastic paralysis, and pseudobulbar palsy after rapid correction of hyponatremia due to noninflammatory demyelination in the brainstem [52]. To prevent this complication, expert opinion suggests gentle sodium correction, not more than 1 mmol/L/h up to 10 mmol/L/day.

Hypernatremia is defined as serum sodium >145 mmol/L and is less commonly seen than hyponatremia in hospitalized patients. Central or neurogenic diabetes insipidus, in which the posterior pituitary fails to release ADH leading to lack of water reabsorption by the distal collecting tubule and collecting duct of the nephron, is the most common cause of hypernatremia in the neurosurgical patient. It is characterized by high-volume, dilute urine and is most commonly seen after pituitary surgery, traumatic brain injury, and SAH, as well as after brain death [53]. Treatment consists of fluid replacement with or without exogenous ADH supplementation with DDAVP.

30.11 Conclusion

No anesthesiologist or intensivist desires complications following neurologic surgery. However, they do occur, and it is essential for providers to

remain vigilant in the identification and management of these potentially catastrophic situations. As with any emergency, airway, breathing, and circulation should be assessed and optimized first. With the knowledge of potential complications, clinicians can identify the most likely diagnosis and intervene prior to patient deterioration.

Key Points

- A venous air embolism occurs most commonly during posterior fossa and cervical spine operations. This event, characterized by decreased end-tidal CO_2, oxygen desaturation, and hypotension, should be treated immediately by notifying the surgeon to flood the field with saline.
- Delayed emergence is caused by residual drug effect, metabolic factors, and neurologic disorders. It is essential to follow a stepwise approach during diagnosis to rule out each potential cause.
- Nonobstructive, reversible stress cardiomyopathy is common after subarachnoid hemorrhage and may manifest as troponemia, ST-segment changes, and regional wall motion abnormalities. Treatment is supportive with management of the underlying neurologic insult.
- In the neurosurgical operating suite, CPR may need to be performed on the prone patient to prevent neurologic injury and delays in care with repositioning. Hemodynamic efficacy of prone CPR has been demonstrated in small trials and case studies.
- There is no standard optimal manner of securing the airway in the patient with a cervical spine injury; however, manual in-line stabilization (MILS) is recommended for any orotracheal intubation attempt when cervical spine injury is suspected.

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Part IX

Pain Management

Pain Management Following Craniotomy

31

Chia Winchester and Alexander Papangelou

31.1 Introduction

Pain following craniotomy, widely felt to be less significant than with other surgical procedures [1], is in fact more severe and frequent than previously thought [2]. About 2/3 of patients will experience moderate to severe postoperative pain acutely after neurosurgery [3]. Interestingly, surgical site has also been shown to influence postoperative pain, with patients who undergo infratentorial craniotomy reporting higher pain scores than patients who undergo supratentorial craniotomy [4].

Opioids have been the mainstay of the analgesic regimen for most surgical patients including those after neurosurgery, but these medications are problematic in the neurosurgical population secondary to potential adverse effects. Sedation and miosis may make postoperative neurological assessment difficult. Respiratory depression may lead to hypercapnia, which can in turn lead to an exacerbation of already present post-surgical cerebral edema. On the other hand, the adverse physiologic effects of pain, such as hypertension and tachycardia, can have devastating consequences on a number of organ systems depending on the comorbidities of the patient. These effects can even include intracranial hematoma formation in the surgical bed [5]. Clearly, the management of pain and use of opioids after craniotomy require careful risk-benefit considerations. Increasing attention to opioid abuse and legislation to curtail chronic opioid use has also driven, in part, the study and perioperative usage of non-opioid analgesics.

31.2 Opioids

This class of drug lends its analgesic effect by stimulating mu, kappa, and sigma opioid receptors that are found in the peripheral and central nervous system. Their profound analgesic effects are paired with potential side effects, which can be deleterious to the postoperative care of a neurosurgical patient. Most problematic are sedation and respiratory depression, which can cloud the neurologic assessment and promote hypercapnia, respectively. These effects reduce the ability to detect neurosurgical complications and may worsen cerebral edema. In addition, pruritus, urinary retention, constipation, nausea, and vomiting can increase length of hospital stay and decrease patient satisfaction scores.

Intravenous (IV) patient-controlled analgesia (PCA) is a safe and effective way of treating postsurgical pain. Two studies have compared IV PCA (fentanyl [6], fentanyl with ketorolac [7]) with intermittent nurse boluses in neurosurgical patients. One of the studies looked at only

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patients who underwent supratentorial craniotomy [6], and the other study included both patients who underwent either supratentorial or infratentorial craniotomies. Both studies concluded that IV PCA was more effective for analgesia (as evidenced by lower pain scores) than intermittent boluses. Furthermore, there were no differences in the number of adverse events between treatment arms in either of the studies. Jellish et al. compared placebo PCA, morphine PCA, and morphine-ondansetron PCA in 120 patients undergoing skull base surgery [8]. The morphine PCA groups exhibited a lower incidence of pain compared to placebo (50% vs. 75%). Placebo PCA also required twice as many analgesic rescue doses.

Another study compared morphine PCA, tramadol PCA, or intramuscular codeine phosphate in patients who underwent both supratentorial and infratentorial craniotomies and assessed pain scores, sedation, and arterial carbon dioxide tension for 24 h postoperatively [9]. Morphine was a more effective analgesic than tramadol and codeine and had a higher patient satisfaction rate. There were no differences in arterial carbon dioxide tension or sedation between any of the groups. Interestingly, nausea and vomiting occurred more frequently in the tramadol group. A smaller study found that morphine PCA was comparable with intramuscular codeine phosphate with no adverse effects in either group [10]. Hassani et.al found a continuous infusion of sufentanil to be comparable to subcutaneous morphine, with both of these medications being superior to intermittent infusion of acetaminophen [11]. However, morphine was associated with higher rates of nausea and vomiting in this study.

Other studies have evaluated an opiate PCA in conjunction with non-opiate analgesic adjuncts in postoperative pain. Dilmen et al. examined the use of a morphine PCA with either IV dexketoprofen 50 mg, paracetamol 1 g, metamizol 1 g, or placebo (administered at skin closure and for 24 h postoperatively) in patients undergoing supratentorial craniotomy. The authors concluded that morphine PCA was safely effective in preventing moderate to severe postoperative pain but were unable to demonstrate any opiate-sparing effect of any of the analgesic adjuncts [12]. In contrast to that study, Tanskanen et al. evaluated an oxycodone PCA in combination with scheduled acetaminophen or ketoprofen in patients undergoing supratentorial craniotomy and found that the ketoprofen group used less oxycodone than the paracetamol group (a difference of 17.5 mg oxycodone in 24 h), with no significant differences in side effects between treatment groups [13]. There was a trend, however, toward more nausea and vomiting in the paracetamol group, possibly because of the use of more oxycodone.

In conclusion, an opiate-based regimen is effective and safe in the neurosurgical patient. Patient-controlled analgesia also seems to be more effective than intermittent boluses of analgesic medications. Larger studies are needed to evaluate the effect of non-opiate analgesic adjuncts on postoperative pain and opiate consumption.

31.3 Dexmedetomidine

Dexmedetomidine is a highly selective α-2 adrenoceptor agonist that produces sedation without respiratory depression. Its analgesic qualities may be derived from inhibition of synaptic responses in the dorsal horn [14]. The opioid-sparing effect of dexmedetomidine has been documented in numerous types of surgical cases including neurosurgical [15]. In addition, its hemodynamic profile, secondary to its centrally mediated sympatholytic effects, can be used to help achieve intraoperative and postoperative blood pressure goals. However, there are concerns that dexmedetomidine has a long context-sensitive half-life which may slow postoperative neurologic recovery [16]. Tanskanen et al. showed that in the setting of an isoflurane/nitrous oxide anesthetic, dexmedetomidine increases perioperative hemodynamic stability and quickens extubation time (by around 2 min) as compared to placebo. At 2 h post-extubation, there was no difference in sedation score between groups [16].

Two studies have examined the opioid-sparing effect of intraoperative dexmedetomidine infusions versus placebo [17, 18]. The effect seems to be most profound within the first 12 h, but can last until at least 24 h postoperatively. The authors also found fewer opioid-related side effects, namely, nausea and vomiting. No patients in either of the studies experienced respiratory depression, hypotension, or bradycardia. One of the studies found no significant differences in Ramsay Sedation Scale scores [18], while another found significantly lower scores in the dexmedetomidine arm for the first 6 h postoperatively [17].

A recent randomized controlled trial (RCT) compared dexmedetomidine and remifentanil in supratentorial and infratentorial craniotomy [19]. Dexmedetomidine decreased pain scores and post-anesthesia care unit (PACU) morphine-equivalent opioid use by 5 mg morphine equivalents. It also decreased postoperative mean arterial pressure (MAP) (88 mmHg for dexmedetomidine group vs. 98 mmHg for remifentanil). Some patients in the dexmedetomidine arm did require vasopressors in the PACU versus none in the remifentanil arm, while more patients required anti-hypertensives in the remifentanil arm versus dexmedetomidine arm. Although PACU discharge times were similar, patients given remifentanil opened their eyes, stated their names, and were judged fit for discharge sooner than those given dexmedetomidine.

Dexmedetomidine may also have a role for patients in the postoperative period. In patients with delayed extubation after craniotomy, those that received dexmedetomidine spent more time under optimal sedation and required less rescue doses of propofol and fentanyl than those who received placebo [20]. Importantly, bradycardia and hypotension occurred more often in the dexmedetomidine group. Of the 75 patients that received drug, 7 patients required drug cessation due to hemodynamic alterations (4 for bradycardia and 3 for hypotension). Su et al., on the other hand, retrospectively studied their standard analgesic approach to neurosurgery with or without the addition of dexmedetomidine. Dexmedetomidine was utilized intraoperatively and also added to a sufentanil PCA after surgery. The control group received no dexmedetomidine intraoperatively and a sufentanil-only PCA for postoperative analgesia [21]. The authors found that patients who received dexmedetomidine had lower sufentanil consumption in the first 72 h after surgery compared to patients who did not receive the drug. This trend was also seen intraoperatively, as patients in the dexmedetomidine group needed approximately 35% less sevoflurane, remifentanil, and fentanyl. There was no difference in sedation scores between the two groups. Patients in dexmedetomidine group had significantly less incidences of hypertension, tachycardia, nausea, and vomiting, and there was no significant difference in the incidences of bradycardia and hypotension between groups.

Although these initial data are suggestive of a potential perioperative analgesic role in craniotomy, larger studies are needed to determine the safety and efficacy of dexmedetomidine in neurosurgical procedures.

31.4 Lidocaine

Lidocaine is a commonly used local anesthetic that has anti-inflammatory properties. Its analgesic effects are mediated via sodium channel blockade and the inhibition of G protein-coupled and NMDA receptors to create selective depression of pain transmission in the spinal cord and reduce neural discharge of peripheral nerve fibers. In abdominal surgery, continuous infusion of perioperative lidocaine provides significant pain relief, reduces postoperative opioid consumption, decreases opioid-induced nausea and vomiting, and promotes a faster return of bowel function [22, 23]. In supratentorial craniotomy, an intraoperative lidocaine bolus followed by an infusion reduced pain scores in the PACU as compared to placebo, with no difference in hemodynamics, dysphoria, or postoperative nausea and vomiting (PONV) between groups [24]. Although not statistically significant, the total number of patients needing supplemental postoperative tramadol during their stay in PACU was lower in the lidocaine group as compared with the control group. No patient in either group had moderate or severe pain, but it is noteworthy that

all patients received a postoperative basal infusion of sufentanil from a PCA. The resulting sedation was significant enough that patients were unable to use the PCA in the PACU. Clearly, further studies are needed to assess the safety, analgesic effect, and sedative effect of continuous lidocaine infusion in neurosurgical patients.

31.5 Gabapentinoids

Gabapentin and pregabalin are antiepileptic and anti-neuropathic medications with opioid-sparing effects in orthopedic, spine, and abdominal surgery [25]. They reduce excitatory neurotransmitter release via their action on N-type voltage-gated calcium channels. While there are several studies that have shown that preoperative oral gabapentin prior to lumbar discectomy reduced postoperative pain and decreased opiate use [26, 27], there are fewer studies on gabapentinoids for perioperative intracranial procedures. Misra et al. examined the effect of 600 mg of gabapentin preoperatively with IV dexamethasone every 8 h in the perioperative period and found that gabapentin reduced the incidence of PONV, but there was no significant difference in opioid consumption or postoperative pain scores [28]. These results are in contrast to a study by Ture et al. [29]. In this study, administration of gabapentin 1200 mg daily for 1 week prior to surgery was effective for acute postoperative pain and decreased morphine consumption after surgery compared to phenytoin (these drugs were being used as prophylactic anti-convulsants). However, tracheal extubation was accomplished about 4.5 min earlier in the phenytoin group, and the postoperative sedation scores were significantly higher in the gabapentin group in the first 2 h postoperatively. It is also important to note that seven patients had severe fatigue and five had dizziness preoperatively in the gabapentin group.

There are even less studies on the effect of pregabalin in neurosurgical patients. In one study, patients were treated with pregabalin 150 mg or placebo the evening before surgery, 1.5 h before surgery, and twice daily for 72 h following surgery [30]. In addition to postoperative vital signs, pain scores, oral morphine equivalents, drug usage, and length of stay, patients were assessed at the 2-week, 1-month, and 3-month time points following surgery for pain score and analgesic use. Pain scores were lower in the pregabalin group on postoperative days 0–5 but however only reached statistical significance after PACU discharge on POD0 and POD1. The out-of-hospital pain scores were 16–43% lower than the controls, and the pregabalin group used 33% fewer medications in the postoperative month, but these findings did not reach statistical significance. Though promising, more studies are needed to determine the safety and efficacy of gabapentinoids in neurosurgery.

31.6 NSAIDS and Flupirtine

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) enzymes 1 and 2 and prevent the conversion of arachidonic acid to pro-inflammatory prostaglandins producing an analgesic effect with efficacy similar to morphine. However, a number of unwanted side effects are associated with NSAID use, including renal dysfunction, gastritis, and decreased platelet function resulting from inhibition of procoagulant thromboxane. Because of the possibility of hemorrhage from platelet dysfunction, which could be severe and devastating to the neurosurgical patient, many providers have been reluctant to use NSAIDs as part of a perioperative pain regimen.

In a large retrospective study of adult patients undergoing elective craniotomy, ketorolac was not associated with increased risk of bleeding (close to null effect) [31]. However, a wide confidence interval prevented the authors from reaching a strong conclusion about the safety of ketorolac after elective neurosurgery. In contrast to this study, Palmer et al. found that in neurosurgical patients who experienced postoperative hematomas, a perioperative bleeding disorder was present in 2/3 of these patients [32]. The administration of an antiplatelet agent was the most commonly associated risk factor. Similarly, another group of investigators found the use of

flurbiprofen intraoperatively to be a risk factor for the development of postoperative intracranial hematoma [33]. However, use of flurbiprofen postoperatively was not a risk factor. The use of perioperative ketorolac was also evaluated retrospectively in pediatric patients undergoing neurosurgery [34]. Short-term therapy (up to 72 h) was not associated with an increased risk of any intracranial bleeding (clinically significant and/or radiologic) on a multivariate analysis, but the authors created a variable for pharmacologic confounders (non-ketorolac) known to increase the risk of bleeding (OR 3.11, CI 1.01–9.57) which did reach significance.

Although not in craniotomy patients, a multimodal pain regimen for patients undergoing transsphenoidal surgery showed that IV ibuprofen significantly improved pain scores and decreased opioid consumption compared to placebo [35]. There were no differences in adverse events between groups, and the study was even terminated early because endpoints had been reached. Finally, Tanskanen et al. found that the addition of ketoprofen to an oxycodone PCA allowed patients who underwent supratentorial craniotomy to use significantly less oxycodone than those that had acetaminophen added [13].

Other studies have been performed in regard to the analgesic effects of NSAIDs in neurosurgical patients. Molnar et al. found that preoperative administration of one 100 mg dose of diclofenac slightly reduced both the incidence and severity of acute post-craniotomy headache for up to 5 postoperative days, with no postoperative surgical bleeding, gastrointestinal, or renal complications [36]. Yadav et al. found that oral flupirtine 100 mg is safe and as effective as oral diclofenac in reducing postoperative pain when compared to placebo, with no differences in adverse effects between groups [37]. There was one incidence of bleeding in the control group ($n = 122$) and in the flupirtine group ($n = 124$) and no incidences of bleeding in the diclofenac group ($n = 125$). This was not statistically significant.

For the sake of completeness, flupirtine is not an opioid nor a NSAID but is classified as an aminopyridine, which acts centrally as a selective neuronal potassium channel opener, N-methyl-D-aspartate (NMDA) receptor antagonist, and GABAA receptor modulator [38]. Unfortunately, flupirtine is only approved in Europe and not in the United States due to concerns over hepatotoxicity.

31.7 Tramadol

Tramadol is a synthetic opioid agonist and also inhibits norepinephrine and serotonin reuptake. It has analgesic properties similar to morphine (50 mg tramadol IV has similar analgesic efficacy to 5 mg morphine IV) [39]. Tramadol is also unique and advantageous in that it has opioid agonism without respiratory depression [40]. In addition, the modulation of noradrenergic and serotonergic pathways may make tramadol effective for neuropathic pain, although only low-quality evidence exists for effectiveness of tramadol in this area [41]. A well-known but rare side effect of tramadol is seizures, especially if taken in conjunction with medications that reduce the seizure threshold or in patients with a history of epilepsy.

One study compared tramadol 50 mg, tramadol 75 mg, and codeine 60 mg for postoperative analgesia in patients undergoing either supratentorial or infratentorial craniotomy [42]. Codeine was found to be a superior analgesic, than either dose of tramadol. Tramadol 50 mg was an ineffective analgesic at 48 h postoperatively (no difference at 24 h), and tramadol 75 mg was associated with significantly greater nausea, vomiting, and sedation. Sudheer et al. found that a morphine PCA was superior to a tramadol PCA with no differences in sedation or arterial carbon dioxide tension between the groups [9]. Similarly, the tramadol group experienced significantly more nausea and vomiting. In another study, Graham et al. compared tramadol with codeine phosphate and needed to terminate the study early for a number of reasons, including the high use of rescue analgesia and co-administration of carbamazepine as an antiepileptic (hepatic enzyme induction which reduces the efficacy of tramadol) [43]. Of the patients who did complete the study, there was

no significant difference between codeine phosphate or tramadol, and patients had inadequate analgesia with both drugs. It is well known that codeine is a pro-drug with no analgesic activity and undergoes highly variable metabolism by the CYP2D6 enzyme to morphine. Given the high rate of variability of metabolism, this drug may be unsafe in the neurosurgical population, (rapid metabolizers) leading to symptoms of opiate overdose, or may provide inadequate analgesia (poor metabolizers) if used as the primary analgesic.

In a more recent study, Rahimi et al. compared an opiate-based regimen (oral oxycodone/acetaminophen and/or intravenous morphine, both on an as needed basis) with or without 100 mg tramadol twice daily [44]. The authors found that the tramadol group had lower pain scores, a lower length of stay (by 1 day), and decreased intravenous morphine use. The tramadol group also showed a tendency to use less oxycodone/acetaminophen, but this was not statistically significant. There was similar antiemetic usage between groups.

From the current data, it seems that tramadol alone does not provide satisfactory analgesia for neurosurgical patients. It is also associated with higher risk of nausea and vomiting which may be detrimental to patients post-craniotomy. Additional studies are needed to determine safety and efficacy of tramadol as a component of a multimodal postoperative pain regimen in craniotomy.

31.8 Acetaminophen

Acetaminophen has been recommended by the American Society of Anesthesiologists as part of a multimodal pain regimen for the management of acute pain in the perioperative setting [45]. Acetaminophen alone has been found to be inadequate for postoperative analgesia following craniotomy [46]. Artime et al. compared IV acetaminophen given at the start of supratentorial craniotomy and then every 6 h after surgery with placebo [47]. The IV acetaminophen group had a lower incidence of severe pain and was more satisfied with their pain regimen than the control group. There was no difference in the amount of opiate consumption, and the rate of opioid-related side effects was unchanged between groups. Similar results were found in studies that included both supratentorial and infratentorial craniotomies [48, 49]. One group compared IV paracetamol (a pro-drug of acetaminophen), IV dexketoprofen, and metamizole (an ampyrone analgesic that is not available in the United States due to concerns of agranulocytosis) as analgesic adjuncts to a morphine PCA. The authors found that there was no statistically significant difference in either pain scores or morphine consumption [12]. Tanskanen et al. found that ketoprofen and not paracetamol was able to provide opiate-sparing effects when combined with an oxycodone PCA [13]. Given mixed data, further studies are needed to clarify the analgesic and opiate-sparing effects of acetaminophen and related drugs after craniotomy.

31.9 Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that provides dissociative anesthesia and profound analgesia. Side effects have been reported to include increased intracranial pressure, nystagmus, hallucinations, and a decreased seizure threshold. However, there is conflicting data on the effects of ketamine on cerebral hemodynamics. For instance, using a transcranial Doppler to measure mean blood flow velocity, Maybert et al. found no increases in intracranial pressure, and analysis of other variables suggested that the relationship between cerebral blood flow and cerebral metabolic rate was unaffected [50].

Given the undesirable effects, it is not surprising that few studies examine the use of ketamine in neurosurgery. Agarwal et al. demonstrated that lidocaine infiltration at skull pin sites along with a sub-anesthetic dose of intravenous ketamine (0.5 mg/kg) attenuated the hypertension

and tachycardia of skull pinning greater than lidocaine alone [51]. There is a need for more studies to confirm the effects of ketamine on cerebral hemodynamics as well as postoperative analgesia, sedation, and undesirable effects in neurosurgical patients.

31.10 Scalp Block

Regional anesthesia of the scalp is performed by infiltrating the greater and lesser occipital nerves, supraorbital, supratrochlear, zygomaticotemporal, and auriculotemporal, and the greater auricular nerves. The technique was initially described by Pinosky et al. [52] and has been further illustrated by other groups. A paradigm shift from ring blockade to a selective nerve block has reduced the risk of severe local anesthetic toxicity, including neurologic complications (seizures) and cardiovascular collapse [53].

Multiple studies have shown scalp blockade to decrease the hemodynamic response to skull pinning [54–56]. Geze et al. also found that patients with scalp blockade had lower plasma cortisol and adrenocorticotropic hormone levels after skull pinning compared with patients who received opioids and local anesthetic infiltration at pin sites [53].

In terms of postoperative analgesia, scalp blockade with 0.5% bupivacaine with epinephrine has been shown to decrease the incidence of moderate to severe pain during the first 12–24 h [57]. Patients with scalp blockade also needed less rescue analgesia than the control group. Similar results have been found by other investigators [58, 59]. However, several studies conflict with these findings. One study compared postoperative pain in patients who received scalp nerve blockade at surgery end versus intravenous morphine at dural closure. Postoperative hemodynamics, total rescue analgesic dosing of codeine, and pain scores were similar between groups at every time interval (up to 24 h) [60]. Tuchinda et al. found that preoperative scalp blockade in elective supratentorial craniotomy with 0.25% or 0.5% bupivacaine and 1:200,000 epinephrine decreased the hypertensive response to skull pinning but did not affect postoperative analgesia or analgesia requirements [61]. In a meta-analysis of seven randomized controlled trials, scalp blockade was associated with significant reduction in pain for several hours after craniotomy [62]. Not surprisingly, it was also found that timing of the nerve block plays a role in the length of postoperative analgesia, ranging from 6-8 h postoperatively from a preoperative block to 12 h when block was administered at the end of surgery.

Interestingly, another study looked at patients who received scalp infiltration of pin sites with ropivacaine and demonstrated significantly lower pain scores for up to 2 months after surgery, indicating a role for scalp infiltration and possibly scalp nerve blockade in chronic post-craniotomy pain [63]. In summary, more studies are needed to determine appropriate dosing, need for adjuvants in the local anesthetic mixture, role of scalp nerve block in the prevention of chronic post-craniotomy pain, and opiate-sparing properties of scalp nerve blockade.

31.11 Conclusion

While opiates remain the cornerstone of postoperative analgesia, their use has been generally limited in the analgesic regimen for neurosurgical patients given concern of potential side effects. However, many studies have shown that opiates are effective and safe in treating post-surgical pain. Non-opiate adjuncts, such as dexmedetomidine, acetaminophen, NSAIDs, and gabapentinoids, have also been proven to be effective as analgesics and have the potential to lower opioid consumption without sacrificing analgesia. In addition, regional scalp nerve block is a useful tool to treat pain both intraoperatively and postoperatively. Larger studies are needed to further determine the effects of these non-opiate adjuncts alone or in combination on postoperative pain. Certainly, current data suggests a role for these adjuncts as opioid-sparing agents for postoperative neurosurgical pain.

Key Points

- Opioids are the mainstay of treatment for post-craniotomy pain.
- Problematic opioid side effects in the setting of neurosurgery include sedation, respiratory depression with resulting hypercapnia and increased cerebral edema, and blunting of the neurological exam. This underscores the need for non-opioid adjuncts.
- Favorable data exists for regional block of the scalp, but optimal timing, anesthetic composition, and dose are still unclear.
- Additional data is needed on acetaminophen, tramadol, NSAIDS, gabapentinoids, lidocaine, and dexmedetomidine to determine their efficacy and role in the management of post-craniotomy pain.

