Management of Elevated Intracranial Pressure

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Introduction

Intracranial pressure (ICP) is defined as the total pressure within the intracranial vault. Much of neurocritical care is focused on the diagnosis and management of increased ICP. Many of the patients admitted to the neurocritical care unit will have diagnoses associated with increased ICP such as intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), subdural hematoma (SDH), ischemic stroke, and hydrocephalus. Elevated ICP has been associated with poor outcomes. It is known from the TBI literature that survival is worse for patients with elevated ICP above 40 mmHg [1].

This chapter will outline the pathophysiology of increased ICP and will discuss the diagnosis and treatment of patients with sustained increases in ICP.

Intracranial Anatomy and Physiology

Anatomy

The contents of the intracranial vault represent a fixed volume, consisting of brain tissue (87%), cerebrospinal fluid (CSF) (9%), blood vessels (4%), and meninges (<1%) [2, 3].

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The average total volume of the intracranial contents is 1700 mL, with brain tissue occupying 1200–1400 mL, CSF volume ranging from 70 to 160 mL, and blood occupying 150 mL. An additional 10–25 mL of CSF can be contained in the spinal subarachnoid space. The intracranial components are divided into several compartments by dural membranes. The two cerebral hemispheres are divided by the falx cerebri, the superior edge of which is attached to the superior sagittal sinus with the free edge attached to the inferior sagittal sinus. The supratentorial (cerebral hemispheres) and infratentorial (brainstem and cerebellum) fossae are separated by the tentorium cerebelli. These dural septa are fibrous and fairly rigid, with the tentorium cerebelli being significantly less flexible as about three-quarters of it are tethered in place [3]. Compression of brain tissue against these septa plays a key role in herniation syndromes (described in the next section).

The close proximity of several intracranial structures results in susceptibility to compression and injury, leading to distinct clinical findings. Among the cranial nerves, involvement of the oculomotor nerve is perhaps the best recognized and can aid in the diagnosis of herniation syndromes. The oculomotor nerve exits from the ventral surface of the midbrain where it travels between the superior cerebellar and poster cerebral arteries before running along the posterior communicating artery (PCOM) and finally penetrating the petroclinoid ligament to enter the cavernous sinus. The oculomotor nerve also courses directly inferior to the medial edge of the temporal lobe, putting it at risk of compression by a herniating uncus. Compression of the oculomotor nerve by either the uncus or PCOM can compress the pupillodilator fibers along the dorsal surface of the nerve leading to a unilateral dilated pupil. The abducens nerve exits the ventral surface of the pons and runs along the midbrain before also entering the cavernous sinus. While mass lesions usually do not result in compression of the abducens nerve unless affecting the cavernous sinus, abducens nerve paralysis is a sign of increased ICP (discussed below). The trochlear nerve is unique in that it exits the midbrain dor-

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sally just inferior to the inferior colliculi, courses ventrally near the oculomotor nerve, and passes through the petroclinoid ligament to enter the cavernous sinus. The trochlear nerve may be injured due to trauma, since displacement of the brainstem into the edge of the tentorium may result in superior cerebellar peduncle hemorrhage with involvement of the trochlear nerve nucleus or exiting fibers [4]. The basilar artery lies on the ventral surface, giving rise to the superior cerebellar arteries before the tentorial opening and then branches off into the posterior cerebral arteries (PCA). The PCAs run along the medial surface of the occipital lobe and are susceptible to compression when tissue herniates through the tentorium. The only opening in the skull through which brain tissue can exit is the foramen magnum, at the inferior end of the posterior fossa. This opening plays an important role in herniation, given the close proximity of the medulla, cerebellar tonsils, and vertebral arteries. Compression of the cerebellar tonsils against the foramen magnum can contribute to infarction and tissue edema [3].

Physiology

The choroid plexus is located on the floor of the lateral, third, and fourth ventricles and is the major site of CSF production. The average rate of CSF formation is 21–22 mL/hour, resulting in about 500 mL/day. After its formation, CSF flow is driven by arterial pulsations transmitted to the choroid plexus. CSF leaves the lateral ventricles and travels through the third ventricle, cerebral aqueduct, fourth ventricle, and then through the foramina of Magendie and Lushka. The CSF then fills the perimedullary space and travels around the brainstem rostrally into the basal cisterns, through the tentorial aperture and bathes the surfaces of the cerebral hemispheres where it is reabsorbed through the arachnoid villi [2].