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Post-operative Pain Management in Spine Surgery

32

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32.1 Introduction

Following spine surgery, the majority of patients report moderate to severe pain that lasts 3–4 days. Postoperative pain is an acute pain syndrome that starts with surgical trauma with an inflammatory reaction and irritation of the afferent neuronal stimulation. This leads to peripheral and central sensitization of nociceptive pathways. Peripheral sensitization from various substances such as injured cells, nociceptors, and enhanced capillary permeability is generated by local enzyme activity. This can lead to acute pain. Acute pain is a predictor of chronic pain. This peripheral sensitization can also lead to enhanced pain responses in the CNS, which helps facilitates nociceptive transmission and causes the release of mediators with the dorsal horn. This may lead to neuronal plasticity and lead to chronic pain. Further, due to the inflammation associated with surgery, there is a reduction in the threshold of nociceptor afferent peripheral terminals. The goal is to prevent the progression of chronic pain, since the acute pain is often easier to manage. Treatment of chronic postsurgical pain can be challenging because there are inflammatory and neuropathic components. Multiple factors affect the presentation of pain including cultural, social, and psychological factors. Further, many of these patients have been receiving narcotic pain medications for extended periods of time, which makes many of them narcotic tolerant. As a result, if narcotics are exclusively used, they may require higher doses to achieve appropriate analgesia. Failure to manage postoperative pain can lead to many unpleasant sensations that are associated with autonomic hyperactivity, reduced mobility, endocrine-metabolic abnormalities, and psychological and behavioral responses. Up to 70% of patients still complain of moderate to severe pain postoperatively [1]. Further, approximately 22.4% of post-spine surgery readmissions are due to pain [2]. In the future, financial considerations may make this level of readmissions cost prohibitive to many medical centers.

In spine surgery, the pain is directly proportional to the number of vertebrae and the invasiveness of the procedure [3]. Significant difference in pain occurs based on the location of the vertebrae (i.e., cervical, thoracic, or lumbar) [4]. Minimally invasive neurosurgical techniques have reduced the amount of pain [5, 6]. Despite the surgical changes, pain management is a very significant concern. The most important surgical outcome to define successful surgical outcomes is early ambulation. In order to achieve this successful outcome, adequate pain relief is required. At the same time, patients need the appropriate

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level of alertness and muscle strength to ambulate. The best method to achieve this is via multimodal analgesia, where multiple pain receptors are targeted. If patients are unable to ambulate in a timely fashion, they are at an increased risk of prolonged hospital stays, respiratory infections, venous thrombosis, or even functional deficits. The purpose of this review article is to outline the techniques to achieve this level of analgesia.

32.2 Multimodal Analgesia Techniques

Multimodal analgesia has improved pain with less side effects by targeting a variety of chemical and neurophysiological pain pathways. Postoperative pain is the result of activation of nociceptive, neuropathic, and inflammatory pain mechanisms. Pain originates from a variety of different tissues such as vertebrae, intervertebral discs, ligaments, dura, nerves, muscles, and other tissues. There is also extensive cross connectivity of the nerves associated so there is often significant referred pain. This acute referred pain is often more common in patients, who have experienced chronic pain [7].

Beyond just the multiple pathways targeted by different medications, timing of medications also has a key role to play. Preemptive analgesia or medications before the surgical operation are important in diminishing future pain and protecting the nervous system from sensitization. It helps to avoid the "spinal wind up." The "spinal wind up" occurs due to peripheral sensitization leading to central sensitization leading to chronic pain and long-term debilitation.

Multimodal analgesia involves the use of neuraxial anesthesia, pharmacologic methods including opioids and non-opioid therapies, and non-pharmacologic methods.

32.3 Neuraxial Techniques

Neuraxial analgesia provides the best pain relief for spine surgery and is often superior to systemic opioids [8]. Neuraxial analgesia is made up of local anesthetics and opioids. It has been shown to lower morbidity and mortality [8–10], reduce pain scores [11], have less bleeding [12], provide lower surgical stress response [12], preserve immune function – reducing infection risk [13], and decrease parenteral opioid requirements [14]. The most common method of neuraxial analgesia is via epidural analgesia [15]. However, for the early postoperative period, intrathecal opioids have emerged as the preferred option [15]. The surgeon can administer the medication as long as the intrathecal sac is still exposed [3, 16]. The preferred opioid is preservative-free morphine (Duramorph), because of its relatively long duration of action, without any motor, sensory, or autonomic deficit. It also accumulates in the cerebrospinal fluid (CSF) due to its high hydrophilicity and exhibits efficacy at very low doses [17]. Another new option that can be used is extended release epidural morphine (EREM), which has been shown to offer even more prolonged analgesic when compared to Duramorph [18, 19]. It may offer continuous pain relief for up to 48 h, at lower systemic levels compared to other formulations [15]. It can be delivered as a single shot, which avoids the potential for the long-term placement of catheters, which is a risk for infection, lead to orthostatic hypotension if used excessively, catheter migration, or sympathetic blockade. Further, patients who received EREM were less likely to receive naloxone and oxygen supplementation [19] and experience nausea or fever [19] or pruritus [18]. However, they were more likely to experience hypotension [19]. Intrathecal morphine can lead to late-onset respiratory depression and significant sedation. As a result, the patient must be closely monitored postoperatively and, in some instances, require a higher level of nursing care than patients not having a neuraxial anesthesia. Of note, in patients that receive thoracic epidurals, respiratory function may be significantly impaired especially in those with chronic lung disease.

Narcotics are often given in combination with local anesthetic because of their synergistic relationship and ability to lower the dosage of narcotics given [20]. If local anesthetics are used without opioids, they can cause motor and sen-

sory block leading to inadequate neurological exam. In pediatric patients undergoing spinal fusion surgery, the average narcotic dose was 0.5 mg/kg less in the first 24 h postoperatively [20]. The preferred local anesthetic is ropivacaine, which has a longer duration of action and selectivity to sensory blockade rather than motor blockade [15]. Epidural analgesia as a whole is associated with improved patient satisfaction. This may be due to lower side effects from reduced use of opioids [20]. Further, the epidural if placed prior to the operation the blood pressure must be closely monitored. Maintaining a mean arterial pressure (MAP) greater than 85 is vital to allow for close intraoperative monitoring and maintaining adequate perfusion to the spinal cord. If placed prior to the procedure, it should be placed before the patient is sedated to help reduce the risk of neurological injury. When the patient is awake, they are able to make the doctor aware of pain, paresthesias, or other abnormal feelings that can indicate a potential neurologic injury. Other complications include infection, urinary retention (based on location), cardiac arrest due to hypoventilation or hypoxia, or headaches.

Absolute contraindications to neuraxial analgesia include coagulopathy or bacteremia. Coagulopathies lead to bleeding around the spinal cord, which can lead to a formation of a hematoma. This can lead to spinal cord ischemia or infarction. Numerous relative contraindications are also present including those associated with use of anticoagulation therapy or previous back surgeries. Antithrombotic drugs should be discontinued prior to placement of the catheter. The exact time of discontinuation varies between the different drugs. This can also affect the timing of the epidural catheter removal.

32.4 Parenteral Therapy

32.4.1 Systemic Opioid Therapy

Opioids often provide the mainstay of therapy whether given neuraxially or parenterally. Opioids affect the modulation of nociceptive input by acting on receptors in the dorsal horn, without producing motor or sympathetic blockade. As a result, motor and sensory function are preserved. Opioids are often the mainstay of therapy but are used in conjunction with other agents. Opioids have numerous dose-dependent side effects, which limit their use. Some of the side effects include pruritus, sedation, respiratory depression, constipation, nausea and vomiting, orthostatic hypotension if dehydrated, and altered mental status. Because of these side effects, patients may have an inability to get out of bed and ambulate, which may increase the risk of complications. Opioids can also lead to increased risk of postoperative nausea and vomiting (PONV) [21]. Patients undergoing spine surgery have a number of risk factors associated with PONV. Spinal surgery may also be performed in those who have spinal metastasis; in these cases opioids should be used judiciously as well, as they may lead to suppression of the immune system and further increased risk of micrometastasis [22].

Postoperatively, additional narcotic medications can be administered via patient-controlled analgesia (PCA) pumps. Often times in the immediate postoperative period, there can be delays in administering narcotics to the patient, which can exacerbate pain. As a result, if the patient has individual control over the narcotic administered, they may be able to administer it in a timelier fashion and avoid the pain getting particularly worse. Several different methods exist in the way that the PCA pump can be used. But the most common method is to utilize a basal rate, which provides a background level and continuous narcotic administration, and boluses that the patient can control to provide relief when the pain gets particularly severe. The balance in dosage between these two methods is patient specific. The ideal medication for the PCA is highly efficacious and has a rapid onset of action and moderate duration of action. Further, the drug should not accumulate or change pharmacokinetic properties with repeated administrations. It should also have a large therapeutic window. The most commonly prescribed drug is morphine at a dosage of 1–1.5 mg with a lockout period of 5–10 min. However, daily review of the patient's

dosing of this medication is required to prevent addiction and unintended complications. Because the patient controls his or her own analgesia, he or she must have a basic understanding of how to use the pump. The individual must be a participant in the treatment program, and this is often not possible in those at the extremes of age due to cognitive abilities. The technique has been shown to be effective in those as young as 5 years old [23]. At the same time, there may be challenges in using this method in individuals, where there might be a communication barrier.

With time, the PCA pump can be discontinued, and the patient can be transitioned to oral narcotic pain medications. Oxycodone is often the drug of choice and can offer fewer side effects associated with altered mental status or hallucinations [7]. Further, in patients who have developed narcotic tolerance, methadone has shown some benefit. In patients given one dose of methadone, the pain scores and narcotic requirements were reduced for 72 h following multilevel spinal surgeries [24]. Methadone is also a N-methyl-D-aspartate (NMDA) receptor antagonist, and as a result it mitigates pain and also reduces opioid tolerance [7]. It also has a long duration of action, which decreases the necessity of a PCA if the patient still has it available. At time of discharge, patient's baseline narcotic requirements must be taken into account to provide additional pain relief once patient has left the hospital. Judicious use of narcotics is important as addiction and drug abuse is a rising problem.

32.4.2 Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) cause their intended effect by reducing the prostaglandin (PGE) synthesis. NSAIDs block the inflammatory cascade and cyclooxygenase (COX), which leads to reduced pain, fever, platelet aggregation, and inflammatory pain response. NSAIDs often do not provide adequate analgesia when used as a unimodal analgesic. However, when it is used in combination with opioids, there is improved pain compared to either one individually [3]. NSAIDs can be used as preemptive analgesia or just postoperatively. Patients given NSAIDs preemptively utilized the PCA postoperatively at a lower frequency compared to those not in the preemptive analgesia group [25]. However, this group reported slightly worse early postoperative pain perception over time (VAS) but reported better quality of life (EQ–5D) scores for pain discomfort and anxiety/depression at postoperative follow-up 2 weeks later [26]. NSAIDs can also be used in pediatric patients to help lower narcotic requirements [7]. NSAIDs can be either intravenous (ketorolac) or oral (ibuprofen, diclofenac). Ketorolac has often been the intravenous intraoperative drug of choice. Ketorolac inhibits both COX-1 and COX-2. However, the primary side effect is that it may delay the early stages of bone healing because it inhibits PGE-2 formation [27]. However, this has been mainly found at much higher doses of 120–240 mg daily [28] and longer duration [29] of treatment with ketorolac. Others argue that NSAIDs may increase the risk of bleeding. While this certainly can be true, many providers prefer celecoxib or parecoxib, which are COX-2 inhibitors. Their selective action preserves platelet function and gastric mucosa. Further, celecoxib use administration 1 h before induction and 12 h postoperatively for the next 5 days improves pain scores and reduces opioid consumption following spinal fusion surgery without affecting the rates of nonunion [28]. COX-2 inhibitors are contraindicated with renal dysfunction and should be used very cautiously in patients with coronary or cerebrovascular diseases. Further, all NSAIDs increase the risk of sodium and water reabsorption, which can lead to increased risk of hypertension and heart failure. These side effects associated with NSAIDs are more pronounced in the elderly.

32.4.3 Paracetamol

Paracetamol and its prodrug acetaminophen play a key role treating postoperative pain especially when given intravenously. It is particularly useful in providing immediate pain relief when there is

still reduced gastric motility or when rapid analgesia is required. The onset of analgesia begins within 5–10 min of administration. Like NSAIDs, paracetamol is not useful as a unimodal analgesia [30]; however it is useful, when used as an adjuvant to opioid therapy [31]. When given as an adjuvant, it can reduce opioid requirements by 40–50% [15]. The mechanism of action is not clear; however, it involves the inhibition of prostaglandins [32] and inhibition of the descending serotonergic pathways [33]. Paracetamol offers a safer analgesia method in patients where NSAIDs may be contraindicated. This is particularly useful in the elderly patients. Intravenous acetaminophen can also be given four times a day in the initial postoperative period to help lower the narcotic requirements. In adolescent populations undergoing scoliosis, this has been found to help reduce the narcotic doses required [34]. At time of discharge, oral paracetamol can also be recommended to provide additional pain relief.

32.4.4 Analgesic Adjuvants

Alpha-2-agonists have been used to potentiate the actions of local anesthetics, opioids, or their combination to provide increased analgesic relief and increase the effects of local anesthetics. These agents serve to help lower the doses of narcotic agents given to patients, which may limit some of the side effects of narcotics including respiratory depression and constipation. Agents often administered include either clonidine or dexmedetomidine. Clonidine can be used intravenously or in the epidural space. Epidural clonidine may lead to bradycardia, hypotension, and sedation [35]. However, if epidural clonidine is used with bupivacaine infiltrated at the incision site, there is often adequate analgesia associated with hemodynamic stability [36].

Dexmedetomidine, a highly selective alpha-2-adrenergic agonist, can also be used. It has similar positive effects to clonidine but has improved hemodynamic stability [37]. It also has the ability to lower the amount of propofol required for adequate sedation [38] and improved anti-inflammatory properties [39]. It can also be used as an adjuvant in neuraxial anesthesia to help provide greater analgesia. When used instead of remifentanil, which is considered the standard of care intraoperatively, there is lower postoperative pain for 48 h after a posterior lumbar interbody fusion [40].

32.4.5 Other Analgesic Agents

Corticosteroids intravenously have been used to reduce postoperative pain after spinal surgery. Surgery is associated with a significant inflammatory response with increased cytokines and growth factors, which may lead to sciatic pain [41]. Steroids help lower this response [41]. Steroids may also inhibit the expression of phospholipase A2 and decrease the release of substance P at the dorsal root ganglion [7]. However, the evidence regarding steroid use is mixed. In a 1984 study, King et al. have recommended 10 mg intravenously during surgery helped to reduce analgesic requirements in patients undergoing lumbar discectomy [42]. Some evidence in animal models has suggested that corticosteroids have reduced the success of lumbar fusion [43]. But in another small study, steroids have shown to improve swallowing function, edema, and shortened length stay in patients who underwent an anterior cervical discectomy and fusion [44]. And in other studies, evaluating patients undergoing microscopic lumbar disc surgery and lumbar spine surgery, steroids have shown to reduce pain and improve functional pain [41, 45]. Further, it may also inhibit the biochemical irritation caused by the nucleus pulposus and decrease the perioperative scar formation [41]. However, most of these trials have been smaller, and no clear consensus has yet to be established, much of this is provider dependent. Larger, randomized trials are necessary to confirm these findings.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, blocks the glutamine receptors in the dorsal root, which plays a key role in the sensitization process after noxious stimuli [46]. In sub-anesthetic doses, ketamine may effectively relieve pain following surgery either as a part of the PCA or as an

infusion [47] and decrease opioid consumption in narcotic-dependent patients [48]. Prior to the operation, many of the patients undergoing spinal surgery are on chronic opioids. There is also an improved side effect profile associated with the addition of ketamine to the PCA, because of reduced opioid side effects and potential prolonged effects of the local anesthetic [47]. In particular ketamine maintains respiratory function. Of note, the psychomimetic effects of ketamine were not particularly greater compared to baseline when given in sub-anesthetic doses [47].

Antiepileptic medications as gabapentin and pregabalin also play a key role in providing multimodal analgesia in these patients postoperatively. Often times patients undergoing spinal surgeries have neuropathic pain in addition to the nociceptive pain associated with the operation. These agents play a key role in reducing neuropathic pain. Gabapentin is a δ-aminobutyric acid analog, which is an anticonvulsant drug. Binding of gabapentin helps reduce the release of glutamate, noradrenaline, calcitonin gene-related peptide, and substance P. The use of gabapentin helps reduce opioid consumption [49–51]. Part of the effect is because gabapentin enhances the effect of morphine [50]. Some of the benefits can be seen with as little as just one dose of the medication [50]. It can be taken as a part of a postoperative multimodal analgesia treatment or as preemptive analgesia. With preemptive analgesia, lower VAS scores are seen as early as the PACU [52]. Gabapentin has a selective effect on the nociceptive process involving central sensitization and reduces hyperalgesia [50]. However, its use has been associated with an increased risk of sedation. The most common dose used is 600 mg [52]. Pregabalin has also shown similar effects [53, 54]. Pregabalin is a gabapentinoid and also a close analog of δ-aminobutyric acid. Pregabalin is more potent than gabapentin. Pregabalin also exhibits linear pharmacokinetics across its therapeutic dose range and low intersubject variability [55]. Further, pregabalin is also associated with improved functional outcomes 3 months after lumbar discectomy [56]. The preferred dose of pregabalin is 150–300 mg. Use of pregabalin or gabapentin is associated with less anxiety, pruritus, postoperative shivering, reduced morphine consumption, and increased patient satisfaction [57].

Tricyclic antidepressants (TCAs) as amitriptyline, nortriptyline, and imipramine and serotonin norepinephrine reuptake inhibitors have proven efficacy in treating chronic pain, but their use in acute pain settings has been limited due to lack of solid supportive evidence.

32.5 Conclusion

Almost all providers agree that multimodal analgesia is key in providing good pain relief along with limiting the side effects. Various combinations of the abovementioned drugs have been used, based on provider and patient preferences. Preemptive analgesia plays a very important role in managing the pain. It can prevent the "spinal wind up," which can lead to central sensitization and chronic pain. Rajpal et al. used preoperative gabapentin (600 mg), long-acting oxycodone (10–20 mg), and acetaminophen (1000 mg) and postoperative gabapentin (600 mg three times a day), long- and short-acting oxycodone (10–20 mg twice a day and 5–20 mg every 3 h), and acetaminophen (1000 mg three times a day) with a success in lowering postoperative narcotic consumption [58]. Use of this regimen was also associated with less nausea, less drowsiness, less interference with walking, and less interference with coughing/deep breathing [58]. Further, research is also being performed to evaluate the benefits of non-pharmacologic therapy including acupuncture or cognitive behavioral therapy to reduce the fear of movement. Some initial evidence has shown some limited evidence for both, but randomized controlled trials are required to confirm this evidence [59, 60]. More research needs to be done to not only evaluate treatment regimens to better treat pain associated with spinal regimens but also develop drugs and evaluate non-pharmacologic therapies that have fewer side effects.

Key Points

- Pain can be debilitating and prolong stay in the hospital.
- Multimodal analgesia is key to effective management of the acute pain. Providing analgesia preoperatively, intraoperatively, and postoperatively is vital to successfully managing the patient's pain.
- Using neuraxial analgesia is the most effective to reduce consumption of narcotics.
- Other agents used include nonsteroidal agents, acetaminophen, dexmedetomidine, corticosteroids, ketamine, and gabapentin/pregabalin.

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Trigeminal Neuralgia

33

Nidhi Gupta

33.1 Introduction

Trigeminal neuralgia (TN) is a unique and most common facial neuropathic pain disorder characterized by agonizing unilateral paroxysmal pain occurring in one or more divisions of the trigeminal nerve territory [1]. It is generally considered a complex and dynamic disease, leading to a chronic course in more than half of patients. Spontaneous recovery in TN is rare, and the condition is cyclical with periods of partial or complete remission and recurrence.

Apart from experiencing sensory pain, patients with chronic TN are also at high risk for cognitive deficits, with subsequent negative impact on normal socioprofessional life [2]. Hence, along with a neuropathic pain condition, TN must also be considered a social, emotional, and psychologic disorder that requires a personalized and multidisciplinary strategy. In this chapter, we shall review the historical aspects, clinical features and diagnostic criteria, pathophysiology, and various treatment modalities of this rare and unique clinical entity.

33.2 Historical Aspects

The first account of TN in history has been accredited to the earliest descriptions of migraine headache in the second century by Aretaeus of Cappadocia [3]. Approximately 900 years later (AD 1037), Avicenna provided detailed description of facial pain consistent with TN. In 1756, Nicolas André conceptualized the disease in terms of convulsions and termed it "tic douloureux," referring to the characteristic wince associated with pain paroxysm. In 1773, John Fothergill published the first case series of 14 cases describing TN as a clinical entity, thereafter referred to as "Fothergill's disease." In the early nineteenth century, several notable clinicians and anatomists including Charles Bell, Herbert Mayo, and Francois Magendie provided the detailed account of the clinical anatomy and separate functions of the facial and trigeminal nerve. It was then that "tic douloureux" was finally known to be related to some pathophysiological derangement in the trigeminal nerve and hence named "trigeminal neuralgia."

The earliest treatment modalities of TN focused on maintaining an adequate sleep, diet, and exercise, limiting the use of addictions like tobacco and alcohol, and inhalation of trichloroethylene. Surgical treatment of TN by removing the trigeminal (Gasserian) ganglion was first reported by Carnochan in 1858 [4]. In the ensuing years, varied surgical approaches were developed for Gasserian ganglionectomy including the middle fossa approach, the subtemporal approach, and the cerebellar or lateral suboccipital approach by Dandy. Compared to middle fossa approaches, Dandy's posterior fossa approach was relatively bloodless and had lower

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risk of facial paralysis and sensory loss. Furthermore, Walter Dandy was also the first clinician to observe the mass effect and pressure on the trigeminal nerve by neighboring vessels and tumors. Dandy's surgical findings (through naked eyes) were later confirmed by Peter Jannetta in 1967, who became the first neurosurgeon to surgically decompress the trigeminal nerve through posterior fossa approach using an operating microscope. Jannetta recommended decompressing the nerve by moving the offending vascular loop and securing them with a small, nonabsorbent, synthetic Teflon. This leads to the development and worldwide acceptance of the microvascular decompression (MVD) surgery, also referred to as Jannetta's procedure, as the open surgical procedure of choice for treatment of TN.

33.3 Epidemiology

The reported prevalence of actual TN in the literature is that of 0.07% in the general population [5]. The incidence of TN ranges between 4.5 and 28.9 per 100,000 per year, increasing with age and having a slight prevalence in women over men (age adjusted ratio, 1.74:1) [6–8]. Patients usually become symptomatic after 40 years of age, with peak observed between 50 and 80 years. In case patients <40 years of age are symptomatic for TN, a secondary cause for the disease should be suspected, present in approximately 14–20% of TN patients [6].

33.4 Pathophysiology

To date, there is uncertainty about the exact pathophysiology of TN, in view of lack of satisfactory animal models, and the difficulty in obtaining essential data from the physiologic pathways of patients. However, several theories and mechanisms have been proposed to explain the pathophysiology of TN, which resolves around a complex interaction of peripheral and central mechanisms [9–13].

As per the most popular neurovascular compression hypothesis, the pulsatile compression of demyelinated axons by an overlying blood vessel may be responsible for initiating the aberrant impulses in some patients [14]. The term neurovascular conflict (NVC), in general, accounts for a gamut of clinical or radiological findings, ranging in severity from simple contact (without nerve displacement or distortion) to severe compression and/or displacement of the nerve. Historically, it has been believed that vascular compression causes focal demyelination only when the NVC occurs at the transition zone between the central oligodendroglia and peripheral myelin, which is found 2–3 mm from the root entry zone (REZ), also called the Obersteiner-Redlich line. Examination of trigeminal nerve roots from patients with nerve root compression by an overlying blood vessel has revealed focal demyelination in the region of compression, with close apposition of demyelinated axons and an absence of intervening glial processes [11].

The other recognized cause of TN is a mass lesion compressing the nerve. It has been suggested that both structural and morphologic changes that occur in the affected trigeminal nerve may be involved in the pathophysiology of TN [15]. Structural abnormalities, such as axonal loss and demyelination may lead to morphologic changes in the nerve including nerve distortion, deviation, groove formation, and ultimately nerve atrophy as a late consequence of the chronic physical stress by vascular compression. Cheng et al. have found that in patients with idiopathic TN, volume of the affected trigeminal nerve was significantly reduced in comparison to that of the nonaffected side and controls [16]. A small posterior fossa volume may also be a risk factor of NVC [17]. Apparently, posterior fossa overcrowding can lead to a closer nerve vessel relationship, thus leading to a higher incidence of NVC.

Neurovascular compression hypothesis alone may not explain the pathogenetic mechanism of TN, as shown by the very high incidence (up to 39%) of vascular compression at the REZ even in asymptomatic population [18]. Similarly, as many as 11–24% of patients with TN do not show

REZ NVC in magnetic resonance imaging (MRI) scans [19]. Apparently, trigeminal REZ NVC, as detected by MRI, is highly likely to be symptomatic when it is associated with anatomical nerve changes [19].

The ignition hypothesis proposed by Devor and colleagues highlights the role of focal demyelination in the pathogenesis of TN [10]. Focal demyelination of primary sensory afferents primarily contributes to their hyperexcitability. In addition, these groups of afferents are also linked functionally, thus leading to generation of spontaneous ectopic impulses and synchronized high-frequency afterdischarges, responsible for the short-lasting spontaneous TN attacks [10, 11]. The substantial loss of myelin as well as abnormal close apposition of trigeminal axons in the area of injury promotes ephaptic transmission between low-threshold, large-caliber sensory afferents (A-b) and smaller-caliber nociceptive sensory axons (A-d and C fibers) which may account for the paroxysms of intense pain triggered by innocuous stimulation [15]. Again, focal demyelination does not occur in all individuals with the vascular contact, and there must be some individual susceptibility which predisposes to the development of focal demyelination at the REZ by vascular contact, thereby causing TN.

The refractory period between pain paroxysms may be explained by the hyperpolarization of the sensory neurons [10]. Their incomplete remyelination and reduced excitability may further explain the unpredictable periods of complete remission that occur in patients with TN.

Sabalys et al. have suggested that the peripheral pathophysiology of TN may involve progressive dystrophy of the trigeminal nerve branches, caused either by compression of nerve by surrounding vessels or by allergic-immune reaction (mast cell degranulation and histamine release) [12]. This progressive dystrophy then stimulates the central pathogenesis mechanism of neuralgia, involving the reticulate, mesencephalon structures, limbo nuclei, limbic system, and brain cortex. Hyperactivity of primary sensory afferents has been proposed to secondarily induce central sensitization of wide-dynamic-range neurons in the spinal trigeminal nucleus [20].