The cranium and dura form a rigid container, therefore a change in the volume of brain, blood, or CSF occurs at the expense of one of the other two in accordance with the Monro-Kellie doctrine. As mentioned above, only an additional 25 mL of CSF may be contained in the spinal subarachnoid space, therefore relatively small increases in brain parenchymal volume results in CSF displacement out of the intracranial space. The CSF space is in equilibrium with capillary and prevenous vasculature; however, changes in arterial pressure have minimal effect on ICP due to cerebral autoregulation [2]. Cerebral perfusion pressure (CPP) is dependent on ICP according to the following equation: CPP = MAP-ICP, where MAP = mean arterial pressure. Cerebral blood flow (CBF) is also directly proportional to CPP via the relationship CBF=CPP/CVR, where CVR = cerebrovascular resistance [5]. ICP is typically around 8 mmHg, and cerebrovascular autoregulation typically holds CBF relatively constant over a range of ICP and CPP values [2]. As CPP increases, CVR correspondingly increases, with the converse also being true. The brain also exerts tight control over MAP. The aortic depressor nerve (a branch of the vagus nerve) senses pressure at the aortic arch, while the carotid sinus nerve (a branch of the glassopharyngeal nerve) senses pressure at the carotid bifurcation. Both nerves terminate on the nucleus of the solitary tract, which provides input to the caudal ventrolateral medulla. The ventrolateral medulla provides inhibitor input to the tonic vasomotor neurons in the rostral ventrolateral medulla. The solitary tract also provides excitatory input to the cardiac decelerator neurons in the nucleus ambiguus. Thus, the brain is able to tightly regulate MAP and heart rate [6]. However, at MAP of 40 mmHg or lower or 150 mmHg or greater, autoregulation fails leading to a decrease or increase in CBF. Acute brain injury such as stroke, TBI, or hemorrhage can also impair the ability to autoregulate, given that it is an energy-dependent process requiring adenosine triphosphate (ATP) for arteriolar dilation or constriction [7]. Therefore, in neurocritically ill patients, CBF may linearly increase with CPP as autoregulation breaks down. On the other hand, autoregulation plays little role on the venous circulation such that increases in venous pressure lead to a relatively quick increase in ICP by increasing the volume of blood in cerebral veins and sinuses. This also explains the quick increases in ICP with maneuvers that increase intrathoracic pressure such as Valsalva, coughing, sneezing, and straining [8].

Diagnosis of Elevated ICP

Clinical Symptoms

Increases in ICP typically present with several early, relatively nonspecific clinical symptoms. The most consistently reported early symptoms include headache, nausea, and vomiting. While the exact mechanisms resulting in headache are unclear, it is likely that increased ICP activates pain receptors in the blood vessels and meninges [3]. Headache may be particularly prominent in patients who have increased ICP secondary to cerebral sinus thrombosis or other etiologies of cerebral venous obstruction. In this case, headache likely results from irritation of the sinus itself. The vomiting reflex is coordinated by neurons in the ventrolateral medullary tegmentum near the nucleus ambiguus. Increased ICP produces vomiting by causing pressure on the floor of the fourth ventricle. This commonly occurs due to the ICP pressure wave produced after the ictus of SAH [3].

Numerous other clinical symptoms have been reported to be associated with early signs of increased ICP. A notable complaint is a brief loss of vision upon standing, which has been termed visual obscurations. This occurs when perfusion

decreases, often after standing up, with a concomitant failure in autoregulation of the posterior circulation leading to brief occipital lobe ischemia. Other symptoms include, but are not limited to: confusion, agitation, air hunger, nasal itch, blurred vision, dysphagia, opsithotonus, facial twitching, pallor, sweating, thirst, salivation, yawning, hiccoughing, and urinary incontinence [3]. While none of these symptoms are specific for increased ICP, the treating provider should take into account the constellation of symptoms and evaluate for causes of elevated ICP as necessary. In patients whose ICP is not controlled, these symptoms often progress to confusion and disorientation followed by impaired level of consciousness. In patients with SAH, an immediate spike in ICP after aneurysmal rupture equilibrates ICP with MAP with a subsequent drop in CPP that may result in loss of consciousness. After the aneurysm tamponades and stops bleeding, ICP decreases, allowing CPP to return to normal levels with restoration of consciousness [3, 9].

Physical Examination Findings and Herniation Syndromes

Several physical examination findings should raise concern for elevated ICP in the appropriate clinical situation. Papilledema occurs in the setting of ICP elevation due to a pressure differential across the optic nerve. The optic nerve is surrounded by dura and arachnoid sheaths putting the exterior of the nerve in communication with the CSF and subarachnoid space [10]. However, the retinal ganglion cells are subject to intraocular pressure. Thus, patients with increased ICP are exposed to a pressure differential across the optic nerve. A high-pressure gradient leads to axoplasmic flow stasis and swelling of the optic nerve fibers with subsequent leakage of fluid into the extracellular space [10].

The abducens nerve is often affected early due to elevated ICP. As mentioned above, it emerges from the ventral surface of the pons and enters the subarachnoid space, penetrating the dura to enter Dorello's canal before coursing along the midbrain and entering the cavernous sinus. The abducens nerve is susceptible to compression due to increased ICP while it passes through the osteofibrous Dorello's canal [11].