Central mechanisms may also account for the occurrence of TN in patients with no structural damage on the trigeminal nerve. Current literature also shows that TN induces gray and white matter abnormalities in central nervous system (CNS) areas involved in pain perception, pain modulation, and motor function, which are important for sensory and cognitive-affective dimensions of pain [21, 22]. It is also possible that TN-induced structural alterations can have functional consequences, resulting in central manifestations of TN pain [23].

Demyelination plaques present in the pontine area have long been ascribed as the causative factor in patients with MS presenting with TN (MS-related TN) [24]. However, recent literature suggests a dual, concurrent mechanism, in which both inflammatory demyelination and mechanical demyelination may coexist and damage the primary trigeminal afferents [24, 25]. The other sensory disturbances, including continuous ongoing pain and dysesthesia, may arise from damage to the second-order neurons in the spinal trigeminal complex.

33.5 Etiology

The vascular compression of the trigeminal nerve by the surrounding vessels in the cerebellopontine cistern is the most common etiological cause of TN, seen in up to 80–90% of TN cases. The blood vessels mostly implicated include the superior cerebellar artery (SCA) followed by the anterior inferior cerebellar artery (AICA), posterior inferior cerebellar artery (PICA), vertebral artery, or rarely a tortuous basilar artery [26, 27]. The implication of venous compression alone as a cause of TN remains a matter of debate. As per literature, the rates of venous compression alone TN range from 3.3% to 29% [28]. Superior petrosal vein and its tributaries are the main veins that commonly compress the trigeminal nerve [29].

Posterior fossa tumors (including acoustic schwannomas, meningiomas, epidermoids, and arachnoid cysts) may lead to compression of the trigeminal nerve root either by the tumor itself or by an interposed blood vessel or by distortion of

the contents of the posterior fossa with displacement of the nerve root against a blood vessel or the skull base [12].

Neurovascular compression at the REZ can also be caused by an aneurysm, vessel aggregation, occlusion due to arachnoiditis, and arteriovenous malformation (AVM) [30]. TN caused by cerebral aneurysms has been reported on different aneurysmal locations, namely, SCA, AICA, vertebrobasilar artery, PCA, persistent trigeminal artery, cavernous ICA, and supraclinoid ICA. Posterior communicating artery aneurysms (PComAAs) cause atypical TN most commonly involving the first and second trigeminal distributions [31]. PComAAs also have a higher tendency to cause oculomotor nerve palsy due to their large size.

It has been suggested that morphological and volumetric changes in posterior fossa may play a role in the genesis of NVC [17]. Several cases of TN have been associated with diseases that include crowded posterior fossa either due to lesions or malformations, such as Paget's disease, distorted petrous bone, Chiari's malformation, achondroplasia, and Dandy-Walker malformation.

The risk of TN in patients with MS is 20 times higher than in the general population, with an approximate prevalence of 2–6% [32]. Diabetes mellitus, rheumatism, otolaryngological pathology, and allergy are some other proposed etiologies of TN that have an indirect supporting evidence [12]. A recent study has demonstrated that gain-of-function Na_V 1.6 mutation potentiates transient and resurgent sodium currents, thus leading to increased excitability in trigeminal neurons in TN patient [33].

33.6 Clinical Features and Classification

To date, numerous terminologies and classifications of TN have been proposed from time to time, often leading to confusion among the clinicians and dishomogeneity in the research being carried out. Nonetheless, the recently published classification system and diagnostic criteria for TN make an earnest attempt to solve this dilemma, by providing detailed description of different types and subtypes of TN, based on a consensus statement of the International Association for the Study of Pain (IASP) and the International Headache Society (IHS) [1].

Trigeminal neuralgia (previously described as primary trigeminal neuralgia) is characterized by "recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the TN and triggered by innocuous stimuli, like chewing, brushing teeth, washing the face, shaving, speech touching the affected dermatome or exposure to a cool breeze." The most frequent maneuvers are gentle touching of the face and talking. Recent literature suggests the presence of trigger zones in more than 90% of patients diagnosed with TN [1, 34]. In a study by Di Stefano et al. using three dimensional (3-D) face model, a trigger capable of provoking a paroxysm could be identified in nearly all patients with the diagnosis of TN based on ICHD-3 beta [34]. Trigger zones were most frequently located in the nasal and perioral region and were variable in size. Other than the triggering phenomenon, most patients with TN fail to show sensory abnormalities within the trigeminal distribution unless advanced methods such as quantitative sensory testing are employed [35]. Nonetheless, in a prospective systematic study of clinical characteristics of TN patients, sensory abnormality (particularly hypesthesia) has been reported in up to 29% of patients with TN [6].

Patients may variably experience multiple painful episodes in a day (ranging from 0 to more than 50), each lasting from few seconds to a maximum of 2 min. Following a painful paroxysm, there is usually a refractory period during which pain cannot be triggered. When very severe, the pain often evokes contraction of the muscles of the face on the affected side (tic douloureux). Mild autonomic symptoms such as lacrimation and/or redness of the ipsilateral eye may be present. Nightly attacks are less common in TN than in cluster headache,

where they are a prominent feature. Spontaneous remission from pain can occur for weeks, months, or years [36].

Classical TN (CTN) is defined as TN developing without apparent cause other than neurovascular compression and not simply contact. The morphological changes in the trigeminal nerve root typically involve nerve root atrophy and/or displacement due to neurovascular compression, demonstrated either on MRI or during surgery [16]. CTN usually affects the right side of the face, in the first and second nerve divisions, probably because of the somatotopic distribution of sensory fibers in the trigeminal root [37]. It rarely occurs solely in the first division, unlike postherpetic neuralgia. Bilateral TN is very rare, except for STN in MS (reported frequency of slightly <10%) [5]. Primary bilateral CTN accounts for 0.3–6% of TN cases [38].

Classical TN with concomitant continuous pain (previously described as atypical TN or TN type 2) have features of CTN along with continuous or near-continuous dull background facial pain in the affected trigeminal nerve territory. Continuous pain may arise either as a result of progressive nerve root damage or because of central facilitation of pain processing pathways [20]. Nonetheless, these patients are significantly resistant to both medical and neurosurgical treatment modalities that are generally effective for CTN.

Secondary TN (STN) is caused by an underlying pathology such as tumors in the cerebellopontine angle (CPA), AVM, skull base bone deformity, dural arteriovenous fistula, MS, connective tissue disease, genetic causes of neuropathy or nerve hyperexcitability, and, rarely, fungal infection or bacterial infections [1, 7, 8, 12]. Compared to patients with CTN, sensory abnormalities are present in significant majority of these patients. In addition to neuroimaging, routine electrophysiological studies such as blink reflex (BR) or trigeminal evoked potentials are also helpful in evaluating STN [7, 39]. Electrophysiological testing of trigeminal reflexes has been able to differentiate CTN from STN with a high degree of sensitivity (96%) and specificity (93%) [39].

The term idiopathic TN (ITN) denotes cases with no abnormality detected either during neuroimaging or during electrophysiological testing. Though NVC may be observed in MRI (a common finding in healthy subjects as well), there is no evidence of any concomitant nerve root atrophy and/or displacement.

Patients with severe, long-standing, and medically intractable pain are at a high risk for cognitive impairments and social withdrawal, which may negatively impact their quality of life. A conscious effort to avoid touching of trigger zones on face ultimately leads to poor personal hygiene along with significant dehydration and weight loss. Furthermore, patients may experience depression, anxiety, mood disorders along with dysfunction in memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, and general cognitive functioning [2]. Cheng et al. have demonstrated the prevalence of depression in patients with TN to be 64.8%, higher than in general population (5–8%) [40]. Female, high pain intensity, ineffective medical treatment, single patients (compared to the married), and patients who were unemployed were at a significant risk for depression and anxiety. Considering these psychological ill effects of the disease, TN has also been called the "suicide disease."

33.7 Diagnosis

Though the symptomatology seems fairly straightforward, clinical diagnosis is often very complex, as the symptoms are frequently mistaken for dental or jaw pain, leading to unnecessary radiological investigations and surgical interventions. In the absence of definitive laboratory or diagnostic tests, the diagnosis of TN is primarily clinical and is determined by a careful history. Investigations including radiological imaging are needed to establish the likely etiology. The latest diagnostic criteria of TN are as per ICHD-3 [1]. The common differential diagnosis for TN includes other cranial neuralgias, trigeminal autonomic cephalalgias, and painful ophthalmoplegias (Table 33.1) [5, 7, 8, 41].

Table 33.1 Differential diagnosis of trigeminal neuralgia [5, 7, 8]

Cranial neuralgias • Glossopharyngeal neuralgia • Hemifacial spasm • Nervus intermedius neuralgia • Tic convulsif • Vagal neuralgia
Trigeminal autonomic cephalalgias • Cluster headaches • Chronic paroxysmal hemicrania • Hemicrania continua • Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) • Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA)
Painful posttraumatic trigeminal neuropathy
Persistent idiopathic facial pain
Painful trigeminal neuropathy attributed to acute herpes zoster
Painful trigeminal neuropathy caused by a connective tissue disease or genetic disorder
Painful ophthalmoplegia • Tolosa-Hunt syndrome • Ocular diabetic neuropathy • Ophthalmic herpes zoster • Ophthalmoplegic migraine
Odontogenic facial pain • Cracked tooth • Caries or pulpitis

33.8 Role of Neuroimaging

The broad spectrum of arterial and venous vessels involved in the pathophysiology of TN necessitates use of a highly sensitive and reliable diagnostic imaging modality to clarify the diagnosis as well as to prepare for the specific anatomical details for surgery. Special high-resolution isotropic 3-D MRI reconstruction sequences which have been shown useful in identifying vascular compression include constructive interference in steady-state (CISS) MRI imaging (for a detailed anatomical examination of the cisternal and cavernous segments of the trigeminal nerve) and time-of-flight magnetic resonance angiography (TOF-MRA) (for visualization of arteries) [42]. In addition to confirming the diagnosis, preoperative imaging may help in surgical decision-making by determining the need of an endoscopically assisted MVD in patients with unclear surgical anatomy [43].

Recently introduced diffusion tensor imaging (DTI) provides better understanding of microstructural tissue changes of the trigeminal nerve root, while fiber tractography helps to measure focal demyelination and edema [44]. Thus, the addition of comprehensive presurgical DTI assessment of trigeminal nerve in patients with TN may play a prognostic role in predicting treatment success by MVD [23].

In the setting of persistent or recurrent pain after MVD, postoperative imaging may allow assessment of the relationship of the nerve, vessel, and interposed pad, pledget, or sling (depending on method of decompression) and for additional sources of NVC or masses compressing on the nerve (e.g., Teflon granulomas and dense arachnoid adhesions).

33.9 Measurement of Trigeminal Neuralgia Pain

To date, multiple scales have been developed to rate and quantify TN. However, their limited use and lack of uniformity have made it difficult to compare the outcomes of varied interventions across multitude of studies. Five commonly used scales to measure TN pain includes the visual analog scale, numeric rating scale, McGill Pain Questionnaire, Barrow Neurological Institute Pain Intensity Score (BNI-PS), and Penn Facial Pain Scale (PFPS).

The BNI-PS is an easy-to-use scale with excellent face validity [45]. However, it is useful only for clinicians to classify patient pain control and medication intake and is not focused on patient's pain perceptions. Recently, the PFPS has been proposed to assess patient's pain and treatment outcomes [46]. PFPS includes a Brief Pain Inventory and seven additional items specific for facial pain disorders, validated by a group of TN experts, and thus seems a solid option for pain measurement in TN.

33.10 Multimodal Management of Trigeminal Neuralgia

Although the exact origin of TN remains elusive, the unique nature of the symptoms and inciting events of this disease have led to the development

Table 33.2 Treatment modalities of trigeminal neuralgia [1, 5, 8, 36, 47–56]

Pharmacological	First line: carbamazepine, oxcarbazepine Second line: baclofen, lamotrigine, pimozide Add-on medications: gabapentin, pregabalin, topiramate, levetiracetam, botulinum neurotoxin type A, topical formulations (phenytoin, ketamine, baclofen, lidocaine)
Interventional	
Peripheral nerve procedures	Infraorbital nerve block Greater occipital nerve block
Percutaneous ablation techniques	Percutaneous balloon compression Percutaneous radio-frequency thermocoagulation Percutaneous glycerol rhizotomy
Radiosurgery	External beam stereotactic radiosurgery Gamma Knife radiosurgery (Gamma Knife®) Linear accelerator radiosurgery CyberKnife
Surgical intervention	Microvascular decompression
Neuromodulation techniques	Peripheral nerve stimulation (supraorbital nerve, infraorbital nerve, and the greater occipital nerve pulsed stimulation) Transcutaneous electrical nerve stimulation Subcutaneous peripheral nerve field stimulation Gasserian ganglion pulsed stimulation Cervicomedullary junction stimulation Noninvasive brain stimulation (repetitive transcranial magnetic stimulation or transcranial direct current stimulation) Motor cortex stimulation Deep brain stimulation

of numerous treatment modalities over the years (Table 33.2). These modalities broadly include medications that affect nerve conduction, peripheral denervation techniques, and surgical decompression of the site of NVC. Though these therapies can provide pain control in most of the cases, their clinical efficacy may vary over time, and many patients need more than one treatment to achieve effective pain control [1, 5, 8, 36, 47–56]. Furthermore, before starting any treatment, the neuropsychological evaluation of patients suffering from chronic pain should also be taken into account. A dynamic and personalized multimodal approach of treatment is then formulated, taking into account all the available TN therapies and the neuropsychologic support to patient. The goal of treatment is to have a patient completely pain-free at an acceptable level of side effects and without fear of its sudden recurrence.

33.11 Pharmacological Management

Pharmacological therapy is the mainstay treatment for TN since it generally carries a lower risk compared with major surgical procedures and is suitable for medically compromised patients who are unfit for such procedures [36, 47, 48]. However, there remain few subtypes such as postherpetic neuralgia of the trigeminal nerve, posttraumatic or surgery-related supraorbital or infraorbital nerve neuralgia, MS or space-occupying lesion-related TN, which resemble neuropathic pain conditions with a high risk of failure of medical therapy [57].

Before starting therapy, an accurate medical history (in order to exclude cardiac disease, pregnancy, and other possible relevant medical conditions) and laboratory analysis of kidney and liver function tests are essential [8]. Laboratory testing should be also repeated if higher doses are used and significant side effects are reported. ECG is needed when a cardiac conduction abnormality is suspected on the basis of medical history, because both first-line medications (carbamazepine and oxcarbazepine) are contraindicated in patients with atrioventricular block.

To date, numerous drugs including anticonvulsants such as carbamazepine, oxcarbazepine, phenytoin, gabapentin, valproic acid, pregabalin, topiramate, clonazepam, levetiracetam, lamotrigine, and lacosamide, muscle relaxants such as baclofen and tizanidine, antipsychotics (pimozide), local anesthetics (lidocaine and proparacaine),

misoprostol (prostaglandin E1 analog), and antiarrhythmics such as tocainide have been investigated as the treatment options in TN [47–50, 58].

Patients with TN frequently have an excellent response to some selected drugs. However, this efficacy is often limited by their disabling side effects, causing either treatment withdrawal or a dosage reduction to an insufficient level in many patients. Hence, it's imperative for the physician to be acquainted with the side effects and dose management of these drugs and the alternative options available (Table 33.3).

Table 33.3 Commonly used medications for trigeminal neuralgia [5, 7, 8, 36, 47–50]

Drug	Main mechanism of action	Starting dose	Titration	Max dose	Main adverse events
Carbamazepine	Voltage-gated sodium channel blocker	200 mg	Increase 200 mg every 3 days	1200 mg (400 mg) (t.i.d.)	Neuropsychologic side effects: drowsiness, ataxia, and a significant reduction of postural stability and alertness Other commonly reported side effects: skin reactions, nausea, vomiting, elevation of transaminases, hyponatremia Serious but uncommon side effects: myelosuppression, leukopenia, irreversible aplastic anemia, hepatotoxicity, lymphadenopathy, systemic lupus erythematosus, Stevens-Johnson syndrome Potent enzyme inducer-accelerated metabolism of concurrently prescribed anticonvulsants, tricyclic antidepressants, antipsychotics, steroid oral contraceptives, glucocorticoids, oral anticoagulants, cyclosporin, theophylline, chemotherapeutic agents, and cardiovascular drugs Short half-life—needs to be administered 3–4 times a day
Oxcarbazepine	Voltage-gated sodium channel blocker	300 mg	Increase 300 mg every 3 days	1800 mg (600 mg) (t.i.d.)	Allergic cross-reactions with carbamazepine Drowsiness Ataxia Dizziness Hyponatremia (6–8% of patients) Transaminase induction

Table 33.3 (continued)

Drug	Main mechanism of action	Starting dose	Titration	Max dose	Main adverse events
Lamotrigine	Acts at voltage-sensitive sodium channels, stabilizes neural membranes, and inhibits the release of excitatory neurotransmitters	25 mg	Increase 25 mg every 7 days	400 mg (200 mg) (b.i.d.)	Dizziness Nausea Headache Blurred vision Vertigo Ataxia Skin rash (7–10% of patients) Stevens-Johnson syndrome (one in 10,000 patients)
Baclofen	Depresses the excitatory synaptic transmission in the spinal trigeminal nucleus	15 mg (5 mg) (t.i.d)	Increase 5 mg t.i.d. every 3 days	60–80 mg/day, administered 3–4 times per day	Lassitude Drowsiness Dizziness Nausea Gastrointestinal discomfort Nausea Constipation Hypotension Withdrawal symptoms on abrupt discontinuation with seizures and hallucinations
Gabapentin	GABA receptor agonist, binds to alpha$_2$-delta subunits of voltage-gated calcium channel inhibiting the release of excitatory neurotransmitters	300 mg/day	Increase 300 mg every 2–3 days	3000 mg (1000 mg t.i.d.)	Drowsiness Unsteadiness Nausea Headache Confusion Weight gain Peripheral edema Hyperlipidemia
Pregabalin	Analog of GABA, structurally related to gabapentin Binds to alpha$_2$-delta subunits of voltage-gated calcium channel	75 mg	Increase 75 mg every 3 days	600 mg (300 mg b.i.d. or 200 mg t.i.d.)	Drowsiness Unsteadiness Weight gain Peripheral edema

(continued)

Table 33.3 (continued)

Drug	Main mechanism of action	Starting dose	Titration	Max dose	Main adverse events
Botulinum neurotoxin type A	Blocks acetylcholine release from presynaptic nerve endings by interfering with the activity of SNARE (soluble *N*-ethylamide-sensitive factor attachment protein receptors) proteins Causes local release of antinociceptive neuropeptides such as substance P, glutamate, and CGRP	–	Mean dose: 3.22 units/cm^2 subcutaneously can be administered intradermally and/or submucosally	20–75 units	Transient facial weakness Focal edema Dysphagia Myasthenia Allergic reactions

Current evidence supports the use of both carbamazepine and its keto-analog oxcarbazepine as first-line pharmacological treatment in TN, initially effective in approximately 90% of patients [47, 48, 59, 60]. However, oxcarbazepine is generally preferred for better tolerability and decreased potential for drugs interactions [59, 60]. The effectiveness of carbamazepine and oxcarbazepine reflects the primary mechanism of paroxysmal pain in TN, i.e., the focal demyelination of primary afferents near the REZ. Both drugs block voltage-gated sodium channels in a frequency-dependent manner, stabilizing hyperexcitable neural membranes and inhibiting repetitive firing, thus reducing both the intensity and frequency of attacks.

Although generally considered effective, these treatments are limited by poor tolerability, the need for well-managed titration, and potential for significant drug interactions [60]. Hence, the doses of the chosen drug should be gradually increased to the maximum allowed daily dose until adequate relief is acquired. Apparently, after a period of stability at a given dose, these medications may lose their efficacy owing to their metabolism consequent to hepatic enzyme induction, thus necessitating even higher doses. Nevertheless, in case patient is having the maximum prescribed dosage of first-line medications without attaining adequate pain relief, it is unlikely that any other medication would be effective. Hence, in these patients surgical MVD should be proposed as second line of management [5, 8].

However, there still remain some patients who are either unable to take carbamazepine or oxcarbamazepine as a result of contraindications or may require their discontinuation because of certain side effects (allergic dermatitis, aplastic anemia with carbamazepine, and CNS depression [more frequent with carbamazepine than oxcarbazepine]). In such subset of patients, second-line medications, including baclofen, lamotrigine, and pimozide, may be beneficial [59].

While patients with TN manifesting with purely paroxysmal pain find adequate relief from carbazepine or oxcarbamazepine, patients suffering from continuous pain between the paroxysms are more resistant to these drugs. Though never tested clinically in a trial, both gabapentinoids and antidepressants are expected to be more efficacious in continuous than paroxysmal pain and are often used as an add-on treatment in this patient population [5].

Baclofen and misoprostol have been most frequently used in patients with MS-related TN. However, recent literature review suggests that the same pharmacological management approach should be used for MS-related TN as recommended for non-MS TN (carbamazepine or oxcarbazepine as the first-line medications and lamotrigine, baclofen, gabapentin, and pregabalin as second-line drugs), as it would help to reduce side effects and potential exacerbations of existing MS symptoms [58].

Topical formulations of analgesics (lidocaine, ketamine, baclofen) have certain advantages, such as lack of side effects, no drug-drug interactions, and higher concentrations of active compound at the pain area, over other systemic medications. Intraoral application of 8% lidocaine is found to drastically reduce paroxysmal pain without serious side effects, thus simplifying the treatment of TN [61]. Phenytoin in topical formulation has been found to act synergistically with other active analgesics in topical formulations (e.g., compounded ketamine 10% cream and baclofen 5% cream), causing faster onset of action, longer duration of analgesia, and intensified pain-relieving effect [62]. Furthermore, phenytoin might be able to reinstate reduced analgesic effect seemingly related to tolerance.

Chemo-denervation with botulinum toxin type A (BoTN-A) has also been found to be useful for treatment of drug-resistant ITN, in terms of efficacy and safety [63, 64]. BoTN-A is a potent neurotoxin that blocks acetylcholine release from presynaptic nerve endings by interfering with the activity of SNARE (soluble N-ethylamide-sensitive factor attachment protein receptors) proteins [63]. This appears to be mediated by the local release of antinociceptive peptides and inhibition of central as well as peripheral sensitization. Current literature supports a moderate evidence regarding the efficacy of BoTN-A in treating trigeminal and postherpetic neuralgia [63]. However, caution should be taken while injecting the drug, as it can lead to unwarranted paralysis, if injected in or spread to the wrong muscle group. Even conventional injection has the possibility to cause dysphagia, myasthenia, or allergic reactions.

Nav1.7 is a sodium ion channel present in the nociceptive neurons at dorsal root ganglion and the trigeminal ganglion. BIIB074, a voltage- and frequency-dependent selective Nav 1.7 sodium channel blocker, has recently been investigated for its safety and clinical efficacy in patients with TN [65]. Overall, BIIB074 seem to have better tolerability profile compared with other drugs used in TN, with lower reported frequency of cognitive impairment and drowsiness.

To date, there have been several meta-analyses which conducted pair-wise comparisons between the abovementioned drugs. However, the lack of a systematical comparison makes the results of each study incomplete, inconclusive, and sometimes contradictory. Moreover, there is a paucity of randomized controlled trials (RCTs) with adequate sample size which hampers the generalizability of trial results. In terms of therapeutic efficacy, a recent systematic review using comprehensive system of comparison and network meta-analysis has suggested using lidocaine, BoTN-A, and carbamazepine as the first possible choice for clinical application [48].

33.11.1 Treatment of Acute Exacerbation

In patients who develop severe exacerbations of unremitting pain, in-hospital treatment may be necessary for intravenous drug therapy, rehydration, and management of hyponatremia (seen with carbemezepine and oxcarbemezepine). Intravenous fosphenytoin is preferred over phenytoin because of better parenteral tolerance [66]. Moreover, the combined use of intranasal local anesthetic (LA) application and intravenous fosphenytoin also seems to be an effective acute pain control therapy [67].

33.12 Neurosurgical Management

Though pharmacologic treatment remains the first-line therapy for TN, surgical intervention may become imperative for patients who are either refractory to pharmacotherapy or are

unable to tolerate medications owing to their adverse effects. Furthermore, patients with psychiatric conditions, vascular disease (cardiovascular, cerebrovascular, or peripheral vascular disease), hepatic disease, or renal disease are often on polypharmacy that may negatively interact with TN medications, thereby limiting the pharmacological treatment option.

At present many surgical techniques, ranging from minimally invasive stereotactic-based Gamma Knife radiosurgery (GKRS) to more invasive percutaneous ablative procedures and surgical MVD, and the latest neuromodulation techniques are available within the armamentarium of a neurosurgeon. Surgical treatment modalities either aim to decompress the nerve (as is done in MVD) or disrupt the afferent pain fibers in trigeminal nerve complex (denervating procedures). Percutaneous ablative procedures [percutaneous radio-frequency thermocoagulation (RFT), percutaneous glycerol rhizotomy (PGR), or percutaneous balloon compression (PBC)] and stereotactic radiosurgery (SRS) are primarily denervating procedures. Purposeful denervation is sometimes carried out during surgical MVD, either when the offending vessel is deforming the nerve and is hard to mobilize, or not present at all [36].

Surgical aneurysmal clipping provides complete trigeminal pain relief in all patients with intracranial aneurysms as the etiological cause. For patients with MS-related TN, there is insufficient evidence at present to either support or refute the effectiveness of surgical interventions [58]. However, considering the plausible dual-concurrent mechanism of pathophysiology of MS-related TN, surgical options (including ablative procedures) should be considered if pain control is poor with medications alone [25, 58, 68].

33.12.1 Intraoperative Monitoring

Neurophysiological monitoring during neurosurgical interventions for TN plays an important role not only in the protection of cranial nerve function but also in the prediction of clinical outcomes [69]. Commonly used intraoperative neuromonitoring techniques used includes brain stem auditory evoked potentials (BAEPs), brain stem trigeminal evoked potentials (BTEPs), electromyography free run, BR, and direct trigeminal and facial nerve stimulation.

Vestibulocochlear nerve is at greatest risk of injury, and implementing intraoperative neuromonitoring, specifically with BAEPs, may reduce the risk of hearing loss postoperatively [69, 70]. BTEPs are a neurophysiological monitoring technique which reflects the function of trigeminal nerve, trigeminal nerve nuclei, and trigeminal nerve conduction pathway. These are not affected by general anesthetics, muscle relaxants, or the consciousness of the patient and hence can monitor trigeminal nerve function in clinical application. With the assistance of BTEP, affected nerve fibers and offending vessels can be accurately localized, which may improve surgical efficacy and reduce the occurrence of complications after MVDs [71]. As evaluated by Zhu et al., the improvement and restoration of BTEP waveforms are closely related to the postoperative curative effect, thus providing guidance for MVD surgery and prognosis evaluation [72].

Intraoperative BR recording, obtained by the electrical stimulation of the supraorbital nerve, might be useful in monitoring the sensory part of the trigeminal nerve, the brain stem connections, and the facial nerve during MVD for TN [73].

33.12.2 Percutaneous Ablative Procedures

33.12.2.1 Peripheral Nerve Procedures

Peripheral nerve procedures, such as nerve blocks, have been used as diagnostic tests and can be effective for many of the patients who are refractory to medical therapy or are awaiting MVD surgery. Commonly performed nerve blocks for TN includes either infraorbital nerve blockade or blocking one or more of the occipital nerves (including greater occipital nerve) [54]. Peripheral nerve blockade for pain suppression is based on the ability of low concentrations of LA to selectively block sensory fibers in

mixed nerves. Ethyl alcohol injected peripherally in the vicinity of the three divisions of the trigeminal nerve at their respective foramina under LA offers transient symptom relief. The procedure is, however, painful with discomfort lasting several days, and fibrosis makes repeat injections technically difficult.

Cryoablation of the peripheral branches of the trigeminal nerve at the infraorbital or the mandibular foramen produces a reliable nerve block with reversible loss of sensation and no aggravation of symptoms [52, 74]. In cryosurgery, a cryoprobe with either nitrous oxide or liquid nitrogen (as a refrigerant) is applied at −50 to −140 °C, in the same way as a needle for a nerve block at the infraorbital or mental foramen, by an intraoral approach. Complete analgesia is achieved within 10–14 days of procedure [74]. However, recurrences have been observed as early as 6–8 months after treatment.

Transient sensory loss and motor weakness appear to be the main disadvantages of peripheral ablative techniques, and pain is expected to recur in most patients.

33.12.2.2 Sphenopalatine Ganglion Blockade

The sphenopalatine ganglion (SPG) is an autonomic ganglion located in close proximity to the maxillary division of trigeminal nerve in the pterygopalatine fossa. SPG blockade through intranasal lidocaine application in the nostril ipsilateral to the pain has been shown to provide temporary relief in TN [75]. Recently, an SPG blockade device called the Tx360 has been designed to minimize discomfort and side effects from the traditional noninvasive cotton swab applicators and the inaccuracy of a nasal spray [76].

33.12.2.3 Percutaneous Procedures for the Treatment of Trigeminal Neuralgia

Percutaneous procedures are minimally invasive and an effective treatment alternative for patients with medically refractory TN, who are either unfit or not willing for more invasive surgical MVD. These approaches center on three types of lesioning methods to disrupt aberrant neuronal activity in the trigeminal nerve complex: mechanical compression by balloon inflation during PBC, chemical lesion by injection of high-concentration glycerol during PGR, and thermocoagulation by radio frequency during RFT [52–54].

The procedures are generally performed either under general anesthesia (GA) or under conscious sedation with short-acting agents such as propofol (for RFT and PGR). The patient is positioned supine with head in 15° of extension. All procedures rely on Hartel's anatomical landmarks to gain entry into the foramen ovale, an oval-shaped opening in the middle cranial fossa located at the posterior base of the greater wing of the sphenoid bone (Fig. 33.1). Percutaneous cannulation of the foramen ovale provides direct access to Meckel's cave, which is a space between two layers of the dura mater at the petrous apex. It contains the Gasserian ganglion, trigeminal cistern, and postganglionic trigeminal rootlets. Dynacomputed tomography and neuronavigation systems may be used to improve visualization and navigation of the cannula to the foramen ovale, especially for patients with anatomic variants. Entry into the trigeminal cistern may at times result in flow of cerebrospinal fluid (CSF) through the needle, which was earlier thought to be associated with better treatment outcomes

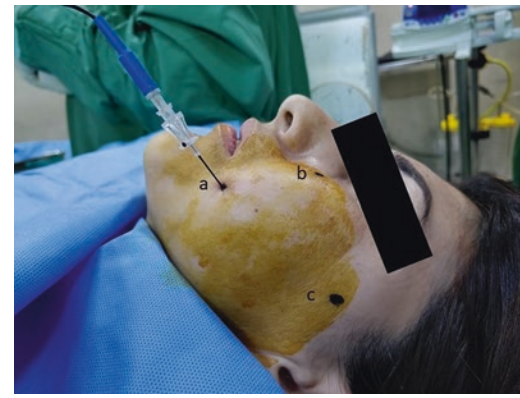

Fig. 33.1 Figure showing percutaneous radio-frequency thermocoagulation needle entering at the skin insertion point, 2.5 cm lateral to the corner of the mouth (a) and following a trajectory toward a point in line with the medial ipsilateral pupil (b) and 3 cm anterior to the external auditory meatus (c)

after PGR [77]. However, recent studies refute any correlation between the presence of CSF flow during needle placement with either the success rate or duration of pain relief [68, 78].

During percutaneous ablative procedures, mechanical stimulation or compression of the trigeminal ganglion (upon needle entry into the foramen ovale or advancement and inflation of balloon) may result in a transient trigeminal depressor response with significant bradycardia and hypotension. Hence, atropine is usually administered prophylactically, except during PBC, where the response is monitored to assess for adequacy of trigeminal compression. Nonetheless, intravenous atropine should be ready for emergent use, and an external transcutaneous or transesophageal pacemaker may be placed preoperatively or after anesthetic induction.

Percutaneous Balloon Compression PBC is performed under GA. A 14-gauge needle is advanced under fluoroscopic guidance until the foramen ovale is entered. A straight guiding stylet is now introduced through the cannulae, till its tip reaches 10–15 mm beyond the needle tip at foramen ovale. Once correctly positioned, the stylet is removed, and a no. 4 balloon catheter is introduced in the same place as the guiding stylet. The balloon is now inflated for 60–90 s with 0.75–1.0 mL of radiocontrast dye to attain a target pressure of 750–1250 mm Hg. According to Chen et al., 90 s of compression provides better long-term results, without apparent added complications [79]. The balloon assumes a classic pear-like shape when correctly positioned and inflated, thus ensuring the safety and maximum success of the procedure. The balloon is now deflated and taken out together with the cannula. The skin entrance site is then compressed for some time followed by sterile dressing. An ice pack may be applied to reduce postoperative swelling of the cheek.

Radio-Frequency Thermocoagulation This procedure involves controlled, selective thermocoagulation lesioning of the trigeminal nerve root complex. A radio-frequency electrode is passed through the 20-G cannula, with its tip into Meckel's cave at the level of foramen ovale (Fig. 33.2). The third, second, and first divisions of trigeminal nerve are then stimulated at 0.2–1 V at 50 Hz (0.2 ms) in sequence by slowly advancing the needle tip by 2–4 mm. A combination of electrophysiological motor and sensory nerve root testing and neuronavigation technology may be used to identify the exact trigeminal nerve division. Lesioning is then done using a thermocouple at 55–75 °C for 30 s to 2 min. In comparison with the conventional RFT, use of pulsed radio-frequency current involves short stimulation bursts at similar temperature but with less thermal damage to the tissues. However, the best treatment results have been obtained with a combination of pulsed radio-frequency and RFT treatments in succession than by either modality alone [80].

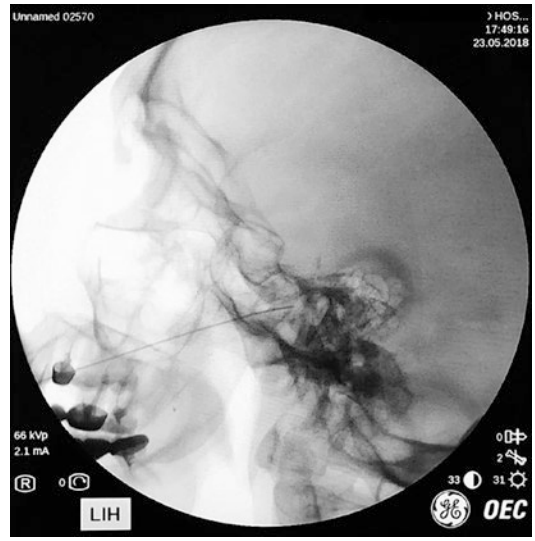

Fig. 33.2 Figure showing the correct position of the tip of radio-frequency thermocoagulation electrode into Meckel's cave, at the level of foramen ovale

Percutaneous Glycerol Rhizotomy PGR is performed by injecting 0.25–0.40 mL of anhydrous glycerol into the cistern of Meckel's cave. After the injection, the patient is made to sit in the upright position to avoid spillage of glycerol out of the cistern. The trigeminal depressor response may be observed again upon injection of glycerol and needs to be managed.

Table 33.4 Complications of percutaneous ablative procedures [36, 52–54, 79, 81]

Percutaneous balloon compression	Percutaneous radio-frequency thermocoagulation	Percutaneous glycerol rhizotomy
• Postoperative facial numbness (4.6% of cases) • Herpes simplex labialis (33.1%) • Masseter weakness (3.4–6.2%) • Dysesthesias (2.8–11.4%) • Hearing and olfactory disturbances • Diplopia (1.6%) • Diminished corneal reflex (0–2.3%) • Conjunctivitis (3.1%) • Anesthesia dolorosa (rarely) • Corneal keratitis (rarely) • Arteriovenous fistula development (rarely) • Meningitis (rarely) • Intracranial hemorrhage (rarely)	• Mild to moderate postoperative facial numbness (>90%) • Anesthesia dolorosa (0.5–25%) • Deficit of the corneal reflex (1–35%) • Corneal keratitis (0–20%) • Dysesthesia (1–24%) • Masseter weakness (8–65%), mostly transient • Diplopia (0.2–4%) • Meningitis • Carotid-cavernous fistula formation • Intracranial hemorrhage (rarely)	• Postoperative facial numbness (60%) • Mild to moderate hypalgesia (seen in up to 70% cases) • Trigeminal hyperesthesia (in 20% of cases) • Corneal anesthesia (0–16%, average 8.1%) • Herpes reactivation (up to 77% cases) • Anesthesia dolorosa (0–5.0%) • Masticatory weakness (0–4.1%) • Hearing loss (1.9%) • Meningitis (1.5%) • Corneal keratitis (rarely) • Intracranial hemorrhage (rarely)

33.12.2.4 Procedural Complications

The close anatomical location of the brain stem and internal carotid artery to the foramen ovale and the trigeminal depressor response observed upon its engagement lead to a plethora of complications during the percutaneous ablative procedures. Though the reported periprocedural mortality is very low (0–0.2%), other commonly encountered complications include hearing loss, postoperative facial numbness or hypesthesia, dysesthesias, masseter weakness, anesthesia dolorosa, corneal hypesthesia, keratitis, cranial nerve palsy, arteriovenous fistula development, carotid-cavernous fistula formation, CSF leak, meningitis, herpes simplex labialis, and, rarely, intracranial hemorrhage [36, 52–54, 81, 82] (Table 33.4). Compared to other treatment modalities, these procedures are associated with a high recurrence rate [81].

33.12.2.5 Selection of Procedure

The existing literature on percutaneous ablative procedures consist of single-center prospective observational or retrospective studies, without a single RCT comparing the three techniques. Furthermore, each procedure has operator-dependent technical variations (such as the level of pressure achieved and duration of compression by balloon during PBC, the amount of glycerol injected into Meckel's cistern during PGR, and the type of electrode and radio-frequency current used for RFT) that limit comparisons via a formal meta-analysis. Hence, the best treatment modality out of three is still dubious, with each technique having its own merits and limitations.

Tatli et al. reviewed 28 studies with at least 5 years of follow-up data on varied surgical techniques for treatment of TN, including MVD, RFT, PBC, PGR, SRS, and partial sensory rhizotomy [83]. As per the review findings, PBC and MVD had similar efficacy and much superior effects compared to those of the other modalities ($P < 0.001$). RFT provided a high rate of initial pain relief but was also associated with the greatest number of various complications and high treatment failures. In comparison, PGR was associated with both low initial pain relief as well as high pain recurrence rates. Among all the surgical techniques, MVD provided the highest success rate and long-term pain relief. According to another review of the three procedures by Cheng et al., PBC provided pain control rates of up to 91% at 6 months and 66% at 3 years, while RFT provided initial pain relief in up to 97% of patients, with only 58% of patients being pain-free at 5 years. PGR offered similar pain-free outcomes of 90% at 6 months and 54% at 3 years but with higher complication rates (25% vs. 16%) compared with PBC [81].

Of the three percutaneous procedures, RFT allows somatotropic nerve mapping and is most division-selective. In general, RFT preferentially damages the small unmyelinated pain fibers which mediate nociceptive pain transmission. Compared to PBC and PGR, RFT carries a higher risk of corneal deafferentation and keratitis, especially with higher lesioning temperatures and in uncooperative patients. On the other hand, PBC and PGR preferentially damage medium and large myelinated pain fibers, sparing the smaller ones. PBC is a safe and effective treatment, especially suitable for patients with persistent or recurrent TN after MVD and first division (ophthalmic) TN pain [84]. In the long-term follow-up of patients treated with PBC, 62% of patients had successful relief from one procedure that persisted for at least 7 years [79]. However, it is associated with significant bradycardia and hypotension and requires GA, thus making it less appropriate for patients with medical (esp. cardiac) comorbidities. On the other hand, RFT or PGR may be preferred for a modest denervation, with acceptable pain relief and minimal side effects (less motor denervation, cheek hematoma, diplopia, avoidance of GA) than with PBC [85]. Nonetheless, controlled lesioning by RFT may be difficult to perform in elderly and uncooperative patients.

To conclude, the procedure of choice is individualized for each patient, considering the expertise of the operator and the advantages and disadvantages of each procedure.

33.12.3 Microvascular Decompression

MVD surgery targets the NVC at the nerve REZ of the trigeminal nerve via a retrosigmoid approach to the CPA in the lateral decubitus position [14]. The primary aim of the surgery is to relieve the conflict between the offending vessel and nerve and to maintain this separation in order to avoid surgical failure. The separation techniques are broadly classified as either "interposing techniques" or "transposing techniques." The interposing techniques involve placing a material between the vessel and the nerve, such as autologous tissue (muscle, fascia, or arachnoid membrane), Teflon, Surgicel, Gelfoam, cotton pads, surgical glue, radiopaque sponge, Silastic ring, and Sundt clips. The transposing techniques (also known as sling techniques) consist of repositioning of the offending vessel with the purpose of avoiding the contact between the two, using either Prolene stitch, aneurysm clips, or titanium bone fixation plates.

Original procedure, as described by Jannetta, involved placing of Teflon pledgets, in view of its good nervous tissue compatibility and soft and elastic fiber structure, thus acting as an effective "shock absorber" [14]. However, the review of cases with surgical failures have revealed the presence of severe adhesions and Teflon granulomas (reported incidence of 1.2–5%), suggesting that it is not absolutely inert and may induce an inflammatory foreign body reaction [69, 86]. Henceforth, in recent years, there is a trend toward an increase in the use of transposition techniques to prevent recurrence.

The ideal surgical management of patients with NVC involving SPV is still dubious [26, 29, 87–89]. Pathmanaban et al. have reported that the incidence of venous infarction associated with SPV obliteration during MVD surgery is <0.5%, with an overall rate of venous complications of 2.7% [87]. SPV sacrifice, thus, may be used where necessary to optimize visualization of the REZ and maximize the chance of effective decompression of the trigeminal nerve. On the other hand, there are many reports in the literature relating both minor and life-threatening complications to SPV sacrifice during MVD [88, 89]. These include brightly colored visual hallucinations and contralateral hearing loss due to venous congestion in the inferior colliculus, facial nerve palsy secondary to ischemia in the middle cerebellar peduncle, sigmoid sinus thrombosis with cerebellar hemorrhage, and vasogenic edema or infarcts in the midbrain and pons causing hemiparesis. During MVD, Liebelt et al. have reported complications secondary to venous congestion in 4.8% of patients when SPV was coag-

ulated and divided to gain better exposure to the nerve REZ, while no such complications were observed in patients in whom the SPV was preserved intraoperatively [89]. Authors, thus, advocate preserving the SPV unless it is deemed absolutely necessary for successful cranial nerve decompression. Alternatively, one may intraoperatively assess the safety of venous sacrifice using either temporary clipping of the SPV while monitoring for BAEPs or assessing the collateral venous drainage with indocyanine green. The use of fully endoscopic or endoscope-assisted microsurgery with and without angled optics may further minimize the extent of venous sacrifice required to obtain optimum visualization during MVD [43].

MVD offers an excellent initial pain control at the rate of 76.4–98.2% along with long-term durability, with 70% of the patients having an excellent result 10 years after surgery and a 73.4% of patients being pain-free at 15 years [30, 69, 83, 90, 91]. Pain relief after MVD is generally instantaneous, although a delay of up to 1 month has been reported. A greater degree of neurovascular compression, greater nerve atrophy, and presence of preoperative trigger points have been associated with better long-term outcomes in some studies [16, 30, 90].

Though MVD is considered safe and an effective treatment option for patients with PBTN, bilateral pain is, nonetheless, correlated with worse outcomes [90]. With regard to the side that should be treated first in patients with PBTN, selection should be based on the severity of pain and 3-D TOF-MRA findings [28]. The role of MVD in patients without NVC is not yet clearly defined [58, 91].

33.12.3.1 Complications

Despite being most invasive procedure, MVD is safe in experienced hands, with a reported mortality rate of 0.15–0.8% [51]. Other perioperative complications reported in the literature include postoperative transient or permanent cranial nerve palsies (i.e., trochlear, oculomotor, or facial nerve palsies, 0.66%), facial dysesthesia (2.30%), hearing loss (1.51%), vertigo (3.53%), aseptic meningitis (11%), CSF leak (2.73%), pseudomeningocele formation, hydrocephalus, cerebellar infarct or hematoma, and the combined percentage of cerebrovascular, cardiac, pulmonary, or thromboembolic events with an incidence of 3.92% [26, 51, 69, 83, 91–93].

The reported annual recurrence rate after MVD varies from 3% to approximately 30% [83]. The varied causes responsible for recurrence include inadequate separation of vessel and nerve, Teflon granuloma formation, adhesion of the interposed Teflon material, excessive Teflon insertion, improper and inadequate operative techniques, Teflon dislocation, and venous compression after the MVD procedure. Predictive factors of eventual recurrence described in the literature include female sex, symptomatology of more than 8 years, venous vascular etiology, inadequate pain relief immediately after surgery, redo surgery, and atypical pain patterns [69, 90].

The existing literature on the safety and efficacy of MVD in elderly has conflicting results [92, 94]. A meta-analysis assessing the difference in outcomes of elderly versus younger patients undergoing MVD for TN found that elderly patients were associated with higher risk of stroke, thromboembolic events, and mortality, while the recurrence rate was low [94]. There was, however, no significant difference in partial or complete success rates and complications such as cranial nerve deficits, cerebellar hematoma, CSF leak, and meningitis. Another recent study found no significant difference in surgical outcome and rate of complications between <60 and more than 60 age group patients [92]. Overall, MVD may be considered a safe and viable alternative for treating intractable TN in older patients.

Intraoperative use of an endoscope may lead to enhanced visualization of the operative site anatomy with better identification of offending vessels, minimal cerebellar retraction, and smaller craniotomy openings when compared with microscopic MVDs [43]. However, in terms of reducing surgical complications, endoscopic MVD may be more suitable for younger patients and those with a narrow CPA [95].

33.12.4 Stereotactic Radiosurgery

SRS for TN involves application of a single large dose of radiation, using x-ray beams, to a stereotactically localized target with minimal radiation delivered to surrounding tissue. SRS causes nonselective, dose-dependent axonal degeneration and necrosis and, thus, may block the nociceptive signals [96]. Some believe that pain relief may be caused by the indirect destruction of ionic sodium channels through slow chemical reactions [97].

With advancement in neuroimaging and external beam technology, newer technologies such as the GKRS, linear accelerator radiosurgery (LINAC RS), and CyberKnife RS have evolved. GKRS can precisely irradiate the cisternal segment of the trigeminal nerve by gamma-ray photons [98]. GKRS was primarily indicated for elderly patients with medically refractory TN and with comorbidities, for whom more invasive procedures are contraindicated. Nonetheless, in recent years more and more young patients are opting for GKRS to avoid GA, prolonged hospital stay, and a higher risk of complications.

The procedure is performed after application of a Leksell G frame to the skull either under monitored anesthesia care or conscious sedation with short-acting anesthetic agents. After frame placement, MRI of the brain is performed, including CISS images. In almost all instances, the cisternal segment of the symptomatic trigeminal nerve is treated using a single 4 mm isocenter to a maximum dose of 70–90 Gy [98]. For recurrent TN, the dose range is 60–90 Gy [99, 100]. The individual dose, however, depends on the radiation dose received by the brain stem as a cumulative brain stem dose of more than 12 Gy tends to be associated with trigeminal nerve deficit.

Recently, Tuleasca et al. performed a systematic review of 65 studies (45 GKRS, 11 LINAC RS, and 9 CyberKnife RS), evaluating the role of SRS in the treatment of TN and developed consensus guideline recommendations [101]. According to these guidelines, SRS yields a better initial response if it is performed in the first 3 years after pain onset (level III evidence).

33.12.4.1 Complications

Most common side effects reported after SRS include permanent trigeminal dysesthesia (mainly hypesthesia, although paresthesias have also been described). Hypesthesia ranges from 0 to 68.8% for GKRS, from 11.4 to 49.7% for LINAC, and from 11.8 to 51.2% for CyberKnife. Other complications include dysesthesias, paresthesias, dry eye, deafferentation pain, and keratitis.

A considerable linear annual risk of recurrence has also been reported, possibly as a result of the persistence of the underlying cause. Recurrence rates range from 0 to 52.2% for GKRS, 19–63% for LINAC, and from 15.8 to 33% for CyberKnife [99]. Another meta-analysis, comparing the safety and efficacy of microsurgical and radiosurgical treatment of TN, showed that at 36 months after the intervention, median percentage of recurrence was 11% for MVD and 25% for SRS management of TN [93]. Facial dysesthesias were more frequent after SRS (28.8% vs. 2.3%), while anesthesia dolorosa (0.04%), tinnitus (0.15%), brain stem edema (0.06%), chronic fatigue (0.79%), and keratitis (2.50%) were reported only after SRS compared to MVD.

Overall, GKRS remains a safe and effective treatment even after a second procedure, with comparable or better initial pain cessation rates, despite a higher toxicity, which appears to be the trade-off for maintaining pain relief [99].

33.12.5 Neuromodulation

Neuromodulation is the latest introduction into the treatment paraphernalia of medically resistant TN. It involves electrical stimulation of the central and peripheral nervous system to alter neuronal function. The techniques range from noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation

or transcranial direct current stimulation and the transcutaneous electrical nerve stimulation to less invasive peripheral nerve stimulation (supraorbital nerve, infraorbital nerve, and the greater occipital nerve pulsed stimulation), subcutaneous peripheral nerve field stimulation, Gasserian ganglion pulsed stimulation, and cervicomedullary junction stimulation and finally to more invasive measures including the motor cortex stimulation and deep brain stimulation [36, 56].

To date, these modalities have been evaluated in small case series and few prospective or controlled trials with limited number of patients and short-term follow-up periods. Henceforth, at present there is no consensus about their role in the treatment paradigm of resistant TN. Nonetheless, the advent of newer miniature wireless devices and less invasive implantation techniques should allow for more widespread use of neurostimulation as a therapeutic modality in resistant TN. Larger studies need to be conducted comparing the traditional pharmacological therapies and emerging interventional pain techniques.

33.13 Summary

Trigeminal neuralgia is a unique and complex neuropathic pain disorder that continues to intrigue neurologists, neurosurgeons, and neuropain physicians alike. Though its recognition as a separate clinical entity dates back to the nineteenth century, its pathophysiological mechanism is still not entirely understood. Consequently, the optimal management modality, either pharmacological or surgical, remains elusive.

With an ongoing research into the pathophysiology of TN, using modern 3-D imaging techniques and electrophysiological studies, clinicians will have a better understanding of this disease, and newer and more effective treatment modalities may become available in the future. Nevertheless, a multimodal treatment approach, targeting the clinical symptoms as well as the neuropsychologic aspects of chronic pain, shall remain at the center stage of the management repertoire of this distinct clinical condition.

Key Points

- Trigeminal neuralgia is a unique neuropathic pain disorder characterized by agonizing unilateral paroxysmal pain occurring within one or more divisions of the trigeminal nerve territory, mostly triggered by non-noxious light mechanical stimuli.
- Neurovascular compression of the trigeminal nerve by an artery (most commonly superior cerebellar artery) at its root entry zone in pons, with focal demyelination of underlying nerve and ephaptic transmission of excitation, accounts for most of the pain paroxysms.
- Pharmacotherapy, with either carbamezepine or oxcarbamezepine, as the first line of treatment is the mainstay of clinical management.
- Surgical microvascular decompression offers effective long-term pain relief and is the procedure of choice if the patient reaches the maximum dosages of either carbamezepine or oxcarbamezepine, without achieving the desired pain relief, or has undesirable side effects.
- Percutaneous ablative procedures, botulinum toxin injections, stereotactic radiosurgery, and neuromodulation are other therapeutic options, useful for patients who have medically refractory pain and wish to avoid surgery or are at high surgical risk.
- Patients with chronic trigeminal neuralgia are also at high risk for cognitive deficits, with subsequent negative impact on normal socioprofessional life, thus necessitating a thorough neuropsychological evaluation and support.