As a mass lesion increases causing ICP to rise, CSF is displaced into the lumbar cistern in order to compensate. When little CSF is left to be displaced, compliance becomes very poor, such that small increases in the size of a mass may lead to substantial increases in ICP. Herniation occurs when there is little or no CSF volume left to displace, and part of the brain parenchyma is displaced into a neighboring compartment with lower pressure. Seven primary patterns of herniation occur: subfalcine herniation, lateral displacement of the diencephalon, uncal herniation, central transtentorial herniation, rostrocaudal brainstem deterioration, tonsillar herniation, and upward brainstem herniation [3].

When a hemispheric mass lesion compresses the cerebral hemisphere medially against the falx, subfalcine herniation occurs. The medial wall of the cerebral hemisphere may develop ischemia due to compression of the pericallosal and callosomargial arteries against or underneath the falx. Compression of the anterior cerebral artery can also occur. Lateral displacement of the diencephalon can be monitored by displacement of the pineal gland, and correlates well with the degree of impairment in consciousness (0–3 mm results in alertness, 3–5 mm in drowsiness, 6–8 mm with stupor, and 9–13 mm with coma) [12].

With uncal herniation, a lesion located relatively laterally in the cerebral hemisphere displaces the medial edge of the temporal lobe over the free tentorial edge into the tentorial notch. As the dorsal surface of the oculomotor nerve is compressed by the herniating uncus, the ipsilateral pupil becomes dilated and may become fixed. Eye movement abnormalities also occur due to third nerve compression and may be elicited by examining oculocephalic responses, as the patient may not be sufficiently awake to be able to follow commands. Impaired consciousness is almost always present by the time a fixed and dilated pupil has occurred. Consciousness can be affected by distortion of the ascending arousal systems passing through the midbrain or compression of the diencephalon. Hemiparesis also occurs as the uncus compresses the cerebral peduncle. Paresis can be either ipsilateral or contralateral. Contralateral paresis occurs when the uncus compresses the adjacent cerebral peduncle, while ipsilateral paresis occurs when the contralateral cerebral peduncle is compressed against Kernohan's notch [13]. The posterior cerebral artery is often compressed in the tentorial notch and can lead to occipital lobe infarction [3, 14].

Central transtentorial herniation results from pressure on the diencephalon. As vessels of the circle of Willis are stretched and compressed, coma results due to ischemia of the ascending arousal system as it passes through the diencephalon. Ischemia results in edema and a cycle of more shift and compromise of blood supply. As shift becomes severe enough, the pituitary stalk may be sheared, leading to diabetes insipidus, a finding usually occurring late in herniation near brain death. A particular pattern of herniation termed Parinaud's syndrome occurs when a mass compresses the dorsal aspect of the midbrain. The syndrome consists of impaired upgaze, impaired convergence, and retractory nystagmus [3].

Rostrocaudal deterioration occurs when the brainstem is displaced, causing impaired vascular supply. Paramedian ischemia results from downward displacement of the brainstem when the medial perforating branches of the basilar are stretched, since they are relatively fixed in place. Duret hemorrhages can occur, which are slit-like hemorrhages that are characteristically seen in the brainstem. The vein of Galen can also be compressed as it runs along the dorsal surface of the midbrain; however, venous insufficiency is typically not a major factor [15].

Tonsillar herniation occurs when a sudden increase in pressure in the posterior fossa pushes the cerebellar tonsils against the foramen magnum, compressing the medulla and causing variable degrees of compression of the fourth ventricle. Compression of the medulla may impair spontaneous respiration, and there may be a compensatory increase in blood pressure to improve perfusion. Increased pressure in the posterior fossa can also result in upward herniation through the tentorial notch. The superior cerebellar vermis and midbrain can compress the dorsal mesencephalon and also the cerebral aqueduct causing hydrocephalus [3].

A relatively late sign of increased ICP is the Cushing response (CR), which is characterized by respiratory irregularities, arterial hypertension, and bradycardia [6]. This occurs when pressure is applied to the floor of the medulla and once a mass has reached a particular volume independent of its rate of expansion [16].

Causes of Increased ICP

Several conditions may contribute to elevated ICP. Commonly, a cerebral or extracerebral mass may elevate ICP. This may be due to a brain tumor, stroke with subsequent edema, trauma, hemorrhage (parenchymal, subdural, or epidural), or abscess. The ictus of aneurysmal rupture after SAH results in increased ICP due to the sudden inflow of arterial blood. Global brain edema may occur due to anoxic injury, hepatic failure, hypertensive encephalopathy, hypercarbia, or Reye syndrome [3]. As mentioned above, increases in venous pressure can also increase ICP and can occur from sinus thrombosis, heart failure, or mechanical obstruction of the venous sinuses. CSF flow obstruction or impaired absorption can also increase ICP, with obstruction of CSF flow leading to hydrocephalus. Meningeal disease from infection or malignancy can impair CSF flow and increase ICP. Finally, any process that increases CSF volume will increase ICP. This can occur in the context of meningitis or SAH. Occasionally, ICP may be increased from increased CSF production caused by a choroid plexus tumor [3, 17].