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Part X

Special Topics

34 Postoperative Cognitive Dysfunction

Suparna Bharadwaj and Sriganesh Kamath

34.1 Overview and Definition of Postoperative Cognitive Dysfunction

Constant advancement in surgical technology and anesthetic care has increased the availability of surgical care to patients at the extremes of age [1]. Unfortunately, the vulnerability of the brain in extremes of age to surgical stress can negatively affect both life expectancy and quality of life. It has been identified that cognitive decline is seen in many patients after surgery [2]. Cognition illustrates the mental activity involving attention, perception, and memory. Postoperative cognitive dysfunction (POCD) describes the deterioration of these fundamental functions, manifesting after a surgical procedure. POCD is a multifactorial syndrome seen mostly in elderly patients who undergo major surgeries and is characterized as decline in attention, perception, memory, thought, information processing, and the sleep-wake cycle [3].

In the last decade, anesthesiologists, surgeons, geriatrists, and intensive care physicians seem to be increasingly involved in the study of POCD [3]. In the cardiac, surgical, and orthopedic settings, POCD is among the most prevalent and difficult clinical problems [4]. The diagnosis involves pre-surgical and postsurgical neurocognitive testing. POCD typically evolves over weeks to months and persists longer. Consequently patients may lose their employment or autonomy which may gravely affect their quality of life [5]. Unfortunately, methodical inspection into the features and cause of POCD have been attempted only in recent times, because of the increasing number of surgical procedures being catered to the elderly, who are at biggest risk for this condition. Although many researchers have studied POCD, the understanding of this clinical syndrome is still limited. This chapter is aimed to discuss POCD after non-cardiac surgery and specifically to review literature on POCD in the neurosurgical population. Readers may refer to available literature for details regarding POCD after cardiac surgery [6, 7].

34.2 Historical Background

One of the earliest contributions to the study of POCD was by George H. Savage, medical superintendent, resident physician, and lecturer in mental diseases at Guy's Hospital, London. In his work, titled "Insanity Following the Use of Anesthetics in Operations" published by The British Medical Journal in 1887, he illustrated a series of cases of insanity (akin to POCD) following the use of anesthetics [8]. Savage explained the potential effects on cognition of interacting variables such as medications and

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many predisposing surgical and patient factors. He contended that, like the symptoms of alcoholic encephalopathy, insanity that follows a surgery could be iatrogenic in origin. Use of chloroform, ether, or belladonna for induction, of anesthesia, resulted in a state of mania, or delirium, or forgetfulness, especially in the elderly. In 1955, Bedford debated that POCD was a complication of anesthesia employed during surgery, rather than the surgery itself or any other factor. Of the total 1193 patients studied, Bedford stated that the near relations or friends of more than 410 patients alleged that the "patient had never been the same since operation" [2]. Other studies are carried out to find out pathogenesis of POCD due to anesthetics, perioperative hemodynamic alterations, oxygenation disturbances, and other associated triggers such as use of benzodiazepines, alcohol withdrawals, presence of cancer, and neurovascular/neurodegenerative comorbidities. However, these studies were deficient in appropriate controls and did not follow uniform clinical assessment tests. Hence it was not possible to determine the influence of these factors as the etiology of POCD [4, 9]. Even though a lot of studies have been undertaken, knowledge about POCD is still primitive. Many more scientific studies will be required to determine the multimodal factors involved in pathogenesis of POCD.

34.3 Epidemiology

POCD has a bimodal incidence including a reversible decline during the early postoperative period and a delayed cognitive decline 3–5 years later which may be relevant to dementia [10]. According to the International Study of Postoperative Cognitive Dysfunction (ISPOCD), the incidences of POCD in elderly patients who underwent major non-cardiac surgery were 25.8% at 1 week after surgery and 9.9% at 3 months after surgery, respectively [3]. In case of cardiac surgery, the incidence of POCD was as high as 40% [11]. Besides, the duration of POCD was mostly transient; however, it can be persistent especially among elderly patients aged over 65 years [11]. The prevalence of POCD in patients after elective hip surgery is 22% [12]. Studies on POCD also tried to establish if the condition is self-limiting or progressive. One-, 2-, and 10-year follow-up of patients in a multicentric study on POCD suggests that POCD developing in the postoperative period can largely be reversible and rarely persists in the longer term [13, 14].

34.4 Classification and Diagnosis

Cognitive deterioration in the postoperative period can be classified into delirium, which may be short-lived (days to a few weeks), and POCD, which may last for an indefinite period of time (days to weeks after surgery) [15]. Delirium is a state of acute confusion characterized by alterations in attention and consciousness. But POCD involves changes in one or more neuropsychological domains. Unlike delirium, level of consciousness does not change nor fluctuate over the course of the day in patients with POCD. Neuropsychological testing is necessary to detect POCD because of its subtle nature. While delirium can be defined as a clear clinical syndrome and easily diagnosed by the clinician, diagnosis of POCD is sophisticated. It is not based on the subjective symptoms alone, and no standalone suitable questionnaire has yet been developed for this condition. The neuropsychological battery of tests must be administered both before and after surgery to maximize sensitivity in the assessment of cognitive function. Many studies have used composite measures of cognitive function to assess patients for the presence of POCD. The most commonly used composite measure was the Mini-Mental State Examination (MMSE); it was included in 21% of the reviewed studies. However these composite measures do not indicate which facets of neuropsychological functions are affected by the surgical experience. Rasmussen has regarded late POCD as a mild neurocognitive disorder [16]. But the North American Diagnostic and Statistical Manual of Mental Disorders (DSM) does not define POCD. There does not exist any standardized criteria to diagnose POCD and is yet to be defined by the scientific community. With the available

evidence, there is a significant variation in the features of neurological tests and the timing of testing.

Depending on the time of onset, POCD has been classified as acute POCD detected within 1 week after surgery, intermediate POCD for changes within 3 months, and long-term POCD for changes 1–2 years following surgery [4]. However, significance of detecting POCD at these various time points is not clear.

It is important to determine if delirium and POCD form a spectrum. In a retrospective analysis of the ISPOCD research data, patients with postoperative delirium had a higher incidence of POCD 1 week postoperatively [17]. The ISPOCD considers POCD as mild cognitive impairment (MCI).

The methods that have been used to detect postoperative cognitive impairment include interviews, questionnaires, mental status exams, and neuropsychological tests [18]. An ideal neuropsychological test (a) has validity, (b) does not have floor (subjects scoring the lowest score possible) or ceiling effects (subjects scoring the highest score possible), and (c) has parallel versions that reduces potential practice effects from remembering test stimuli from earlier administrations [18]. Tests of mental status are the most frequently used methods of assessing cognition in postoperative recovery studies [19]. The most common of these is the MMSE [20]. However, neuropsychological testing provides the most reliable and sensitive indicator of postoperative cognitive impairment [21]. Most of the neurocognitive tests lack sensitivity and specificity and are time consuming. Most popular preoperative neurocognitive tests used include the Montreal Cognitive Assessment Tool (MoCA), Addenbrooke's Cognitive Exam (ACE-III), and the Quick MCI Screen (Qmci).

34.5 Risk Factors of POCD

Several risk factors for occurrence of POCD are described including patient factors, factors relating to anesthesia and surgery, comorbidities, and others; these are detailed in Table 34.1.

34.6 Pathogenesis

The exact pathophysiology of POCD is not defined. Previous studies point toward inflammation as a possible mechanism for the pathogenesis of POCD [26]. Cognitive decline in mice after surgery was associated with increased expression of interleukins in its hippocampus corroborating with the principle of neuro-inflammation resulting in cognitive decline. Presence of pro-inflammatory cytokines has been demonstrated in both the central nervous system and systemic circulation in surgical patients, and the degree of cognitive decline is related to the extent of inflammatory process [27]. Considering that neuro-inflammatory changes observed in rodents are also seen in humans, reasons are still unknown why POCD is not always associated with the presence of neuro-inflammation [27]. Neuro-inflammatory changes are quickly fading, which may explain self-limiting consequences in the animal models [28]. Any other super-added clinical condition may convert the self-limiting post-surgical neuro-inflammatory response into one that is persistent [29]. Reasons for prolonged neuro-inflammation may be due to defective inflammation initiation or resolving mechanisms.

34.6.1 Surgery

Damage-associated molecular patterns (DAMPs) that are recognized by pattern recognition receptors (PRRs) trigger an immune response [30]. Tissue trauma, such as in surgical insult, releases DAMP. Among PRRs, Toll-like receptors (TLRs) are important as they promote the synthesis and release of pro-inflammatory mediators. Function of TLR4 during lipopolysaccharide (LPS) endotoxemia has been thoroughly studied. However the pathways of infection-mediated neuro-inflammation and cognitive decline seem to be different from that of aseptic surgical trauma [31]. One of the critical DAMPs, dispensed from dead or dying cells through non-apoptotic processes, is the high-mobility group box 1 protein (HMGB1) [32]. Clinical circumstances like sepsis, arthritis, and stroke release

Table 34.1 Risk factors of postoperative cognitive dysfunction [22–25]

Risk factors for POCD		Assessment in days	Incidence of POCD (%)
Patient-related factors	Advanced age	≤1 week	41.4
		1 week to 3 months	12.7–14
		>1 year	16
	Education (<high school)	≤1 week	27
		1 week to 3 months	9
		>1 year	10
	Male sex	≤1 week	No clear data
	Menopause	≤1 week	No clear data
	Apolipoprotein E4	≤1 week	11.7
		1 week to 3 months	10.3
Comorbidities	Preoperative depression		Variable data
	Metabolic syndrome		Variable data
	Preoperative cognitive impairment		Variable data
	Other comorbidities		Variable data
Surgery and anesthesia	Second surgery	≤1 week	43
		1 week to 3 months	20
	Prolonged surgery/anesthesia	≤1 week	33
		1 week to 3 months	9
		>1 year	11
	Postoperative infection	≤1 week	39
		1 week to 3 months	14–19
		>1 year	19
	Respiratory complication	≤1 week	59
		1 week to 3 months	14–15
		>1 year	14
	Anesthetic type		Variable data
	Pain management		Variable data
Other	Tobacco use		Variable data
	History of alcohol or drug abuse	≤1 week	26.8

massive amounts of HMGB1, which stimulates NF-κB which increases the production and release of pro-inflammatory cytokines. Pro-inflammatory cytokines like TNF-α disrupt blood brain barrier (BBB) integrity [31]. Early stimulation of the immunity through DAMPs (HMGB1 and cytokines) will present the initial reaction to surgery developing neuro-inflammation and concomitant cognitive decline. After surgery, a transitory inflammation is required for tissue repair which promotes healing. Following surgery, neuro-inflammation mostly consists of a pro-inflammatory phase and an anti-inflammatory phase (neural and humoral pathways mediate the switch between these two phases) [33].

Inflammatory state is resolved by neural pathways, called the cholinergic anti-inflammatory pathway. The function of T cells is regulated by the cholinergic anti-inflammatory pathway. T cells produce anti-inflammatory cytokines (IL-10 and IL-4) and bring about macrophage activation that promotes the resolution of inflammation [34]. Abnormalities of the switching mechanism between pro- and anti-inflammatory cascade may result in a persistent chronic inflammatory state that could lead to prolonged cognitive decline. Cholinergic function declines with increasing age, which explains the high prevalence of POCD in elderly patients [35]. Hippocampus is accountable for learning and memory process. It contains a large number of pro-inflammatory cytokines and activation of which leads to cognitive impairment [36]. The endothelium in the blood vessels of hippocampus is rich in TNF-α receptor which may

explain the susceptibility to systemic pro-inflammatory cytokines [36]. Many studies indicate that expression of cyclooxygenase-2 amplifies cerebral injury after ischemia [37]. Concomitant rise in pro-inflammatory cytokines in the CSF has been also observed in patients after peripheral surgery, as a marker of neuro-inflammation [38].

34.6.2 Sleep

Sleep is a critical damage control mechanism of many types of injury and diseases of the central nervous and immune systems. It also has anabolic and restorative properties [39, 40]. Sleep disturbance is commonly seen in the hospital environment. Quality and architecture of sleep is altered in the form of sleep fragmentation. Lack of healthy sleep results in cognitive decline which amounts to delirium and impaired immunity and independently contributes to both morbidity and mortality [41]. Sleep disturbances during hospital admission may adversely affect patient outcome and has a direct impact on financial cost with respect to the length of hospital stay and depletion of healthcare resources.

34.6.3 Cerebral Ischemia

Stroke is the leading cause of morbidity and mortality in adults and an important risk factor for long bone fracture. Old stroke in a patient undergoing surgery may predispose to POCD. Preoperative ischemic brain insult could exaggerate POCD after surgery in the elderly [42].

34.6.4 Metabolic Syndrome

Metabolic syndromes have inflammatory consequences and may predispose to POCD in patients [43].

34.7 Anesthetics and Postoperative Cognitive Dysfunction

Many studies investigating the effects of different anesthetic drugs or techniques on cognitive function have yielded conflicting results. To ascertain or refute the role of anesthetics on the occurrence of POCD, further studies with rigorous experimental design are needed. The relationship between anesthetics and POCD is described in Table 34.2 [44].

34.8 Biomarkers of Cerebral Damage

Biochemical tests are useful diagnostic tools in the examination of functional brain disorders including POCD [45]. Elevated serum concentrations

Table 34.2 Relationship of anesthetics and postoperative cognitive dysfunction

Anesthetics	Clinical signs	Molecular mechanism
General anesthesia with isoflurane and nitrous oxide	Impair spatial memory of old rats, may last for >2 weeks	Enhanced amyloid-β oligomerization and phosphorylated tau levels
Sevoflurane anesthesia	Spatial memory decline	Increase tau phosphorylation
Desflurane anesthesia	Spatial memory decline	Potent inhibitor of nicotinic acetylcholine receptor
General anesthesia vs spinal anesthesia	No significant differences of POCD incidence	Effects of anesthetic drugs on POCD are limited
Monitoring depth of anesthesia by BIS	Decrease rate of postoperative delirium	
Intravenous anesthetics	Protective effect	
Benzodiazepines	Increased incidence and duration of delirium	
Postoperative use of opioids	Increased incidence of POCD	

of the markers of brain damage indicate a neuronal and/or glial injury. These biomarkers may be used to localize pathological changes and identify the degree of tissue damage and the time that has passed since the onset of these changes in patients with POCD. The biomarkers released into either blood or CSF are as follows: S100B protein, neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), tau protein, metalloproteinases (MMP), ubiquitin C-terminal hydrolase-L1 (UCH-L1), microtubule-associated protein 2 (MAP 2), myelin basic protein (MBP), αII spectrin breakdown products (SBDP), and micro-RNA (miRNA).

34.9 Treatment

In the postoperative setting, diagnosis of POCD is established by demonstrating the worsening of cognitive performance from the preoperative period by administering an appropriate cognitive test. Organic psycho-syndromes should be ruled out and treated appropriately. In the postoperative period, various clinical conditions (Table 34.3) [46] may manifest POCD. Treating the underlying condition will take care of POCD as well. The treatment of symptoms of POCD makes supportive therapy indispensable. Supportive therapy (i.e., sufficient ventilation and oxygenation, hemodynamic support) should be secured to achieve an optimal environment for recovery. Additionally, the control of postoperative pain is important, as there is a correlation between higher pain levels and the development of POCD. Inpatient care usually requires several non-pharmaceutical interventions. The regular measurement of vital signs and the frequent communication of the health professional team with the patient ensure that any aberrant behavior will be recorded immediately, the sleep-wake cycle will be estimated, and the intake and output of liquids during 24-h period will be calculated. Mechanical restrictions are often used in aggressive patients with manic symptoms. Single-bed rooms help in reducing stimulation. A clock mounted in a prominent position, a calendar, and watching the news on television can help reorientation. Providing adequate room light with variations in light intensity in order for the patient to achieve a normal circadian rhythm can be helpful. The assessment of the ability of swallowing is useful before the start of oral intake. Recent studies have demonstrated that leptin could produce therapeutic effects for cognitive impairments of patients with Alzheimer's disease (AD). Postoperative cognitive dysfunction (POCD), defined as a significant dysfunction in cognitive performance for several weeks after surgery, probably has a pathogenesis similar to that of AD. Specifically, they are both characterized by cognitive impairment. Leptin plays a critical role in neuronal development and also promotes structural and functional activities in the central nervous system. Leptin signaling pathway may be involved in the pathogenesis of POCD and has been shown to have a therapeutic benefit of alleviating symptoms of patients with POCD.

Table 34.3 Clinical conditions manifesting POCD

Clinical condition	Treatment
Myocardial infarction	Medical/surgical management/radiological intervention
Sepsis syndrome	Antibiotics/intravenous fluids
Drug induced	Record patient medications including herbal medicine Identify potential toxic substance and reduce dosage
Latent infection	Appropriate antibiotics
Urinary tract infection	Appropriate antibiotics
Pneumonia	Appropriate antibiotics
Electrolyte disturbances	Correction of electrolytes
Dehydration	Adequate hydration
Endocrine/kidney/liver/neurological disease	Diagnosis and appropriate management
Hypoglycemia	Glucose supplementation

34.10 Prevention

Susceptible patients need to be recognized, and risk/benefit should be evaluated before planning of surgical intervention. Advanced age, metabolic syndromes, neurological diseases, poor selection of anesthetics/sedative drugs, and perioperative hypotension may each result in exaggerated and persistent neuro-inflammatory response to surgery. Further studies are necessary to define which patients will suffer from exacerbated inflammation with an intention of developing a biomarker that is quick to measure for clinicians and easy to appreciate for patients and their families. Similarly clinical interventions need to concentrate on resolution of neuroinflammation in the postoperative period. It is wise to target the preventable factors in vulnerable patients, thereby reducing long-term consequences like POCD and postoperative neurodegeneration.

34.11 POCD After Cardiac Surgery

Cognitive dysfunction is the most common clinical manifestation of brain injury after cardiac surgery [47]. Its occurrence is related to a combination of three factors that are often associated with cardiopulmonary bypass (CPB): embolism, hypoperfusion, and inflammatory response. However, such factors and their potential cerebral consequences are not exclusive to CPB. POCD also afflicts patients who undergo cardiac surgery without CPB as well as non-surgery patients who undergo transcatheter interventions. There is growing evidence that patient-related factors such as the presence of (cerebro)vascular risk factors play an important role in both early and late postoperative cognitive dysfunction.

34.12 POCD After Neurosurgery

Post neurosurgery it is difficult to predict what proportion of cognitive dysfunction is a direct result of brain surgery and its associated complications. Preoperative cognitive testing helps to quantify the pre-existing cognitive dysfunction secondary to disease. However postoperative worsening of cognitive function may be attributed to brain surgery and its associated complications or exposure to anesthetics or the presence of other risk factors listed in Table 34.1. Tuffiash et al. found 4% incidence (1 of 25) of cognitive impairment, 3–6 months after craniotomy for repair of unruptured aneurysms. This patient had a perioperative stroke causing aphasia and right hemiparesis. Glasgow outcome scale (GOS) score at 3–6 months was 4. At 3–6 months after surgery, no patients with GOS scores of 5 demonstrated any cognitive impairment [48]. In another study, multivariate analysis revealed three major contributory factors for POCD to be intraoperative tight brain, postoperative cerebral vasospasm, and infarction which was present in 40%, 90%, and 40% cases, respectively. Also in this study, pharmacologic neuroprotection with propofol during temporary clipping in patients undergoing intracranial aneurysm surgery following SAH did not offer any advantage as far as preservation of cognitive function was concerned [49]. The observations by Heyer et al. suggest mean arterial pressure (MAP) management ≥20% above baseline during cross-clamp of the carotid artery may be associated with lower risk of early cognitive dysfunction after carotid endarterectomy [50]. More prospective work is necessary to determine whether risk factors other than handling/manipulating brain will manifest POCD.

34.13 Conclusions

Many studies in the last decade have shown an acute cognitive decline in adult patients after major surgery. Most evidence suggests that these early cognitive changes are transient and do not persist in the long term. However, providing patients with appropriate and accurate information can be difficult because of many uncertainties. Additional studies on POCD are essential to elucidate risk factors and underlying pathophysiology and to determine important preventive strategies. If future studies are

successful in recognizing susceptible patients preoperatively, interventions can be judiciously and appropriately applied.

Key Points

- Postoperative cognitive dysfunction (POCD) is a disturbing reality which can result in considerable morbidity and increased mortality.
- Advanced age, metabolic syndromes, neurological disease, and poor selection of anesthetics/sedative agents may each result in increased and persistent neuroinflammatory response to surgery. And perpetual systemic inflammation in the postoperative period is a key factor that contributes to pathogenesis of POCD.
- By recognizing patients prospectively or early enough in the advent of persistent inflammation, appropriate interventions can be judiciously planned.
- POCD also has long-term consequences of high costs associated with the care of the cognitively impaired.
- Comprehensive knowledge about POCD may provide a direction to identify, manage, and prevent POCD in most vulnerable patients.

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35 Enhanced Recovery After Neurosurgical Procedures (Craniotomies and Spine Surgery)

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35.1 Introduction

Enhanced recovery after surgery (ERAS) is a group of interdisciplinary strategies with the goal of improving the postoperative quality of recovery. ERAS programs are patient centered and based on three pillars: (a) individualized patient care directed by various different healthcare providers, (b) evidence-based medical strategies, and (c) continuous evaluations of outcomes through periodic audits.

In 1994, Engelman et al. proposed the concept of accelerated recovery in a studied titled "fast-track recovery of the coronary bypass patient" [1, 2]. Their work demonstrated a decrease in inpatient hospital stay after implementation of a perioperative multimodal approach. Later, Kehlet suggested that this multimodal approach involved a group of elements in the care of the patient that were strongly interrelated and worked synergistically [3]. For instance, an optimized pain management would facilitate early ambulation and decrease postoperative ileus. Further research demonstrated that perioperative modulation of the endocrine and metabolic responses is a key component of enhanced and faster recovery and are associated with fewer complications [4].

In this chapter, we summarize the recent research and evidence for ERAS programs for neurosurgical procedures.

35.2 Why Is ERAS Important in Neurosurgical Procedures?

The main goal of ERAS in neurosurgical procedures is to improve the quality of postsurgical recovery through modulation of the inflammatory, metabolic, and stress responses associated with the surgical insult along with minimization of the use of opioids. Improved postsurgical recovery would ideally contribute to earlier ambulation, less postoperative nausea and vomiting, better pain control, and earlier discharge.

35.3 Elements of ERAS Programs in Neurosurgical Patients

ERAS programs are comprised of preadmission/preoperative, intraoperative, and postoperative phases. Each phase has different elements that are implemented with the coordinated efforts of a multidisciplinary team (Figs. 35.1 and 35.2).

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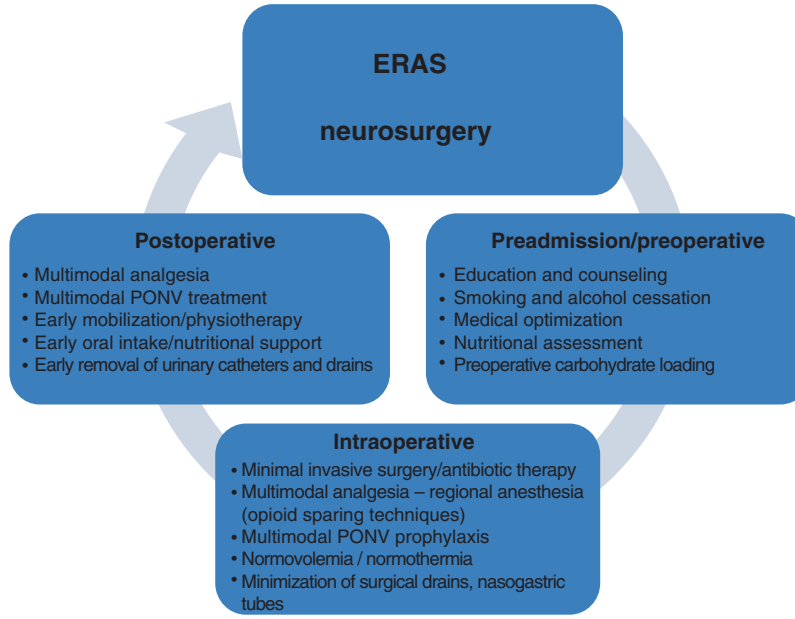

Fig. 35.1 Phases and elements of ERAS neurosurgery

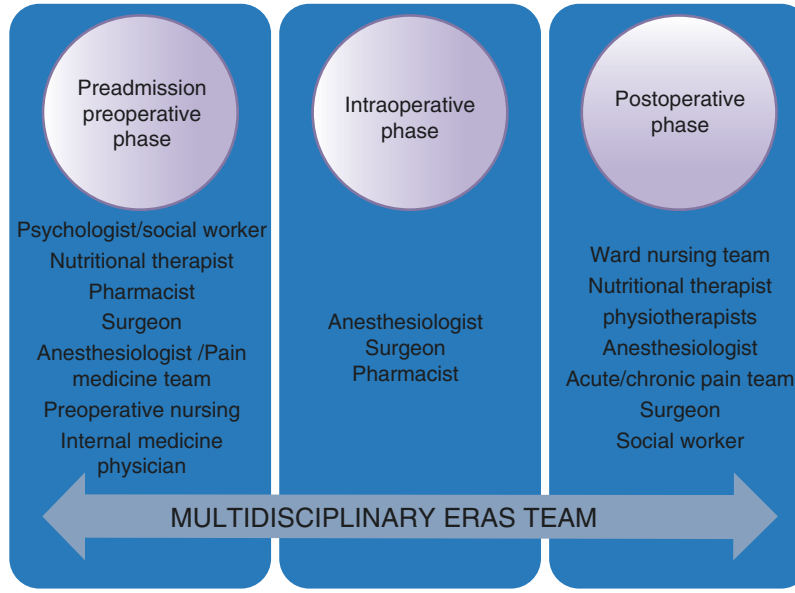

Fig. 35.2 Healthcare professionals involved in ERAS neurosurgery

35.3.1 Preadmission/Preoperative Period

35.3.1.1 Patient Education

Health literacy is the capacity of patients to understand and follow basic health information and instructions. As expected, patients with low levels of health literacy are at risk for poor outcomes [5]. Patient education is an essential element in an ERAS program. The goal of preoperative education is to clearly inform the patient about the perioperative journey and surgical plan. This can be achieved with early introduction of easily understood reading/visual materials and dedicated personnel to address all aspects of the procedure and manage expectations [6]. A recent study suggests

that anxiety can be decreased with education about the surgical procedure [7]. Educating the patient and clarifying her or his expectations about postoperative pain can improve outcomes. More importantly, patients' expectations are potentially modifiable. This is important as unrealistic expectations may be associated with patient frustration and lack of compliance with postoperative recommendations, which may delay recovery [8].

35.3.1.2 Prehabilitation and Nutritional Support

The goal of prehabilitation in the context of neurosurgery is to improve the postoperative functional status of patients through preoperative interventions including physiotherapy and exercise, smoking cessation, alcohol abstinence, avoidance of medications such as benzodiazepines, and psychological counseling. In patients undergoing degenerative spine surgery, the impact of prehabilitation, specifically exercise, has also shown to improve quality of life before surgery, improve physical activity after surgery, and be cost-effective [2, 9]. In the same patient population, a poor nutritional status is an independent predictor of postoperative complications after spine surgery. Low albumin or prealbumin levels in the preoperative period increase the risk of infections and pulmonary complications after elective spine procedures more than two folds [10, 11]. However, obesity is also a risk factor for postoperative infections and deep vein thrombosis [12]. In oncologic patients, the presence of a poor nutritional status prior to surgical treatment for spinal metastasis is an independent risk factor of reduced survival [13]. To the best of our knowledge, there are no studies that address the impact of a comprehensive of perioperative nutritional support on recovery after neurosurgical procedures.

Smoking cessation is an important component of the preoperative optimization phase. Previous research has shown that a minimum of 4 weeks is necessary to improve postoperative outcomes. Smoking cessation can reduce the number of pulmonary complications by 40%. Nicotine has systemic effects including an impairment of the blood supply to the vertebral disk, which predisposes patients to failed surgeries and delayed recovery [14]. Smokers report higher pain scores associated with spine disorders, which also complicates their postoperative pain management and recovery [15, 16].

35.3.1.3 Medical Optimization

Preoperative risk assessment and optimization of organ dysfunction have the goal of addressing medical conditions, especially those affecting the pulmonary, cardiac, metabolic, and hematologic systems. It should be done individually and focused on patients who are physiologically compromised. Careful control of blood glucose levels in diabetic patients should be considered a priority in the perioperative period. These patients suffer from a higher rate of postoperative complication, re-interventions, and mortality when glycemic control is poor [17, 18]. ERAS programs suggest scheduling elective surgeries for diabetic patients as the first cases of the morning, to avoid long periods of fasting.

35.3.1.4 Frailty Evaluation

Frailty is a clinical syndrome associated with poor postoperative outcomes [19]. Its incidence increases with age and has other associated conditions including a high comorbidity burden, impaired cognition, and geriatric syndromes [20]. The number of neurosurgical procedures is expected to increase in elderly patients, and it has been recommended that patients with high frailty should participate in prehabilitation programs [5, 21].

35.3.1.5 Preoperative Carbohydrate Loading

Healing after surgery is metabolically demanding. The stress response mobilizes amino acids, glucose, and free fatty acids from body stores and diverts substrate from biochemical reactions used in other metabolic pathways. Insulin resistance is a consequence of the metabolic stress during surgery. Hence, strategies to minimize insulin resistance have been proposed as a mean to accelerate patient recovery.

The results of carbohydrate loading on postoperative insulin sensitivity are controversial. In

patients undergoing major spinal surgery, the preoperative administration of 12.5 g/100 mL (800 cc before 11:00 pm and 400 cc 2 hours before surgery) did not have any impact on glucose, biomarkers of insulin sensitivity, or markers of systemic inflammation. Along these lines, a more recent study showed similar results [22]. However, it is worth mentioning that carbohydrate loading reduced anxiety, hunger, and thirst immediately before surgery [23]. The impact of preoperative carbohydrate loading on recovery after surgery has not been investigated in patients undergoing craniotomies.

35.3.1.6 Prophylaxis Against Nausea and Vomiting

Nausea and vomiting is one of the most common complications after neurosurgical procedures. Patient-related factors (younger women, nonsmokers, a history of motion sickness or postoperative nausea and vomiting), opioids, volatile anesthesia, neostigmine, and blood in the cerebral ventricles have been implicated in the pathogenesis of postoperative nausea and vomiting (PONV) [24]. Different studies show the efficacy of antiemetics, especially in the high-risk patients [5, 25]. Risk stratification and a multimodal therapeutic approach have been recommended to prevent PONV in patients undergoing spine surgery or craniotomies. 5-Hydroxytryptamine receptor antagonists (ondansetron, palonosetron, ramosetron, and granisetron), diphenhydramine, dexamethasone, transdermal scopolamine, promethazine, aprepitant, and droperidol have shown significant antiemetic effects. The administration of one drug is recommended in low-risk patients; two or three antiemetics should be given to intermediate-risk patients and more than three agents for those with high-risk scores for PONV [26].

35.3.1.7 Preoperative Prophylaxis Against Infection

The administration of antibiotics is an effective intervention to decrease the incidence of surgical site infection. Patients undergoing spine or intracranial surgery benefit from the administration of broad-spectrum antibiotics with coverage of *Staph. aureus*. Antibiotics (typically cephalosporins) should be given within 30 min of surgical incision and re-administrated every 4 hours for the duration of the surgery [27].

35.3.1.8 Thromboprophylaxis

Neurosurgical procedures can be associated with an incidence of thromboembolic events that can as high as 30%. Mechano- and chemoprophylaxis can decrease the rate of thromboembolic events to less than 1% in this patient population [28]. Mechanoprophylaxis should be attempted in all patients undergoing neurosurgery. Chemoprophylaxis should be considered only in high-risk patients such as those with expected long-term immobilization, history of thromboembolic disease, varicose veins, significant neurological deficits, and complex spine procedures. [28] The initiation of chemoprophylaxis to patients undergoing craniotomies should be considered when the risk of bleeding is low [29].

35.3.2 Intraoperative Period

35.3.2.1 Minimal Invasive Surgery

Several neurosurgical procedures can be accomplished via minimally invasive approaches including discectomies, major spine stabilization, and intracranial surgery. The goal of minimally invasive surgery (MIS) is to effectively perform procedures with less surgical trauma, minimize postoperative pain, increase postoperative mobility, reduce length of stay, and decrease morbidity. Overall, the literature supports this concept. Endoscopic resection of ventricular, posterior fossa, skull base, and pituitary tumors is a well-described intervention. More recently, patients with large metastatic spine disease or brain tumors may be candidates for laser interstitial thermal therapy (LITT) [30, 31]. The actual impact of LITT and endoscopic procedures on ERAS programs has not been studied. However, it is worth mentioning that in the context of spinal metastasis, the use of LITT is associated with a significant reduction in length of stay [30]. Wang et al. effectively included minimally invasive surgery for transforaminal interbody fusion (TLIF)

as one of the elements in their ERAS program [32]. The authors reported that some of the limitations of MIS included technical difficulties in achieving optimal decompression and steep learning curve [32].

35.3.2.2 Anesthesia and Analgesia Techniques

Neurosurgical procedures can be performed under regional, volatile-based anesthesia, total intravenous anesthesia, or their combination. Awake craniotomies for supratentorial tumors have been described in the context of ambulatory surgery for selected patients [33]. While no study has addressed the impact of one technique over the other on ERAS for neurosurgical procedures, the evidence indicates that minimization or avoidance of volatile agents could facilitate the postoperative recovery of patients. It has been demonstrated that propofol-based total intravenous anesthesia for craniotomies reduces extubation times, provides a quicker awakening, and reduces the time from admission to readiness for discharge from the postanesthesia care unit (PACU); however these benefits are small in terms of "real" clinical benefits [26, 34]. Perhaps, the primary clinical benefit of total intravenous anesthesia with agents like propofol is a reduction in PONV in high-risk patients [26].

A multimodal analgesic technique with avoidance of long-acting opioids or large dosages of these medications is recommended in ERAS guidelines for colorectal and gynecological procedures. The role of adjuvant intraoperative anesthetics and analgesics such as dexmedetomidine, ketamine, and lidocaine in the context of ERAS after craniotomies and spine surgery has not been fully addressed. Certainly, those agents can provide hemodynamic stability, reduce anesthetic consumption, and decrease inflammatory response and opioid consumption. However, they may also delay cognitive recovery [34, 35]. The routine preoperative administration of nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, acetaminophen, and gabapentinoids in patients undergoing neurosurgical procedures is still subject to debate. Two studies focused on recovery after transforaminal lumbar interbody fusion (TLIF) and scoliosis surgery indicated that patients in the recovery pathways receiving multimodal analgesia showed a significant reduction in opioid use and less opioid-related adverse events (ORADEs) [32, 36]. It is worth mentioning that in certain patients, the risks (bleeding and postoperative sedation) of administering these non-opioid agents might outweigh their proposed benefits (analgesia, less PONV, and opioid-sparing effects) [37–39]. In a recent study, the intraoperative administration of flurbiprofen was an independent risk factor for intracranial hematoma [40]. Therefore, careful selection of preoperative analgesics is recommended.

It can be argued that regional anesthesia techniques (scalp blocks, pin site infiltration, and neuraxial analgesia) could also accelerate the recovery of patients undergoing neurosurgical procedures by reducing opioid and anesthetic consumption, modulating the inflammatory response to surgery, and providing superior analgesia [41–43]. However, little information exists about the impact of regional anesthesia in ERAS programs for neurosurgical procedures. Wang et al. recommended the administration of long-acting anesthetics including liposomal bupivacaine in their ERAS program for spine surgery [32].

35.3.2.3 Fluid Balance

No study has rigorously addressed the role of hydration or volume maintenance on recovery after neurosurgical procedures. Overhydration and restrictive replacement of the intravascular volume during spine or intracranial surgery may lead to complications that can delay recovery. For instance, overhydration is an independent predictor of prolonged length of intensive care unit and hospital stay in patients undergoing spine decompression with fusion or MIS TLIF, respectively [44, 45]. Intraoperative fluid monitoring with minimally invasive technologies has been used in patients undergoing craniotomies and spine procedures. Wang et al. reported the use of noninvasive cardiac output monitoring to assess intraoperative fluid status in patients undergoing MIS TILF under an ERAS program [32].

While the type of fluid used is still a subject of extensive debate, it is worth mentioning that the aggressive use of 0.9% saline can worsen postoperative recovery by inducing hyperchloremic acidosis and coagulopathy [46, 47]. Therefore, balanced salt solutions might be the preferred choice in patients undergoing neurosurgical procedures.

35.3.2.4 Control of Body Temperature: Normothermia

Intraoperative hypothermia is associated with complications (i.e., myocardial ischemia, insulin resistance, cold diuresis, and infections) that can delay recovery after neurosurgery. While intraoperative-induced hypothermia may be considered in selective intracranial cases, the routine use of this technique for neuroprotection is not indicated. Postoperative hypothermia can also be observed immediately after spine surgery. In fact, Kiekkas et al. reported that 73.5% of the patients who underwent spine surgery developed hypothermia in PACU [48]. Shivering and delayed PACU discharge can occur as the result of hypothermia. Therefore, preoperative, intraoperative, and postoperative warming is recommended in the context of ERAS for neurosurgical procedures [32, 49].

35.3.2.5 Nasogastric Tubes and Surgical Drains

The routine use of surgical drains or naso-/orogastric tubes is not recommended in ERAS programs for colorectal and gynecological surgery. No study has been conducted to test the impact of those interventions on neurosurgical ERAS patients. Although orogastric tubes are rarely placed for craniotomies or spine surgery, they are placed to suction the stomach after pituitary or anterior skull base surgery. It has been hypothesized that the accumulation of blood in the stomach during those surgeries can be a contributor of PONV.

Wang et al. advised against the use of surgical drains after MIS TILF [32]. Others have suggested that the use of surgical drains in spine surgery is associated with a reduction in surgical site infections but their use should be limited to the first 48 hours after surgery [50]. Whether the use of subgaleal drains is a risk factor for postoperative complications or delayed recovery after routine craniotomies is unknown. However, the placement of drains after burr hole drainage of chronic subdural hematoma is recommended [51].

35.3.3 Postoperative Period

35.3.3.1 Early Removal of Urinary Catheters and Mobilization

It has been shown that early removal of urinary catheters is associated with a lower rate of urinary retention and infections and early mobilization and ambulation. The use of multimodal analgesic techniques also facilitates the early removal of urinary catheters [36]. Postoperative urinary retention (POUR) can be a frequent complication after neurosurgical procedures, especially after spine surgery [52]. Advanced age and long duration of surgery are risks factors for POUR. In those patients, early removal of the indwelling urethral catheter and encouragement of regular voiding are recommended [53].

While ERAS guidelines in non-neurosurgical patients promote mobilization of patients the day of surgery, the implementation of this element in neurosurgical patients can be challenging due to postoperative cognitive and motor deficits. However, in selected patients such as those who underwent minimally invasive spine surgeries, LITT procedures or small craniotomies mobilization as early as the day of surgery should be considered [32]. In patients undergoing more extensive surgical procedures, ambulation should be attempted within 24 hours after surgery. A recent study indicates that in patients 65 years of age or older, early postoperative ambulation (within 24 hours) is associated with fewer complications, enhanced functional status, and early hospital discharge [54]. Gornitzky et al. included early mobilization (postoperative day 1) as one of the measures of the "rapid recovery pathway" after spinal fusion in adolescents with idiopathic scoliosis [36].

35.3.3.2 Early Oral Intake

Early oral administration of fluids and solids provides energy support and protein supply and reverses insulin resistance. Neurological status permitting early oral intake should be considered in every neurosurgical patient. Gornitzky et al. and Wang et al. included early feeding with full diet or at the patient will, respectively, in their recovery after spine surgery programs [32, 36].

35.3.3.3 Multimodal Analgesia and Treatment of PONV

Opioid-sparing multimodal analgesia techniques are recommended in all ERAS guidelines. The objective is to provide adequate pain control while minimizing the use of opioids. This has several implications including a reduction of ORADEs, rapid mobilization, early tolerance of oral liquids and solids, and reduction of insulin resistance. To achieve that goal, around the clock analgesics are indicated to avoid breakthrough pain. Gabapentinoids, intravenous acetaminophen, NSAIDs, amantadine, and tramadol have shown opioid-sparing effects and are effective analgesics in the context of neurosurgery [55]. Garcia et al. reported that a multimodal analgesic approach reduced postoperative morphine use by 58% and improved postoperative pain controls in comparison to opioid use alone [56]. It should be noted that high dosages or prolonged exposure to NSAIDs have been associated with high nonunion rates after spine surgery. In patients undergoing craniotomies, the use of NSAIDs is still controversial due to the risk of intracranial bleeding. Jian et al. demonstrated that patients treated with flurbiprofen after surgery did not show an increased risk of bleeding [40]. While nonpharmacological interventions such as music therapy, aromatherapy, and acupuncture have been studied in the context of postsurgical pain, their efficacy appears to be limited and only beneficial in patients with high levels of anxiety.

35.3.3.4 Audit of Outcomes

The healthcare providers involved in ERAS programs include perioperative physicians, nurses, nutritionists, rehabilitation specialists, and physiatrists and psychologists. The teamwork inherent to an ERAS program requires continuous audit to identify gaps in care and assess the level of compliance with each element of the program. In fact, ERAS programs showing a compliance rate of 70% or more have shown a substantial reduction in mortality [57].

Key Points

- ERAS is a coordinated effort of evidence-based perioperative interventions focused on minimizing the surgical stress, inflammatory, and metabolic responses.
- ERAS programs promote preoperative strategies such as short period of fasting, perioperative multimodal opioid-sparing analgesia, and early postoperative nutrition and ambulation.
- The success of ERAS programs is based on continuing auditing process of each medical intervention.

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Robot-Assisted Neurosurgery

36

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36.1 Introduction

The technology in medical field is progressively growing with regard to its accuracy, compliancy, safety, tactile feedback, and hand-eye coordination. Robot-assisted surgery or robotic surgeries are technological developments that use robotic systems to add on surgical procedures. Robots not only enhance the capabilities of surgeons performing various surgeries; it also improves the overall patient outcome both in terms of morbidity and mortality. With the help of robots, surgery is performed with greater distinctness, smaller incision, less bleeding, and faster healing time. As compared to the traditional surgical approach, robotic surgeries lead to reduced transfusion rate, decreased use of analgesics, better access to point of surgical interest, short recovery time, lesser duration of hospital stay, and minimal scars and marks (Table 36.1) [1, 2]. Robotic surgeries have been performed in many complex cardiac, thoracic, or gynecological procedures [3–5]. As per the Cochrane Database of Systematic Reviews, total duration of surgery is prolonged with robotic procedures, but the hospital stay is found to be shorter [6, 7].

The first introduction of robot in surgery happened in 1985 in which the surgeons performed a neurosurgical biopsy. Robotic surgeries are not commonly performed in neurosurgical procedures compared to other fields, for example, urology, cardiology, gynecology, and gastroenterology surgeries. This could be because of greater anatomical complexities in the brain and also because the brain contains extremely sensitive vital centers.

Table 36.1 Advantages and disadvantages of robotic surgery

Advantages	Disadvantages
• Greater precision • Improved visualization • Minimal blood loss thus less transfusion of blood products • Smaller incision, minimal scarring • Lesser infection rates • Decreased pain and discomfort • Early mobilization • Shorter intensive care or hospital stay	• Highly technical procedure • Requires expertise in the robotic procedure • Higher cost • Time-consuming

36.2 Types of Robots

Robots range from being completely independent to fully dependent. In the former, robot reproduces pre-programmed instructions without the control of the surgeon during the surgery. This is most commonly utilized for the purpose of stereotactic positioning in neurosurgery. In a fully controlled robot, the surgeon has full authority

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over the system for the particular procedure. Most common systems at present in robot surgery are controlled systems which are used for performing telesurgeries while sitting in a console, distant from the patient, where the surgeon has full command over the surgical instruments. It is also known as telesurgery where surgeons can perform minimally invasive surgery. It gives a three-dimensional, high-definition view, functional design, and an instrument that can bend and rotate like a human hand. It received FDA approval in 2000, and since then it has been used in around 3 lakh surgeries. Another type of surgical robot is a shared control system which is a hybrid between independent and controlled system. Here a passive arm can be hooked up to a surgeon's hand and that moves only when allowed or ordered. It can further filter unwanted hand motions such as hand tremors. Few commonly used robots available for neurosurgery are the Neuromate, Pathfinder, the NeuroArm, and the SpineAssist.

36.3 Role in Adult Neurosurgery

The first ever neurosurgical robot "Neuromate" with an integrated stereotactic system was introduced commercially for stereotactic neurosurgery in 1997. It can perform both craniofacial and spine surgeries [8, 9]. Neuromate has been used in thousands of electrode implantation procedures for deep brain stimulation, endoscopy, stereoencephalography, and brain biopsy surgeries [10]. Another robot, *ROSA* (robotized surgical assistant), is now used in various neurosurgical procedures (Fig. 36.1). ROSA has two main parts, a computer "brain" and a robotic "arm," which work together under the neurosurgeon's control, making the surgery much faster. It can be used in all types of neurosurgical procedure that requires surgical planning, exact position, and handling of instruments. The main disadvantage with the use of these robots is its high cost.

Following the endoscopic third ventriculostomy (ETV), current evidence suggest 16.6% incidence of neural injuries which is quite high.

Fig. 36.1 ROSA (robotized surgical assistant) with two main parts: a computer "brain" and a robotic "arm"

Incidence of hyponatremia (3.9%), thalamic contusion (1.8%), and hypothalamic contusion (1.5%) are also found following ETV. New-onset neurological deficits have been observed in 1.5% of cases; out of them, one-third became permanent [11]. In another case series, ROSA-assisted ETV was performed in nine patients that demonstrated improvement of preoperative symptoms with no bad outcomes related to the procedures. The ROSA system provides a more precise, minimally invasive approach to ETVs. More clinical trials are required to find out whether hydrocephalus outcomes might be improved and adverse events reduced with the aid of robot-assisted technology [12]. A recent retrospective study compared the accuracy of robot-guided screw insertion versus hand-guided (CT/fluoroscopic) screw placement for spinal instrumentation. Authors found no difference between these two surgical methods of screw placement [13].

With increasing age comes comorbidities like hypertension, diabetes, chronic pulmonary disease, arthritis, and peripheral vascular diseases. These diseases increase the risk of general anesthesia in this patient population. Because of improved medical facilities, the number of elderly has increased worldwide. More elderly population will be presenting for operative procedures. It has been observed that elderly age does not appear to be associated with an increased morbidity, or poor outcomes in patients undergoing robotic gynecological surgeries. Further research is required in elderly patients to ensure safety of robotic minimally invasive surgery [14]. Literature is lacking in providing a study which can give us above data in elderly patients undergoing neurosurgical procedures. Robots offering improved quality of life of the elderly with Alzheimer's or/and other forms of dementia are available with features of monitoring of physiological parameters, cognitive training, or occupational therapy. These robots are however underutilized and are in developmental phase [15].

36.4 Role in Pediatric Neurosurgery

The use of robots in pediatric neurosurgical patients are of special interest. Many conditions like epilepsy, hydrocephalus, tumors, and movement disorders are of challenge for neurosurgeon because in children developing structures are more prone to insult than the developed structures in adults, specifically in relation to micro- and deep-seated targets [16]. The neurosurgical management of these cases requires high precision and careful planning to correctly identify the disease location and resection of target structure without harming the surrounding eloquent areas. Robotic procedures have been reported less frequently in children undergoing neurosurgical procedures. The literature describes mainly of urological, abdominal, and cardiac surgeries [17].

In a recent study, the authors retrospectively evaluated 116 consecutive pediatric patients who underwent 128 neurosurgical robotic procedures for various indications. It is the largest series reported of pediatric robot-assisted neurosurgical cases. The authors found the versatility of the ROSA device, which, given the possibility to integrate different tools, improves the safety and feasibility of several minimally invasive procedures while minimizing risks and surgical time. Further clinical trial or large studies are needed to validate past results and to optimize the impact of robotic stereotactic systems on the quality of neurosurgical procedures [18]. ROSA device is also used for pediatric epilepsy and neurooncology surgery. It has been observed that the ease of use, precision, and versatility of the ROSA system in pediatric epilepsy and other neurooncology surgeries make it well suited for pediatric neurosurgical practice [19].

In a series of pediatric patients with childhood tumor, i.e., pontine glioma, all stereotactic biopsies using ROSA showed no surgical complications. This type of system allowed single-session surgeries in these patients [20]. Introduction of the ROSA system to the ETV procedure in pediatric population has shown successful results with no complications [21]. The robot-assisted spine surgeries in pediatric patients have shown lower robot-assisted screw misplacement rate compared to conventional (non-robot-assisted) procedures [22].

36.5 Role in Minimally Invasive Neurosurgery

Cadaveric studies have been done in recent past to find out the possibility and potential advantages of robotic technology in minimally invasive neurosurgery. The *da Vinci robot* surgical system was used to perform the surgery (Fig. 36.2). It was difficult to pass both endoscope and instruments simultaneously through the keyhole craniotomy, limiting visualization. The da Vinci robotic system provided greater mastery than conventional tools. The da Vinci robot allows the surgeon to remain stable, unsterile, and seated comfortably during procedure. Further studies are required to evaluate the usage and safety of the da Vinci surgical system [23, 24]. Another

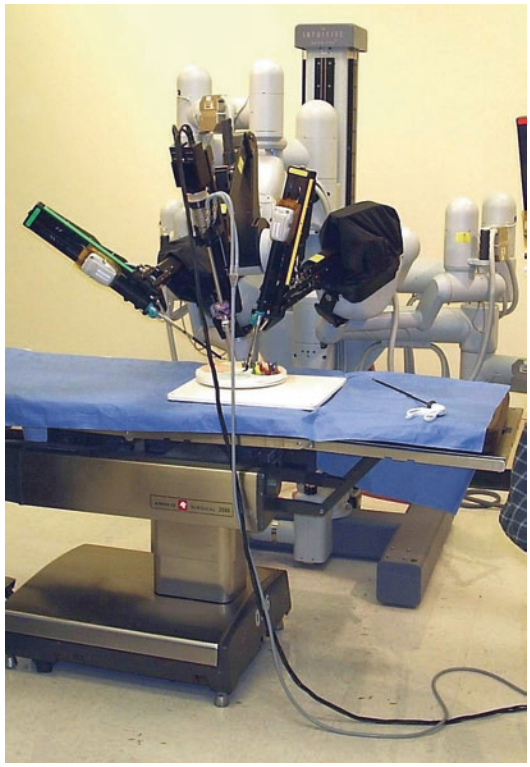

Fig. 36.2 Da Vinci robot with wristed instruments that bend and rotate far greater than the human hand. (Source: https://goo.gl/images/ccnNTf. Photo by Nimur at the English language Wikipedia. Licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license)

innovative transoral robotic surgery (TORS), for patients with sellar tumors, offers a new minimally invasive approach with da Vinci surgical system. This system might avoid the side effects and technical disadvantages of the classic route for sellar tumor. It also allows an inferosuperior approach to the sellaturcica, as the tumor is approached in the direction of its growth [25].

Minimally invasive spine surgery is associated with poor visibility of anatomic landmarks leading to higher incidence of malpositioning of pedicle screw. Nowadays intraoperative three-dimensional fluoroscopy and navigation are being used to overcome these drawbacks. It has been observed that operating room three-dimensional robotic fluoroscopy arm provides spine navigation based on three-dimensional images that helps to reduce radiation exposure. This approach provides 99.6% accuracy for percutaneous pedicle screw placement in the safe zone [26].