ICP most commonly leads to symptoms by compromising cerebral arterial perfusion. As ICP increases, a larger gradient must be overcome by the systemic arterial circulation to provide adequate perfusion to the brain. As perfusion pressure drops below that necessary to maintain ionic gradients across cell membranes, more edema develops further increasing ICP and decreasing perfusion in a vicious cycle. Two main types of edema exist: cytotoxic and vasogenic. Cytotoxic edema results from energetic failure and the inability to maintain ionic gradients, while vasogenic edema occurs due to extravasation of plasma proteins into the brain interstitial fluid. Different methods for treating increased ICP are effective against particular types of edema. The pathophysiology and natural history of different types of edema have been expertly reviewed elsewhere [18] and will be briefly discussed below.

After ischemia, lack of blood flow limits the availability of ATP and results in energetic failure. Cytotoxic edema occurs due to the cellular influx of osmolites (sodium and chloride). As active transport fails, cells take up sodium primarily through secondary active transport. As ions accumulate intracellularly, a transmembrane gradient forms providing the driving force for water to enter cells, leading to swelling. As mentioned above, swelling can compress nearby tissue, further compromising blood supply and leading to energetic failure and edema. Uptake of calcium can also trigger cellular apoptosis [19].

Vasogenic edema occurs due to permeability of the blood-brain barrier (BBB) allowing extravasation of water and plasma proteins into the brain interstitium. Vasogenic edema occurs as a result of paracellular transport past endothelial cells. Endothelial cells undergo rounding and retraction after ischemia or inflammation leading to increased permeability. Hydrostatic pressure is the main driving force behind vasogenic edema [20], which means that intracranial pressure and blood pressure are still important driving forces. Primary brain tumors and brain metastases produce angiogenic factors promoting the growth of new capillaries with abnormal ultrastructure and abnormal BBB with leaky tight junctions [21–23]. In addition to the abnormalities in the tumor blood vessels themselves, the effects of cytokines, most importantly vascular endothelial growth factor (VEGF), may affect blood vessels near the tumor. VEGF binds to its ligands on the endothelial cell surface called tyrosine kinase receptors flt-1 (VEGFR-1) and Flk-1/KDR (VEGFR2) [24, 25]. VEGF triggers decreased expression of tight junction proteins [26, 27], thereby increasing vascular permeability and promoting the formation of edema [28]. However, VEGF is not only expressed by tumors but also as a result of stroke or TBI [29–31]. Therefore, patients who initially develop cytotoxic edema may progress to developing vasogenic edema.

Algorithm for Management of ICP

Once a patient is suspected to have increased ICP, a series of medical and surgical treatments can be instituted. While the exact sequence may vary from patient to patient, our suggested algorithm is summarized in Fig. 1.1.

Elevated ICP is often first recognized either in the emergency department or by emergency medical services prior to hospital arrival. Initial treatments can include several simple and noninvasive maneuvers. The patient's head should be maintained at 30°. The patient's head and neck should be maintained in a neutral position in order to avoid any obstruction to venous outflow. If central access is emergently