36.6 Role in Automated Neurosurgery

A large lineup of neuroscientific techniques, including in vivo electrophysiology, microdialysis, lesions, and two-photon imaging, feel the necessity for access to the brain through the skull. Craniotomies could be performed in an automated fashion, without damaging the brain tissue. A robotic device can perform craniotomies with either homebuilt hardware or commercially available hardware that can automatically detect such changes and create large numbers of precise craniotomies, even in a single skull. This technique can be adapted to automatically drill cranial windows several millimeters in diameter. Such type of robots will be useful for neuroscientists to perform all types of craniotomies. Automation of craniotomy in neurosurgery could help neuroscientists to perform in vivo neuroscience experiments with greater precision and productivity [27].

36.7 Role in Non-neurosurgical Cases

Robotic surgery has been used in treating various cardiological procedures like repair of atrial septal defect [ASD], coronary artery bypass grafting [CABG], and the mitral valve repair [MVR] as well as cardiological problems including arrhythmia, atrial fibrillation, etc. [28]. Robotic surgery has been performed successfully in various gynecological procedures like fibroid, cancers, and other ovarian tumors [29]. CASPAR robot has been used successfully in orthopedic surgeries like reconstruction of anterior cruciate ligament [ACL], total hip replacement, total knee replacement, etc. [30]. Robots have also been used successfully in various congenital anomaly repairs like congenital diaphragmatic hernia repair, tracheoesophageal fistula repair, etc. [31]. Robots have also been

used successfully in organ transplant procedures like kidney transplants [32]. Robotic plastic and reconstructive surgery is still in its early stage, with surgeries such as transoral robotic surgery and microvascular procedures the dominant areas of interest at present. Robotic surgeries have a number of benefits over conventional open surgery, like greater mastery, improved access, etc. These points must be balanced against disadvantages such as cost implications [33].

36.8 Anesthetic Implications

Fast employment of robot-assisted surgery has raised a concern about the need for re-evaluation of the suitable form of anesthesia. Anesthetic technique should be tailored to decrease perioperative risk and discomfort for patients. Anesthesia for patients posted for robotic surgery is different from anesthesia for patients undergoing conventional open surgery. There are few anesthetic concerns with regard to robot-assisted surgery. According to recent Cochrane systematic review, it is unclear which anesthetic technique is superior—total intravenous anesthesia or inhalational anesthesia—for various transabdominal robot-assisted surgeries in urology, gynecology, and gastroenterology, as existing evidence is scarce and is of poor quality [34]. Evidence on the choice of anesthetic technique in robot-assisted neurosurgery is lacking, and additional research is needed.

Other concerns in robotic surgeries include invasive monitoring while a robot-assisted procedure is done by a junior or less experienced surgeon, arterial blood pressure monitoring for patients with cardiac or respiratory comorbidity, complete muscle relaxation when robot is applied to the patient, remove robot immediately if uncontrollable bleeding at surgical site. One can cardiovert the cardiac dysrhythmias with the robot docked [35]. The main concerns of anesthesiologists during robot-assisted surgery are inexperienced surgeon and assistant, limited access to the patient, and unanticipated visceral or vascular injury. Moreover, to master the technique, the surgeons may take more time to operate resulting in an overall extended anesthetic time. This may have some long-term cognitive implications especially in geriatric population which are not yet clear. Hopefully, as the learning curve plateaus, this will be less of a problem.

36.9 Robotic Surgery: A Bliss?

The advantages of robotic surgery are much more to count on compared to its disadvantages (Table 36.1). Robotic surgery is a safe and has advanced and improved the skills with the help of computer assistance. In the last one decade, there is tremendous increase in the rate of various types of robot-assisted surgeries because of availability of equipment following improved infrastructures in the country as well as increase in the interests among medical personnels and increase in training programs. Surgeons are now well experienced in robot-assisted surgery during training even before establishing their practice.

36.10 Impact Factors

Sources that contribute to the noise in the operating room include anesthesia monitors, suction machines, and conversations [36]. Shapiro and Berland et al. measured the noise levels to be as great as 70 dB to 86 dB [37], and they are far higher than the recommended levels of 45 dB [38]. During neurosurgical procedures, the peak levels of noise can be as great as 100–120 dB [39]. Such a noisy environment could be dangerous to staff and patients. It could also have an impact on performance of surgeons in the operating room. It has been observed that noise has negative impact on robotic surgical performance. More research is required to identify how different types of noises can affect the surgeon's performance using robots [40].

Obesity is another factor which can affect the performance in robotic surgery. However according to recent retrospective study, morbid obesity is not a factor leading to increased morbidity or mortality when these procedures were performed using a robots [41]. Though this may be an important impact factor for thoracic/abdominal

surgeries, neurosurgical procedures may not be affected by it.

Little is known about specific effects of stress in surgical practice in general literature. It has been studied that coping strategies to overcome stress are not taught during surgical training [42]. A recent study however is suggestive of less stress associated with robotic assistance. Less stress could therefore improve surgical outcomes for patients as well as decrease the negative effects of long-term stress exposure on the surgeon [43].

36.11 Future of Robots in Neurosurgery

The future of robotic surgeries is very promising, looking at the present increase in the number of procedures being performed with their assistance. Days are not far when robots will completely replace humans in performing all types of surgeries. It will reduce the workload on medical professionals and also improve the success rate among patients undergoing surgeries leading to overall improvement in morbidity and mortality. Due to the greater increase of robot-assisted procedures, it is highly important to ensure patients' safety and surgical outcome. Worldwide societies for different surgical procedure have been formed to set good standard for training in robotic procedures [33].

36.12 Conclusion

Robot-assisted surgery is an upcoming and interesting revolution in the field of neurosurgery; however, the usage of this technology in this field is limited because of anatomical complexities of the brain. Though dependent robots are used in various neurosurgical procedures, autonomous robot in the future could be interesting to watch for. Researchers are working continuously to provide a more advanced machine which could able to perform complex neurosurgery independently.

Key Points

- Robot-assisted surgery enhances the skills of surgeons performing all types of neurosurgeries.
- Robotic surgeries in children are mainly performed in urological, abdominal, and cardiac surgeries and have been found to be infrequent in neurosurgical procedures.
- Robots offering improved quality of life of the elderly with Alzheimer's or other forms of dementia are available with features of monitoring of physiological parameters, cognitive training, or occupational therapy.

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Gene Therapy for Neuroanesthesia

37

Ellen S. Hauck and James G. Hecker

37.1 Introduction

An ischemic central nervous system (CNS) event during neurosurgery, or during any other major surgical procedure, is potentially devastating and requires early recognition and rapid implementation of appropriate therapies. Prevention is the better approach. Anesthesiologists are in the unique position of being able to predict when a patient is at risk of an ischemic event, and may therefore be able to protect the CNS prophylactically. Unfortunately, anesthetic *neuroprotection* at present is limited to the acute management of physiologic variables such as mean arterial pressure (MAP), cerebral blood flow (CBF), intracerebral pressure (ICP), O_2, and CO_2, which ensure oxygenation, ventilation, and perfusion while preserving CNS autoregulation and managing fluids and hemodynamics judiciously to match the clinical circumstances. Intraoperative ischemia, which is usually accidental, can also be an unavoidable consequence of the surgical procedure.

Neuroprotection, as the term is most commonly used, is the practice of preventing or minimizing the effects of the extensive secondary or tertiary injury that occurs after ischemic, surgical, or traumatic CNS insult. *Neuroprotection* is, however, more accurately defined as the ability to protect the CNS (or other organ systems) before the injury occurs [1]. Fukuda and Warner [2] define *neuroprotection* as treatment initiated before an ischemic insult, with the goal of improving tolerance to ischemia or other significant ("near-lethal") stressors. The authors thus distinguish *neuroprotection* from *neuroresuscitation*. They define *neuroresuscitation* as treatment(s) begun after a severe CNS insult with the goal of minimizing *secondary injury*, via whatever pathway, and of maximizing recovery [2]. Neuroresuscitation therefore means therapies or therapeutics after any CNS insult, including surgery, stroke, traumatic brain injury (TBI), or spinal cord injury (SCI). Therapies for neuroresuscitation and neuroprotection will likely overlap, and therapies for both are dependent on a full understanding of the molecular biology of ischemic injury. Currently our arsenal for neuroresuscitation is limited, with some controversy, to adequate MAPs, moderate hypothermia, normoglycemia, reactive oxygen species (ROS) antagonists, steroids, Ca^{2+} chelators, barbiturates, and possibly hyperbaric oxygen [1, 3, 4]. On the other hand, neuroprotection by anesthesiologists may in the near future include the administration of prophylactic drugs, gene expression, or other cellular manipulation before the stressor that leads to injury. *This chapter will focus on advances in one of these future therapeutic areas, gene therapy for neuroanesthesia*.

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37.2 Molecular Biology of Ischemic Injury

Gene therapy for neuroprotection or neuroresuscitation requires an understanding of the molecular biology of ischemic injury. Initial insult to the neurons and glial cells in the white and gray matter is caused most often by cessation or severe reduction in blood flow or oxygen to one or more regions of the brain, which can stem from a wide variety of severe insults including (but not limited to) traumatic brain injury, ischemic or hemorrhagic stroke, and surgery. Ischemia during surgery can occur inadvertently (such as with the use of excessive force during tissue retraction), or it may be unavoidable due to the surgical procedure (necessary clamping of a parent vessel during aneurysm surgery). The injury caused by the ischemic event may have an ischemic core with a surrounding penumbra of more limited injury [5]. Such an insult to the cells and tissues of the brain elicits a cellular stress response consisting of the activation of interleukins, CD cell markers (cluster of differentiation cell markers; cell surface markers that can trigger a signaling cascade), heat shock proteins (HSPs), and toll-like receptors (TLRs) both on the cell surface and also secreted into the extracellular space [6–9]. Before cell death, there is a triggering of the immediate early gene (IEG) stress, HSP, and immune responses which result in both local and distant signaling [10, 11]. The stress response changes over time, and how the response changes may be of both prognostic and diagnostic value, and such information may be of value in guiding advances in neuroresuscitation [12]. A list of the pathways activated after an ischemic insult is provided in Table 37.1.

Table 37.1 A list of pathways activated after an ischemic injury

Pathways activated after ischemic injury: a partial list
Energy depletion
Transcription factor and IEG activation
Translational arrest
Loss of cellular polarization
Loss of calcium and potassium channel integrity
Excitotoxic neurotransmitter release
NMDA complex activation
Inflammatory cell activation and signaling
Cytokine release
Membrane fluidity and potential changes
Nitric oxide and free radical release
Loss of calcium homeostasis
Excitatory amino acids release
Activation of apoptosis pathways (calpains, caspases, and poly(ADP) ribose)
Cell necrosis which releases further inflammatory mediators

Pathways listed may not occur in the order listed

The body's response to the stress of ischemia is a cascade of pathways that can lead to widespread secondary injury. Apoptosis is a slower form of cell death than cell necrosis. It is a more controlled process and causes less activation of the immune system than cell necrosis. Apoptosis plays an important role in cell pruning during development, but it also has a role after an ischemic event. In the setting of ischemic injury, apoptosis is triggered by trophic signals from cells that are injured but have a chance of rescue. In such cells, apoptosis can be modulated, and the pathway for this reason is a target for interventions that could prevent further cell loss after CNS injury. However, a live cell is not necessarily a functional cell [13]. In a parallel process, caspases are proenzymes that can be released as part of events triggered by ischemia, even after translational arrest. These proteins are both pro- and anti-apoptotic. Other pathways that are activated include macrophage infiltration, edema and reperfusion injury, release of free radicals, membrane destabilization, release of excitatory amino acids, failure of the calcium regulatory systems, mitochondrial failure, and protein denaturation.

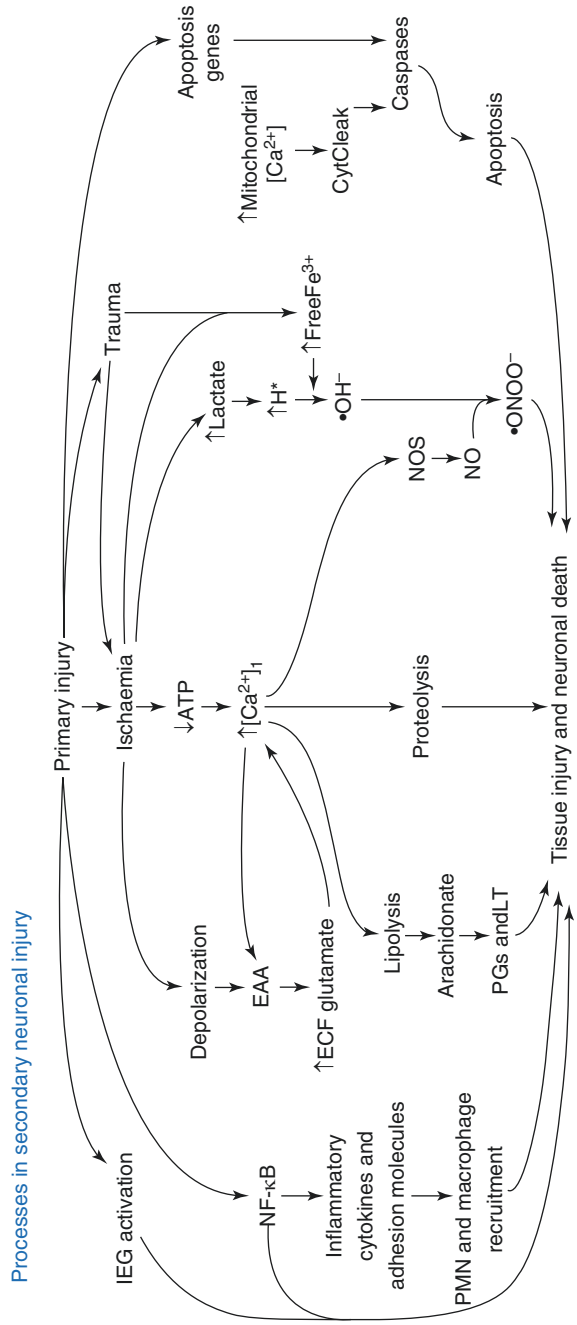
But these same pathways are also part of, or a trigger for, the recovery cascade that is also initiated after (or perhaps simultaneously with) the initial stress response. This counter-regulatory cascade balances and helps control the initial and subsequent responses to the ischemic insult. Competition between pathways leading to recovery and those leading to necrosis or apoptosis determines whether a particular ischemic injury is irreversible. These physiologic responses to ischemia or to any severe stress are called the acute phase response (APR). This is a tightly regulated response with involvement of tumor

necrosis factor (TNF), toll-like receptors (TLRs), interleukins, kinases, phosphorylation cascades, and second messengers. Acute and counter-regulatory generalized immunosuppression helps to control the acute pro-inflammatory responses to the insult or stressor [14].

This is a pattern of response/counter-response seen in many physiologic systems: the immune system, the inflammatory response, the coagulation/fibrinolytic cascades, and the excitatory/inhibitory neurotransmitters. The APR to any severe stress initiates both feed forward and feedback inhibitory responses, likely to allow for the possibility of survival after injury. The feedback inhibitory mechanisms prevent the overreaction of the immune, inflammatory, procoagulant, and excitatory pathways which in and of themselves could lead to cell or tissue death and organ failure. Generation of an appropriate physiologic response to a severe stressor requires tight control of the complex array of pathways initiated by this stressor. Loss of tight control could lead to diseases such as autoimmune (diabetes, arthritis, etc.) and coagulopathic disorders (both hypercoagulation and bleeding). A patient surviving a severe trauma for a week due to sophisticated medical care may still have an upregulated stress response, not entirely balanced by feedback pathways, that is no longer beneficial. Evolutionary stress responses were only 'designed' for short term survival to pass on genes. However, protection from a future severe stressor (particularly an ischemic event) may depend on the induction of this feedback response (preconditioning). Preconditioning has also been reported in patients exposed to anesthetics. Certain anesthetic medications may induce a stress response with its feed forward and feedback pathways, resulting in neuroexcitation, neuroprotection, as well as neurotoxicity, depending on the balance of the competing pathways. Reducing anesthetic neurotoxicity may be possible by simple avoidance of certain anesthetic agents, but neuroexcitation may elicit the stress response balanced toward repair, and result in neuroprotection after a recovery period. Too much exposure may lead to overexcitation, then the balance of the stress response shifts toward apoptosis or cell necrosis. Individual genetic susceptibilities and genetic variabilities likely affect the balance of the inflammatory/immune and survival responses.

Menon and Wheeler [14] have illustrated a proposed sequence of the events of secondary injury from the period immediately following the initial injury. Figure 37.1 depicts the most important mechanisms as far as they are understood. Another excellent summary of the known pathways, signals, and triggers for injury and apoptosis is found in Kass et al. [15]. These pathways do not explicitly state the type of initial insult to the CNS, but there is likely considerable overlap in the pathways that follow ischemia, traumatic brain injury (TBI), or spinal cord injury (SCI). The complexity of these pathways and their overlapping mechanisms and triggers and signals suggest as stated by Loane and Faden, "it is unlikely that targeting any single factor will result in significant improvement in outcome after…human injury" [16]. Indeed, little is known about the importance of individual mechanisms after any particular insult, and how the key roles of different pathways change over time. In addition, key pathways may also be determined by the severity of the insult and its location in the CNS. These are all significant gaps in our current understanding of secondary injury, and this at least in part explains the failure of clinical trials after stroke or other CNS insult when animal models have shown benefit [14].

In order to begin to understand which of the pathways is of key importance at a given time after ischemic injury and/or after a given severity of ischemic injury, models which integrate the multiple simultaneous pathways in response to the injury (stress, inflammation, immune, and reparation) are needed, but probably not yet possible. For example, inhibition of nitric oxide synthase (NOS) to reduce the production of nitric oxide (NO) and thus the production of free radicals would seem to be a neuroprotective intervention. However, various animal studies have been shown in contradictory studies to reduce, have no effect, and even increase neuronal injury [17, 18]. NOS has several isoforms which are active at various times after injury. Immediately after injury, endothelial NOS (eNOS) produces NO



ATP, adenosine triphosphate; $[Ca^{2+}]$, cytosolic calcium concentration; cyt C, cytochrome C; EAA, excitatory amino acid; ECF, extracellular fluid; IEG, immediate early gene; LT, leukotrienes; NF-κB, nuclear factor κB; NO, nitric oxide; NOS, nitric oxide synthase; $•ONOO^-$, peroxynitrite; PMN, polymorphonuclear leukocytes; PGs, prostaglandins

Fig. 37.1 Processes in secondary neuronal injury (following ischemia). Reprinted from Menon DK, Wheeler DW. Neuronal injury and neuroprotection. Anaesth Intensive Care Med. 2005;6(6):184–8. [14], with permission from Elsevier

which acts to dilate blood vessels and inhibits platelet aggregation. Inhibition of eNOS could therefore increase neuronal injury. Later, neuronal NOS (nNOS) and inducible NOS (iNOS) produce large amounts of NO in the brain parenchyma, and this is the time NO becomes neurotoxic [14]. The multiple roles of any given molecule and/or pathway will eventually need to be mapped out for a complete understanding of the process of secondary injury and recover. However, as shown in Fig. 37.1, modeling just one cell's reaction to an insult is highly complex, let alone modeling a larger region of injured CNS. This figure, used with permission from an article by Menon and Wheeler [14], shows the multiple interactions among pathways of injury within a cell after an ischemic event. Protective mechanisms and recovery pathways are also induced by the ischemic brain, and offer insights into what is likely to be coordinated neuromuscular programs that function as endogenous neuroprotection [19]. To add an additional layer of complexity, the unique architecture of the CNS means that injury in one area can result in dysfunction in another distant from the original site. The term for this is diaschisis, and it is due to axonal disruption. For example, a crossed cerebellar diaschisis means that a loss of function in the cerebellum results from a cerebral injury to the opposite hemisphere via the corticopontocerebellar tracts. Cerebellar diaschisis may be a prognostic sign of poor outcome after stroke. Thus, in addition to mapping out intracellular interacting injury and recovery pathways, molecular intercellular communication and the structural implications of the CNS must be factored into any experimental or computational model.

37.3 Gene Therapy

37.3.1 Targets

With all that is known about the pathways of stress, injury, and recovery, gene therapy for neuroanesthesia holds the promise of tilting the balance of the coordinated mechanisms toward neuroprotection or neuroresuscitation. Given the known complexity of these pathways, no one single intervention (a single gene delivery for overexpression or inhibition) is likely to be successful in preventing CNS injury or minimizing secondary injury after CNS insult. There are hundreds of articles that describe animal models in which proteins, antibodies, receptors, small interfering RNAs, and genes all provide a degree of neuroprotection either before or immediately after an ischemic event. Examples include [20–24]. These articles provide insight into some of the most promising targets for further research. Such targets include calcium and sodium channels, mitochondria, reactive oxygen species, tight junctions, edema, and membrane function; each listed area touches more than one pathway, yet none have yet proven to be successful on their own.

Targets for gene therapy that hold the greatest promise will be those that can act in multiple pathways or the final common pathways. Preconditioning and hypothermia reprogram gene and protein expression which subsequently changes the overall response to subsequent ischemic insults. Preoperative stress conditioning before aortic surgery has been shown to prevent paralysis [25]. Gidday and colleagues' work on ischemic tolerance and CNS preconditioning shows evidence of transient ischemic preconditioning [26, 27]. Animals in hibernation and those living underwater or at high altitudes for prolonged periods habituate to a degree of ischemia. Arousal from hibernation shows similarities with the mechanisms activated during reperfusion after stroke, but without the resulting injury [27]. In both of the above examples, induction of members of the heat shock protein family may be part of the protective mechanisms. Hsp70 has been shown to be overexpressed in hibernating turtles [4] and in cardiac tissue in humans suffering myocardial ischemia [28]. HSP27 and 70 in particular are known to be rapidly induced during severe stress [29]. These proteins have been shown in newborn pigs subjected to fluid percussion brain injury to provide protection from K^+ and Ca^+ channel modulations known to be part of the inflammation process [30]. And finally, in patients undergoing thoracic aneurysm repair, elevated the

levels of HSP27 and 70 in the cerebral spinal fluid of the patient have been shown to correlate with the likelihood of permanent paralysis, again suggesting the induction of these proteins during spinal cord ischemia [31]. The heat shock protein family is therefore an important possible target for gene therapy, one not shown in Fig. 37.1. In another approach to the analysis of the response to preconditioning, Stenzel-Poore and colleagues [32] used microarray analysis of the gene expression of mice after exposure to ischemia. Their work revealed three distinct gene expression patterns, all of which add more potential targets for gene therapy. These findings open the possibility of delivery of gene(s) that produce protein(s) induced in the presence of ischemia that would trigger the identified gene expression patterns, attenuating secondary injury.

As the search for the most promising targets for gene therapy continues, multiple interventions are anticipated to be necessary to significantly attenuate the neurotoxic pathways once initiated after injury. Such interventions may need to occur in a sequential manner over a determined time course. Multiple types of nucleic acids could be involved in such a series of interventions, including small interfering RNAs (siRNAs) and genes coding for trophic factors, anti-apoptotic factors, HSPs, and cytokines. In addition, these therapies may be combined with pharmacologic therapies such as steroids and neuroprotective drugs including anesthetics. Gidday [26] reviewed a long list of US Food and Drug Administration-approved drugs that show preconditioning effects.

37.4 Delivery of Gene Therapy

While there remains much to be learned about the complex mechanisms of CNS injury, repair, and protection, gene therapy holds the promise of being able to deliver inhibition, induction, or modification of the known pathways using nucleic acid (siRNA or antisense RNA) and/or protein therapeutics. Gene therapy includes a spectrum of methods designed to deliver a therapeutic nucleic acid or protein to the intracellular environment of target cells, tissues, or organs. Some of these methods include delivery of genes via viral and nonviral vectors, and through delivery of the gene to target tissues in vivo or by implantation of cells that have been first transfected with the nucleic acid in vitro (ex vivo). The therapeutic goal of the therapy can determine the choice of delivery method. For neuroprotection and neuroresuscitation, gene delivery that provides transient expression of the nucleic acid or protein therapeutic may be preferred since stressors like ischemia are presumed to be temporary. Gene therapy for neuroprotection will need rapid and widespread distribution throughout the CNS, while gene therapy for neuroresuscitation may more appropriately target one cell type or one tissue region within the CNS. Whatever the application, successful gene therapy will depend on the appropriate gene delivery system as much as the right therapeutic target. And just as efforts are underway to fully understand the molecular biology of CNS injury, all details of the gene delivery system should be fully understood, including the dose response and time course of gene expression of the delivered gene.

Nonviral vectors include naked DNA or RNA as well as nucleic acids complexed with particles such as lipids and other more complex assemblies of lipids, proteins, polymers, and scaffolding. CNS delivery paradoxically is probably much easier and efficient than delivery via the bloodstream to distant organs without uptake or degradation. Nonviral DNA vector delivery of the reporter gene luciferase to the cerebral spinal fluid of rats has been shown to provide widespread expression of the enzyme throughout the CNS [33]. Uptake of the "naked" nonviral vectors is usually accomplished by physical methods such as electroporation, gene gun (gold particles coated with nucleic acid and propelled into cells by pressurized carrier gas), hydrodynamic injection, and microinjection [34, 35]. These are the most common methods used when transfecting a small population of cells ex vivo for later implantation into the target site (tissue or organ), although viral vectors are finding increasing utility in ex vivo applications as well [36]. Lipid-mediated vector

delivery occurs by endocytosis followed by endosomal release into the cytoplasm [36]. Currently this process is not very efficient with estimates of 1–2% of vectors making it into the cytoplasm. Recent advances have led to improvements in the efficiency of such gene transfer [37–40]. Patel and colleagues very recently published work providing insights into this process of uptake of lipid/nucleic acid complexes and demonstrating improved efficiency of uptake [41]. Nonviral vectors are historically less immunogenic than viral vectors, and they are not designed to integrate into the genome. Transient gene expression was seen as a problem early along in the development of the field of gene therapy, but there are many applications which would be better served with transient expression, such as neuroprotection for the duration of surgery with a high risk of CNS ischemic or embolic events. Hauck et al. showed such transient and self-limiting gene expression. Rats transfected with a nonviral DNA vector carrying the luciferase gene (delivered to the CSF) expressed luciferase, peaking at approximately 72 hours after transfection and remaining detectable for 10 days [42].