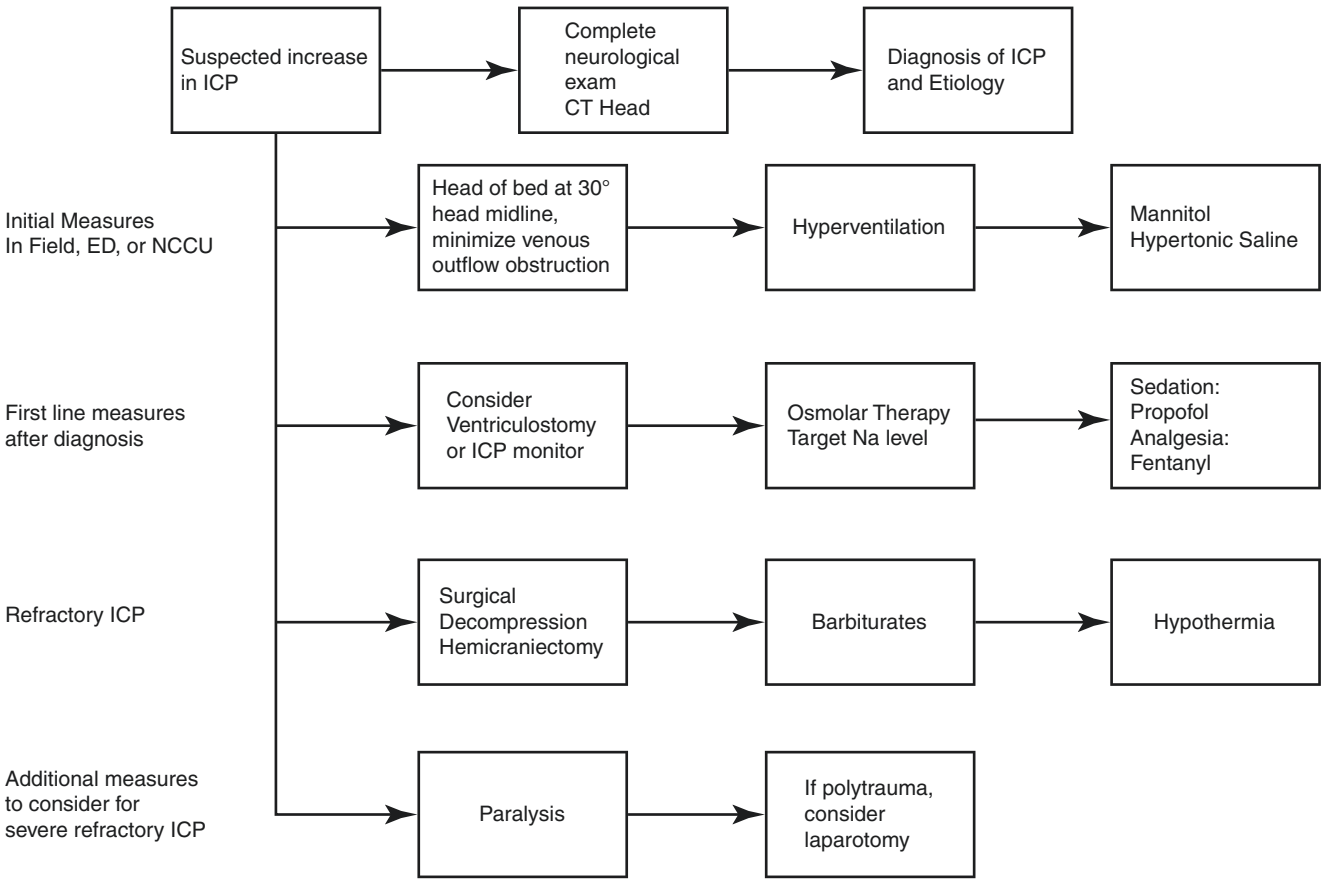

Fig. 1.1 Algorithm for the management of increased ICP. Suggested individual steps are listed after clinical suspicion for increased ICP. Abbreviations: ICP: intracranial pressure, CT: computed tomography

needed, we recommend placement of a femoral central venous catheter (CVC). This prevents any possible obstruction of venous outflow from an internal jugular CVC, and obviates the need to lie the patient flat or in Trendelenburg position, which can lead to herniation [32].

As with any critically ill patient, airway, breathing, and circulation must be addressed initially. Many patients with increased ICP will have depressed levels of consciousness and will require intubation for airway protection [33]. While intubation should not be delayed unnecessarily, it is often helpful to document a neurological examination prior to intubation. Generally, intubation is recommended for patients with Glasgow Coma Scale (GCS) less than eight. This is reflected in the Brain Trauma Foundation guidelines [34]. Rapid sequence intubation (RSI) is commonly recommended when patients have not been fasting, in order to prevent vomiting and aspiration. Succinylcholine is an option for short-term neuromuscular blockade; however, it has been associated with small elevations in ICP along with rhabdomyolysis and hyperkalemia. Rocuronium is likely a safer alternative in patients with elevated ICP, seizures, or following prolonged immobilization [35]. Hypotension is a common problem encountered during intubation and should be dealt with cautiously given that impaired cerebral autoregulation in the neurocritical care population puts patients at risk for decreased cerebral perfusion pressure (CPP) with significant decreases in mean MAP. Use of propofol or fentanyl for induction have been associated with significant hypotension secondary to vasodilation [36]. Etomidate is an alternative and causes less vasodilation and thus less hypotension. However, care must be taken with its use in patients in status epilepticus or at high risk for seizures, since it can lower seizure threshold [37–39].