The most notable benefit of viral vectors is their potential to provide highly efficient transfection and long-term expression of the gene of interest into the target tissue. This long-term expression is achieved by either integration into the host genome or establishment of a stable self-replicating episome. However, viral vectors require complex genetic engineering to produce, although many are now commercially available through a variety of companies, making the task somewhat easier. Viral vectors can be highly immunogenic, and Wilson et al. found the adeno-associated virus 9 to be both hepatotoxic and neurotoxic in juvenile nonhuman primates and piglets. All but two animals required euthanasia due to this toxicity [43]. The control of and level of expression of the gene of interest are also issues that must be overcome with each vector construct [44]. In addition, while transfection efficiency can be high, some vectors do not reach tissues far from the delivery site [45]. Anatomically limited transfection may be of value for neuroresuscitation, but widespread gene uptake (reaching all of the CNS) is needed for neuroprotection. Finally, stable somatic cell genome integration of a viral vector has been reported to cause additional disease in the host [46]. Studies continue looking at a variety of viruses as potential vectors for gene therapy, including forms of adenovirus, adeno-associated virus, SV40, lentivirus, herpes simplex virus, and retroviruses. Immunogenicity, efficiency, and longevity must all be examined with each vector construct.

Both DNA- and RNA-encoded genes have been studied for neuroprotection. Successful transfection of cells or tissues with DNA leads to longer-term expression of the gene of interest, but the results are not always permanent. Abdellatif and colleagues have compared the time course of gene delivery to the spinal cord of rodents using lentiviral, adenoviral, and retroviral vectors. A gene coding for a neurotrophin was injected into the spinal cord white matter of rats carried on one of the three vectors. Lentiviral vectors seemed to result in the most stable expression of the neurotrophin after 4 weeks, while the retroviral vector-transduced tissues showed significant loss of protein expression after 2 weeks [47]. Thus, transient gene expression can be achieved by the use of either DNA or RNA, depending upon the definition of "transient." The required transit of DNA into the cell nucleus means that protein production (and therefore therapeutic effect) requires transcription of the gene into mRNA (for protein therapeutics) and then translation of the mRNA into protein which occurs in the cytoplasm. The delivered DNA is also replicated once it arrives in the nucleus, providing for amplification of the gene and ultimately of the therapeutic protein production. However, travel into the cell nucleus is also an additional barrier to overcome for DNA-based therapies, and potentially slowing down the time from transfection to therapeutic effect. While less stable than DNA, RNA does not have to cross the nuclear membrane and can be available for protein synthesis once it arrives in the cytoplasm. Zou and colleagues demonstrated that expression of green fluorescent protein in lipid-mediated mRNA transfected primary cell cultures was

detected at least 3 hours sooner than in cells transfected with lipid-complexed DNA [48]. More rapid production of the therapeutic protein and one less barrier to delivery (no crossing the nuclear membrane) make the delivery of RNA transfection an appealing alternative to DNA transfection, but the cost is a less stable nucleic acid and one that is not amplified by replication in vivo. These two barriers have meant much lower levels of detectable protein production with RNA transfection. Advances have been made in both the stability and efficiency of translation of in vitro synthesized mRNA, making use of mRNA more appealing for use in transient gene therapy (i.e., neuroprotection). Both the 5′ cap and the poly-A tail of the RNA help protect the molecule from degradation by nucleases. Modified 5′ caps have been formulated which increases the stability of the RNA and also enhances initiation of translation from the 5′ end of the molecule [49]. The length of the poly-A tail that maximizes RNA half-life has also been determined [50]. Finally, chemical modifications of the RNA bases have helped disguise the RNA from cells' immune systems, enhancing the nucleic acid's stability in vivo [51, 52].

37.5 Measurement of Experimental Outcomes and Systems Biology

Since part of the state of wellness of the CNS is consciousness, advances in the modeling and understanding of consciousness and unconsciousness (the effects of anesthetic agents) are critically important to understanding the effects of ischemia. Modeling consciousness has made some rapid advances, some made in fact, by the study of the effects on the CNS of anesthetic agents. Consciousness is another biological state that results from interactions among many brain network systems. Unconsciousness may be a disruption of interactions required for consciousness or may be additional networks of mechanisms that interacts intimately with those creating and maintaining the conscious state. Mashour and colleagues have followed the interactions between the frontal and parietal regions at baseline consciousness and under general anesthesia using electroencephalography. They found that anesthetic agents interfere with frontal-parietal feedback connectivity that is present in the conscious state [53]. Tononi developed an integrated information theory of consciousness and uses it to analyze pathological cognitive function, obviously relevant to recovery from CNS ischemia [54]. Tymianski and colleagues summarized the known pathways of cellular signaling after CNS ischemia, indicating the signaling cascades "mediate cross-talk between redundant pathways of cell death" [55]. While his analysis focused on excitotoxicity and was therefore incomplete, the concept of redundant, overlapping, amplifying, and antagonistic pathways is critically important. DeGracia created a Boolean model of ischemic injury [56]. In such a model, each functional molecule (RNA, enzyme, etc.) is either "on or off." The outcome of CNS injury then depends on the interactions of all disease-relevant alterations of the functional molecules. This model is entirely different from models which superimpose individual injury pathways that have been experimentally elucidated. A better knowledge of oscillatory networks may also further our understanding of how the CNS achieves awareness or consciousness and thus how it can recover from ischemia. Siegel and colleagues have described spectral fingerprints of neuronal interactions which are large-scale, frequency-specific neuronal interactions and may define consciousness [57]. Thus, trying to understand how to detect the perturbations in a complex system of pathways and mechanisms that would result from gene therapy will depend on better methods to detect these perturbations.

The complex interactions among the pathways of injury and repair after CNS insult suggest that multimodal therapy is most likely to be necessary to provide either neuroprotection or neuroresuscitation. Designing experiments to demonstrate the clinical efficacy of such therapies will be next to impossible until the multi-pathway interactions are better understood. Researchers are making headway in understanding and measuring

some of the variables that determine how cells survive, but tools to measure CNS function do not have the resolution (functional MRI or positron emission tomography (PET)) to precisely measure the effects of a given intervention. There are a multitude of detection methods currently under study, however. Measurement of cerebral blood flow (CBF) and monitoring autoregulation within a cerebrovascular bundle has been followed using near-infrared spectroscopy, combined laser-Doppler flowmetry, and photospectroscopy [58–61]. The latter techniques were used in real time during intracranial procedures. While blood flow to the CNS is a factor in neuroprotection and neuroresuscitation, such measurements are very broad strokes when attempting to tease out the benefit of one or even several interventional therapies. As more is learned about the proposed mechanisms and pathways of CNS injury, genome-wide association studies may become helpful in identifying risks for ischemia and individual patient responses to therapy. Such studies will simultaneously reveal more about the details of the involved molecular biology. Ultimately, systems biology, the attempt to model complete physiologic systems, will be the needed approach to gain a better understanding of the overlapping and widely interacting mechanisms of CNS injury and repair. Modeling at this level of complexity will need a computational neurosciences approach [62].

37.6 Conclusion

Use of gene therapy for neuroprotection and neuroresuscitation during or before anesthesia is not ready for prime time. The techniques for delivery of genes are ready as can be seen by FDA approval of particular gene therapy techniques for cancer therapy. However, our understanding of the most critical aspects of cell survival versus cell death after an ischemic or other CNS injury is lacking enough specifics to disallow us of rationally choosing targets for such therapies yet. Given the complex nature of the response to ischemia and repair as well as the molecular complexity of the conscious state, such targets are likely to be many, and required to act in a coordinated fashion.

Key Points

- Neuroprotection is not the same as neuroresuscitation, which is what we actually practice to minimize the secondary injuries after an initial CNS insult.
- The current standard of care for prevention of secondary injuries is based on classic elements of neuroanesthesia; avoid hypotension, hypoxia, hyperthermia, low CPP, high ICP, hyper-/hypocarbia, and hyper-/hypoglycemia.
- Current controversies involve hypothermia, hyperoxia, hypertonic infusions, alternate energy substrates, and inflammatory factors in continuing injury.
- True neuroprotection, that is, delivery and expression of prophylactic molecules before an anticipated, potential near-lethal stressor, is feasible with current gene therapy techniques, which might also be useful after injury.
- Much additional research is needed to determine which of the many injury pathways are important at which times after injury and will probably necessitate a sophisticated computational biology modeling approach.

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Intra-arterial Drug Delivery for Brain Diseases

38

Jason A. Ellis and Shailendra Joshi

38.1 History

The idea of selectively treating disease with negligible nontarget exposure by IA drugs has intrigued researchers for a very long time. The treatment of brain tumors was the leading application for the development of intra-arterial (IA) drugs. As early as 1950, Calvin Klopp at George Washington University used IA chemotherapy for treating glioblastoma multiforme. The rationale for IA chemotherapy was simple: local delivery of drug will decrease the dose and improve the efficacy of cancer treatments. Vigorous research in the next three decades failed to show clinical benefit from various IA delivery protocols. At the same time, significant complications from IA drug delivery to the brain were also being reported. While IA treatment of brain cancers failed to improve brain tumor patient outcomes, IA approaches were rapidly being developed for the treatment of other cancers including retinoblastoma, liver tumors, and other malignancies.

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The early failures seen during the 1970s and 1980s could not have come at a worse time. The 1990s ushered in the field of neuroendovascular surgery which held the potential to significantly advance the field of IA drug delivery to the brain. Yet, IA pharmacology had not advanced a great deal in contrast to the delivery technology. As a result, many clinical trials remain in the Phase I and II stages. Thus, the IA brain cancer treatments typically focus on feasibility and safety rather than the therapeutic response or survival. Nonetheless, spectacular treatment results have been reported in literature.

Beyond IA chemotherapy for brain tumors, there are many other applications for IA drug delivery to the brain. IA drugs have been used for localization of brain function since 1949. IA thrombolytics have been used for the treatment of embolic strokes. IA vasodilators have been used for the treatment of cerebral vasospasm. IA mannitol is used to disrupt the blood-brain barrier (BBB).

38.2 Rationale for IA Treatments

Modern techniques for effective drug delivery have been in evolution for many years. For example, intravenous drug delivery evolved over three centuries. The first experiments utilizing intravenous injections occurred in the 1600s, and IV drug delivery protocols are still being optimized today. On a comparative time frame, catheter technology at the

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Table 38.1 IA drug delivery

Pros	Cons
• Targeted delivery to pathological sites	• Limited tissue uptake due to blood-brain/tumor barrier
• Instantaneous, concentrated delivery	• Rapid clearance of drug
• Simultaneous, multiple drug delivery	• Streaming
• Dose reduction	• Invasive
• Precise drug delivery monitoring	• Significant/fatal complications possible
• Systemic rescue possible	• Unproven benefit

heart of IA drug delivery did not emerge until 1929 thanks to the efforts of Werner Forssmann. It was not until the late 1940 that the first attempts with IA drug delivery for neurological applications began in earnest. Nonetheless, IA drug delivery protocols are still in the early stages of evolution. Effective IA drug delivery to a complex organ such as the brain is far from being fully understood and optimized.

The intuitive simplicity of IA drug delivery (Table 38.1) is misleading because the underlying hydrodynamic, pharmacokinetic, and pharmacodynamic factors that affect such delivery are very complex and poorly understood. In addition, the brain is perhaps the most unfavorable tissue bed for the application of IA treatments. High resting cerebral blood flow (CBF), the presence of a BBB that restricts drug uptake, and low injury tolerance are major hurdles to IA drug delivery. Yet the refractoriness of many brain diseases, including brain cancer, stroke, and cerebral vasospasm, to conventional treatments highlights the need for a unique approach such as IA delivery. A cogent argument can therefore be made to employ treatment strategies like IA delivery that carry greater risks but premise better outcomes.

38.3 Pharmacokinetic Basis of IA Drug Delivery

38.3.1 Hydrodynamic Factors

Having investigated the pharmacology of IA drugs for more than two decades, we see IA drug delivery to be primarily a hydrodynamic problem. The pharmacokinetic issues remain downstream of the hydrodynamic factors that affect IA drug delivery. The hydrodynamic factors are related both to tissue vascular characteristics and the injection profile. These vessel characteristics include anatomy, injection site (proximal vs. distal cerebral arteries), vascular wall biomechanics (volume and wall compliance), as well as physiological factors such a resting flow and vessel response to injection. Injection factors that affect IA drug delivery include site of injection, type of catheter, timing of injection with respect to the cardiac cycle, volume rate of injection, and the concentration and the frequency of injections. These interactive hydrodynamic factors determine the concentration and the contact duration between the drug/carriers and the vascular endothelium. The drug concentration, and time of contact with the vascular endothelium, is the input function for the classic pharmacokinetic factors that determine uptake and distribution at and beyond the endothelium. Maximizing drug delivery therefore requires optimization of injection volume, safely manipulating blood flow, optimizing drug design for maximum first-pass retention—not just initial uptake—of the drugs, and effectively penetrating the blood-brain/tumor barrier.

38.3.2 Pharmacokinetics Factors

The central concept of IA drug delivery is to ensure rapid uptake of the drug during its first pass through the cerebral circulation. Dedrick and colleagues using a simple pharmacokinetic model explained that IA drug delivery is effective when there is high regional extraction, low regional blood flow, and high systemic clearance. The classic Dedrick model assumes equilibrium conditions with steady-state infusions and was not meant to describe bolus drug injections. Additionally, this model does not provide any measure of drug-tissue binding and therefore provides little conceptual insight into drug deposition after IA injections. Nonetheless, we can apply the Dedrick model to help us identify the desirable properties of IA drugs and drug formulations. In this model the advantage of IA delivery over intravenous delivery (R_d) is given by the equation:

$$R_d = 1 + \frac{\text{Clearance from the body}}{\text{Regional blood flow} \times \left(1 - \text{First pass regional extraction}\right)}$$

38.3.2.1 High Regional Extraction

This key property of the drugs suggests high—preferably irreversible—first-pass extraction during the initial pass through the cerebral circulation. The maximum benefit of IA drugs delivery can be expected for drugs that are rapidly taken up by the brain tissue. Ideally, this rapid uptake should also be accompanied by increased tissue retention; however, this is not always the case. For example, increased lipid solubility alone will not improve the effectiveness of IA drug delivery with bolus injections. Highly lipid-soluble drugs will rapidly diffuse forward when the arterial concentration is high but will diffuse back when the arterial concentrations decline after the drug bolus transits the cerebral circulation. We consider extraction to have two components, uptake and retention, and unless drugs are avidly bound to the target site, they will have limited retention over time.

Extraction does not simply imply diffusion across the BBB but retention in brain tissue. Unless significant proportion of the drug is extracted during its first pass through the cerebral circulation, the benefits of IA delivery will be limited. An extended version of the Dedrick model when applied to drug delivery shows that even with effective delivery across the BBB, the concentrations of drug rapidly decline unless the drug avidly binds to the target site. One way to do so is by ionization within the tissue or cells due to pH differences. For example, the pH in the GBM cells is relatively acidic and could be used for trapping drugs like mitoxantrone.

Similarly, much of the research in nanoparticle development has focused on defining the characteristics of the particles that maximize the properties of particle uptake during capillary transit. The factors collectively determine the probability of particle endothelium adhesion. It has to be noted that shear stress also affects the first-pass extraction of certain nanoparticles by as much as 20-fold or more. In vitro studies of nanoparticles with endothelium-targeting ligands show dramatic improvements in regional delivery with low wall sheer stress. It has been suggested that the low sheer stress in some tumors helps in targeting the tumor endothelium.

38.3.2.2 Low Regional Blood Flow

Decreased regional blood flow enhances local IA drug delivery by increasing arterial blood concentrations, increasing the transit time, and decreasing clearance after injection. In addition, decrease in blood flow helps to better target the drugs to the tumor site. Low regional blood flow decreases the variability in tissue concentrations due to streaming. Additionally, this situation will minimize contact of drug with blood and blood proteins to improve targeted drug delivery. Decreasing blood flow to improve IA drug delivery has been effective in other organs; however due to the potential risk of stroke, its application to the treatment of brain tumors has been somewhat limited. The recent availability of balloon-tipped microcatheters makes it possible to deliver drugs while reducing the regional blood flow in distal regions of the brain.

38.3.2.3 High Systemic Clearance

The selectivity of drug IA delivery to target site can be greatly increased if the drug is rapidly cleared from systemic circulation. While increased systemic clearance does not affect tissue deposition, it permits a safe increase in the delivered dose of IA drugs. Rapid clearance from the body decreases the recirculating concentrations and minimizes side effects.

Drugs that are not extracted during their first pass through the regional circulation will reach the pulmonary and systemic circulations. If they are rapidly metabolized, then the pharmacological effects of the IA drugs will be limited to the brain tissue. Rapid systemic elimination also decreases the risk of injury to other organs. Strategies such as hemoperfusion during intracarotid infusion were used with some effectiveness in the past. In the future, drugs must be specifically designed to optimize systemic clearance through biological mechanisms.

38.3.2.4 Suitable Regional Clearance

A challenge with IA drug delivery is that an arterial irrigation may contain gray matter, white matter, as well as the pathology that is being targeted. Each tissue component has its own perfusion and drug uptake characteristics. The key to effective intra-arterial drug development is to enable uptake of drugs selectively by the target tissue and retention to achieve the desired duration of effect, while it is rapidly cleared from intracranial and extracranial nontarget sites.

38.4 Optimizing IA Delivery

The location of IA drug delivery is one of the first parameters that should be determined prior to initiating an IA delivery protocol. Should the drugs be selectively infused into a feeding artery that irrigates the target pathology, or should delivery be less selective to the entire cerebral hemisphere? Hemispheric drug infusions are simpler to undertake and achieve uniform tissue concentrations. However such infusions are not selective for the pathology, can cause inadvertent nontarget site injuries, and due to the high resting cerebral blood flow are likely to lead to considerable wasting of drugs. Therefore, super-selective drug infusions are favored when possible. On the other hand, super-selective injections are technically demanding, are associated with streaming that results in considerable differences in tissue drug delivery, and may not irrigate the entire pathological region through the selected vessel.

38.4.1 Streaming

The assumption of uniform drug mixing in the blood stream after IA delivery is not always valid. Maldistribution of drug in the arterial stream is termed “streaming” and can be quite common depending on the infusion parameters employed. The baseline blood flow, volume rate of drug injection, and the site of infusion affect the extent of streaming. Distal injections, low volume infusion rates, and high baseline blood flow favor streaming. Measures that decrease streaming include increasing the volume rate of injection beyond 20% of baseline flow, utilizing pulse dose injection, timing pulse doses with diastole, and use of side-port delivery catheters.

38.4.2 Bolus Injection

Precise control of drug injection volume can be challenging. Excessive volume can lead to drug wastage and errors in the determination of brain uptake index. Using optical coherence tomography, we found that the optimum bolus volume in rats to may be around 65 μl. In clinical practice, optimum bolus volume is often determined by the amount of contrast needed to opacify the vessels. Modulation of drug concentrations, bolus volume, and frequency can have significant effects on the effects on drug uptake.

38.4.3 Transient Cerebral Hypoperfusion

Transient interruption of blood flow is often used in neurovascular surgery such as during aneurysm clipping. Injecting drugs as boluses during transient cerebral hypoperfusion (TCH) radically changes the IA pharmacokinetics of drug delivery. Such injections (1) generate exceedingly high arterial blood concentrations, (2) minimize drug contact with blood and blood proteins to increase free drug concentrations, (3) decrease non-specific opsonization of circulating blood cells and proteins, (4) increase the transit time of the drug trough the cerebral circulation enabling greater diffusion, (5) decrease streaming and generates consistent peak concentrations, and (6) decrease shear stress on larger molecules, thereby increasing uptake by the endothelium. Injecting drugs during TCH increases drug uptake and/or drug effectiveness by as much as three- to tenfold. In small animals transient cerebral hypoperfusion that is completely reversible can be achieved by bolus injection of adenosine and esmolol followed by cold saline. While adenosine has been used for decreasing cerebral blood flow in humans, it could also be achieved by balloon-tipped catheters that have a distal port for drug infusion.

38.4.4 Injection Strategy

IA drug delivery protocols vary considerably and are application and operator dependent (Table 38.2). A plethora of infusion methods have been used to treat brain tumors. Over the years there has been a shift from steady-state intracarotid infusion to super-selective pulsed injections. Super-selective drug infusions are advantageous in targeting the pathology by physically restricting the volume of distribution of the drug. However, distal brain infusion can cause variability in drug delivery due to streaming. Pulse injections achieve uniform drug delivery in the region of arterial distribution, but the increase in blood concentration is transient. To increase transit time, cerebral blood flow can be reduced. There are many advantages of transiently reducing cerebral blood flow during bolus injections. These include less dilution with arterial blood to achieve higher arterial blood concentrations, increasing contact time with the vascular endothelium, decreasing the shear forces on drug molecules that will displace drug entities from the vascular endothelium, and minimizing non-specific binding with blood proteins and cell elements.

Table 38.2 Strategies for IA injection

Technique	Rationale	Application
Intracarotid drug delivery	Treatment to entire hemisphere	Multifocal or diffuse tumor
Continuous intracarotid infusion	Low-dose infusion with systemic rescue over days	Tumor treatment
Super-selective infusions	Increasing local delivery	Focal tumor
Super-selective pulse delivery	Avoids streaming and consequently more homogenous delivery	Local drug interventions
Diastolic phase pulsations	Avoids streaming and consequently more homogenous delivery	Tumor treatment
Fractional drug delivery	Minimizing local toxicity, safer drug delivery	Tumor treatment
Flow arrest pulse delivery	Improved local targeting	Tumor treatment
IA infusion with hemoperfusion	Decreases systemic toxicity	Tumor treatment

38.5 IA Chemotherapy Treatments

While the benefits of IA chemotherapy for brain tumors remain unproven, IA chemotherapy has achieved clinical acceptance for the treatment of two cancers: retinoblastoma and advanced metastatic liver cancer. The issues to explore here are the differences in chemotherapy of brain tumors versus non-central nervous system cancers. In the case of liver cancer, most are perfused by the hepatic artery, while the normal liver tissue is perfused by the portal vein enabling selective tumor targeting. There is also the low risk for embolic injury to the liver permitting the use of larger particles (20–50 μm) with targeted chemo- and radiotherapy. Finally, liver tissue and tumors show a robust first-pass uptake of certain drugs such as 5-FU. Though care is needed in IA catheter placement in the liver, implantable infusion pumps have been used on an outpatient basis for chemotherapy delivery with improvement in survival times. The treatment of retinoblastoma poses different challenges and is closer to the treatment of brain tumors. IA chemotherapy for retinoblastoma is primarily used to avoid disfiguring surgery. Selective IA infusion of drug combinations can now be utilized allowing surgery to be avoided in a majority of patients. In some instances, IA chemotherapy has led to an improvement of visual function. Currently over 30 centers in the USA provide IA retinoblastoma treatments.

So why has IA chemotherapy for brain tumors not been equally as successful as that seen with some other cancers? Given the physiological complexity of brain, the high resting cerebral blood flow, the presence of a blood-tumor barrier, and the potentially catastrophic effects of embolic injury, the limitations of IA chemotherapy for brain tumor treatment are obvious. Compounding the problem further is the refractoriness of malignant brain tumors to virtually all treatment modalities.

Although IA treatments have been used for over 60 years, most applications represent the off-label use of conventional intravenous drugs. Though drugs are sometimes assessed for IA

delivery in preclinical trials, they are seldom screened or developed specifically for IA applications. We believe that the greatest hurdle to effective IA treatments for brain tumors is the ability to achieve uniform, effective, and safe drug delivery. Given that the high arterial concentrations generated by IA injections are exceedingly brief, it is of paramount importance that drugs are rapidly extracted and retained by the tumor after such an injection.

The general complexity of cerebral circulation at a regional level is usually dichotomously perceived to follow a gray and white matter pattern. Such a simple description in regional brain perfusion is misleading because there are at least six patterns of regional cerebral perfusion with differing lengths of penetrating arteries and arterioles. Furthermore, the vascular anatomy of malignant glioma is not restricted to a single feeding artery. The tumor supply is diffuse and can bridge arterial distributions. As the disease advances, pathological changes can lead to regional variations within the tumors from regions of angiogenesis to ischemic necrosis and frank hemorrhage. IA treatments must offer greater effectiveness for drug delivery in such a heterogeneous tissue environment.

38.6 Future Perspective and Conclusion

IA chemotherapy has been used successfully in the treatment of liver cancer, retinoblastomas, locally invasive breast cancer, pancreatic cancer, urogenital malignancies, penile cancer, and extracranial head and neck cancers. While progress has been made in the treatment of these and other cancers, interest in IA treatment of brain cancers has generally declined. This is primarily due to the observed neurotoxicity in the absence of a demonstrable improvement in survival. In the future it is likely that knowledge of a brain tumor's genetic profile will inform our selection of patients who are most ideal for IA treatments. We believe that the vast potential of IA drugs remains unexploited for the treatment of brain pathology. Presently, drugs are seldom screened or specifically formulated for IA applications. Unless drugs are specifically developed for rapid brain uptake with utilization of precise injection parameters, the success with IA treatments will be limited.

Key Points

- IA drug delivery protocols are still in the early stages of evolution. Effective IA drug delivery to a complex organ such as the brain is far from being fully understood and optimized.
- IA drug delivery is primarily a hydrodynamic problem. The pharmacokinetic issues remain downstream of the hydrodynamic factors that affect IA drug delivery.
- The central concept of IA drug delivery is to ensure rapid uptake of the drug during its first pass through the cerebral circulation.
- The selectivity of drug IA delivery to target site can be greatly increased if the drug is rapidly cleared from systemic circulation.
- A challenge with IA drug delivery is that an arterial irrigation may contain gray matter, white matter, as well as the pathology that is being targeted.
- IA chemotherapy has been used successfully in the treatment of liver cancer, retinoblastomas, locally invasive breast cancer, pancreatic cancer, urogenital malignancies, penile cancer, and extracranial head and neck cancers.

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