Once the patient has been stabilized, a computed tomography (CT) scan of the head should be obtained. This is pivotal for diagnosing the etiology of the increased ICP and determining if there is radiographic evidence of herniation. After recognizing the clinical signs of increased ICP and typically around the time the patient is being taken for CT, hyperventilation is often the most readily available treatment modality. Hyperventilation may be utilized after the patient's airway has been secured by intubation as well as in those not yet intubated by utilization of a bag valve mask. Hyperventilation reduces ICP by decreasing PCO_2 in the

blood and CSF, which leads to cerebral vasoconstriction and decreased cerebral blood volume. Hyperventilation results in a rapid decrease in ICP; however, prolonged use of hyperventilation is not recommended given gradual loss of effectiveness and the risk of cerebral ischemia due to vasoconstriction. However, hyperventilation is very useful for patients in the emergency department when increased ICP is suspected as a bridge to initiation of osmolar or surgical treatment. We also use hyperventilation once the patient is in the neurocritical care unit after recognition of an ICP crisis. Jugular bulb oximetry may aid in the detection of cerebral hypoxia [40]; however, in practice it is seldom used. In patients with ICP crisis or showing signs of herniation, $PaCO_2$ can be transiently targeted to 25 mmHg [5, 40].

While the airway is being secured and hyperventilation provided, osmotherapy should be instituted. Mannitol is often the first agent administered and can be given without central venous access. Mannitol is usually made as a 20% solution and administered as a bolus. The dose ranges from 0.25 to 1 gram/kg; however, if there is concern for uncontrolled ICP, we suggest bolusing with 1 gram/kg initially. Given the profound diuresis that can occur after administration of mannitol, the provider should be careful to avoid hypotension from intravascular volume depletion. Hypertonic saline (HTS) may also be used, alone or in conjunction with mannitol. HTS may be given as a bolus of either 2% or 3% solutions, or if central access is available, a 30 mL bolus of 23.4% may be given. While HTS has the advantage of not resulting in diuresis, subsequent volume overload may be an issue in patients with decompensated heart failure or pulmonary edema.

It is around this stage in management that a decision should be made regarding placement of an ICP monitor or external ventricular drain for CSF diversion. Invasive ICP monitoring is generally indicated for patients with GCS<8 and with evidence of mass effect on head CT. While there is significant clinical equipoise, ICP monitoring should also be considered in patients who show signs of posturing on clinical examination or who have a systolic blood pressure less than 90 mmHg, particularly in those patients older than 40 years of age. The specific types of ICP monitors are discussed later. In patients with obstruction to CSF flow from intraventricular hemorrhage or from mass effect, placement of an external ventricular drain (EVD) is preferred. An EVD not only provides the ability to monitor ICP, but also allows ICP to be treated by CSF diversion. In patients with TBI or with slit-like ventricles making placement of an EVD impossible, a parenchymal ICP monitor can be placed [40].

Sedation can be a valuable tool in ICP management. Agitation can increase ICP by increasing the cerebral metabolic rate. ICP can also be affected if agitation results in increased MAP or increased thoracic pressure. Fentanyl can be used to treat agitation, either in boluses or as a continuous infusion. However, providing sedation with propofol is often a more effective way to control ICP. In a patient whose airway has already been secured and who experiences a sustained increase in ICP, a bolus of propofol can be administered with or without initiation of a continuous infusion [41]. More detail regarding other available agents, and the relevant pharmacology and side effects, will be discussed in the next section.

In patients whose ICP remains poorly controlled despite osmotherapy and optimized sedation, consideration should be given to surgical decompression with hemicraniectomy. By removing the rigid constraints of the skull, hemicraniectomy can allow for expansion of brain tissue outside of the cranial vault, thereby eliminating downward pressure on the midbrain and brainstem. In many cases hemicraniectomy can be pursued prior to initiating other therapies such as hypothermia or barbiturate-induced coma. Hemicraniectomy has been found to be particularly effective in patients with mass lesions and in those with malignant MCA stroke [42–44].

If ICP remains poorly controlled, consideration should be given to barbiturate-induced coma. The typical agent used is pentobarbital, and it lowers ICP by causing a marked decrease in the cerebral metabolic rate. Pentobarbital can be administered in 5 mg/kg boluses every 15–30 minutes until ICP is controlled. A continuous infusion at 0.5–5 mg/kg/hour with continuous EEG monitoring can then be instituted [45].

When all of the above methods have failed to adequately control ICP, hypothermia to 32–34°C can be used to lower ICP. Similar to barbiturates, hypothermia decreases ICP by suppressing cerebral metabolism. Hypothermia may be effective in patients who are refractory to barbiturates [46]. While effective at decreasing ICP, hypothermia is associated with numerous complications (discussed later), without clear evidence of improvements in functional outcomes.

If ICP remains poorly controlled despite all of the above interventions, last-ditch efforts have included the use of paralytic agents and laparotomy. Increased intraabdominal pressure can exacerbate ICP by transmission of pressure to the spinal subarachnoid space. Several small studies have demonstrated that laparotomy may be beneficial for decreasing refractory ICP [47, 48]; however, larger studies are needed to define its role in practice.

At every point during ICP management, consideration should also be given to whether a patient is having or at risk for seizures. Given that seizure activity raises ICP [49], seizures should be treated aggressively with benzodiazepines (lorazepam, midazolam, or diazepam) followed by or concomitantly with fosphenytoin, valproic acid, or levetiracetam. For patients at risk for increased ICP, there should be a low threshold for initiating continuous EEG (cEEG) monitoring given the high rate of progression to nonconvulsive status epilepticus (NCSE) [50, 51].

Monitoring ICP

It has long been thought that invasive monitoring of ICP is beneficial given the variable clinical signs of elevated ICP. In general, placement of an invasive ICP monitor is indicated in patients with a depressed level of consciousness (typically GCS<8), imaging revealing a mass lesion with cerebral edema, and a prognosis meriting aggressive care in the ICU [52]. ICP can be monitored using a number of different devices. An EVD is the gold-standard for measuring ICP and also allows for in vivo calibration and recalibration. In addition to being able to transduce ICP, an EVD has the advantage of being able to treat ICP by diverting CSF flow. An EVD should be placed whenever a patient has symptomatic hydrocephalus with GCS<8 [53–55]. In the NCCU, this commonly occurs in the setting of subarachnoid hemorrhage or ICH with intraventricular hemorrhage but can be caused by any obstruction to CSF flow. However, an EVD is associated with risks such as tract hemorrhage (up to 22%) [56] and ventriculitis (5.5–22%) [55, 57–59]. Parenchymal intracranial pressure monitors can also be used. While having a lower risk of infection and bleeding [52, 60], CSF cannot be drained to treat ICP. Furthermore, drift can occur after about 7 days, without the possibility to recalibrate [52, 60]. Intraparenchymal monitors are of most benefit in patients with low GCS and suspected high ICP without hydrocephalus, such as diffuse TBI or hepatic encephalopathy. ICP monitors can also be placed in the epidural or subarachnoid space [55], although this has largely fallen out of favor. While the Brain Trauma Foundation recommends monitoring ICP for patients with severe TBI [40], it remains unclear whether this intervention improves outcomes [61].

Drainage of CSF from an EVD can be performed continuously or intermittently. The question of which method is superior has recently been addressed. One study found that continuous drainage was associated with lower mean ICP values [62]. However, the study was relatively small and was not designed to assess differences in outcomes or mortality. Although there is not very strong evidence, our general practice is to allow for continuous CSF drainage that depends on a specific EVD pressure-based pop-off set by the provider.

Patient Triage and Flow

Management of increased ICP should begin upon a patient's initial presentation, which is often in the field before arriving to a hospital. Important measures can be taken in the prehospital setting and in the emergency department [63]. Signs of increased ICP (described above), including decreased level of consciousness, a unilateral dilated pupil, posturing, or changes in vital signs such as hypertension and bradycardia (Cushing reflex), may occur well before a patient reaches the NCCU. The head of the bed should be elevated to 30°C as soon as possible, while minimizing the time period that the patient is flat. This can be accomplished *en route* to the hospital by placing rolled blankets or towels beneath the patient's head [63]. In addition to the standard ABCs of resuscitation, an end-tidal pCO_2 of 28–32 mmHg can be targeted after intubation as a temporizing measure. Once in the emergency department, a CT of the head should be obtained as soon as possible to characterize whether a mass lesion is present. Mannitol can be given through a peripheral line before central access is established. If there is evidence of obstructive hydrocephalus contributing to increased ICP, neurosurgery should be consulted as soon as possible in order to facilitate ventriculostomy placement. This can occur in the emergency department if needed or on arrival to the NCCU. While a patient requiring ICP management can be managed in a number of different ICUs, data have emerged indicating that treatment in a dedicated NCCU staffed by neuro intensivists results in better outcomes and lower ICU lengths of stay [64–66].

Individual Methods for ICP Control

In the following sections, we will describe in more detail each individual method in the algorithm for ICP control. Current evidence and guideline recommendations are reviewed. Within each section, relevant pharmacology of each medication is discussed. Salient pharmacological features are summarized in Table 1.1.

Head Positioning

It is now common practice to maintain the head of bed at 30° in patients with elevated ICP. It has been recognized for decades that a moderate degree of head elevation is of benefit in decreasing ICP. As the head is raised, the weight of the CSF column is progressively displaced onto the lumbar subarachnoid space, thereby decreasing ICP. Raising the head also likely decreases intrathoracic pressure and improves venous outflow [67]. Concern has been raised in the literature that head elevation results in decreases in CPP, in some cases resulting in the occurrence of CSF pressure waves [68]. However, the preponderance of data currently available suggest that head elevation to 30° is effective in decreasing ICP without comprising CPP, cerebral oxygenation, or systemic hemodynamics [69–71]. On average, this maneuver results in 3–4 mmHg decrease in ICP. For any patient with suspected increases in ICP, we favor placing the head of bed at 30° and assuring minimal head rotation to limit obstruction of jugular venous outflow. We also try to minimize the amount of time any patient is flat. For this reason, when central access is needed emergently for a patient

Table 1.1 Relevant pharmacology. Dosing, monitoring, and side effects are listed for each category of medications used to treat ICP

	Medication	Dosing	Monitoring	Side effects
Osmolar Therapy	Mannitol	0.1–1 g/kg, every 4–6 hours	Osmolar gap, goal <20 mOsm/kg	Dehydration, hypotension, rebound edema, AKI, electrolyte abnormalities
	Hypertonic aline	Bolus of 23.4% Infusion or bolus of 2% or 3%	Target set Na range Na check every 8 hours on 2% Na check every 6 hours on 3%	Pulmonary edema, CHF exacerbation, osmotic demyelination, metabolic acidosis, coagulopathy
Sedation	Propofol	1–2 mg/kg bolus 5–100 μg/kg/minutes	BP, RASS, triglycerides, acid/base status, CK, LFTs, K	Hypotension, PRIS, anaphylaxis, hypertriglyceridemia
	Fentanyl	12.5–100 μg bolus 25–700 μg/hour infusion	Respiratory status, RASS	Respiratory depression, nausea, vomiting, diaphoresis
	Midazolam	0.01–0.05 mg/kg bolus 0.01–0.1 mg/kg infusion	Blood pressure, RASS	Hypotension, respiratory depression, anterograde amnesia
AEDs	Lorazepam	0.1 mg/kg IV push (up to 4 mg per dose)	Respiratory status, BP	Respiratory depression, hypotension
	Fosphenytoin	20 PE/kg loading dose 4–6 mg mg/kg/day maintenance	Target 10–20 μg/mL total or 1–2 μg/mL free level	Hypotension, bradycardia, numerous drug interactions
	Valproic Acid	20–40 mg/kg loading dose 10–15 mg/kg/day	Target 50–150 μg/mL level	Hepatotoxicity, hyperammonemia, thrombocytopenia
Barbiturates	Pentobarbital	5 mg/kg boluses every 15–30 minutes 1–4 mg/kg/hour infusion	Titrate to burst suppression on cEEG Can follow levels	Hypotension, cardiac depression, ileus, immune compromise
Paralytics	Vecuronium Cisatracunium	0.05–0.1 mg/kg bolus 0.05–1.5 μg/kg/minute infusion 0.1–0.2 mg/kg bolus 2–10 μg/mg/kg infusion	Follow TOF while paralyzed Maintain adequate sedation	Pneumonia, neuropathy, myopathy, anaphylaxis, malignant hyperthermia

Na sodium, *AKI* acute kidney injury, *CHF* congestive heart failure, *BP* blood pressure, *RASS* Richmond Agitation-Sedation Scale, *CK* creatine kinase, *LFTs* liver function tests, *PRIS* propofol related infusion syndrome, *K* potassium, *IV* intravenous, *cEEG* continuous electroencephalogram, *TOF* train of four

with ICP crisis, we advocate placing a femoral CVC rather than placing a patient flat or in Trendelenburg for placement of a subclavian or internal jugular CVC [32].

Hyperventilation

As described above, hyperventilation reduces ICP by decreasing $PaCO_2$, which decreases cerebral flow. Given its ability to reduce ICP, hyperventilation was once commonly used prophylactically for patients with increased ICP. However, there is evidence to suggest that prophylactic and long-term hyperventilation can be deleterious. In fact, the Brain Trauma Foundation provides a Level IIB recommendation against the use of hyperventilation for control of ICP [40]. In patients with TBI, outcomes were found to be worse in patients treated with prolonged hyperventilation [72]. Patients were randomized to normal ventilation, hyperventilation, or hyperventilation with tromethamine. Tromethamine treatment was added in order to counter the effects of loss of bicarbonate from the CSF after prolonged hyperventilation. For patients with a motor GCS of 4–5, the GOS scores at 3 and 6 months were significantly worse in patients being hyperventilated. There are a few possible explanations for the lack of benefit of hyperventilation. The effects of hyperventilation on cerebral artery diameter are transient, lasting at most 24 hours [73]. Furthermore, loss of bicarbonate from the CSF during prolonged hyperventilation may result in decreased buffering capacity and subsequent hypersensitivity to small changes in $PaCO_2$ [74]. While there

is concern that prolonged hyperventilation may contribute to ischemia by reduction of CBF [72], a significant reduction in CBF has not been demonstrated after prolonged hyperventilation given the compensatory increase in arterial oxygen extraction [72]. Overall, hyperventilation should not be used prophylactically or for prolonged ICP management. However, we believe that hyperventilation still plays an important role in treatment during ICP crises and will commonly use hyperventilation as a bridge to other treatments.

Osmolar Therapy

The utility of hypertonic solutions has been known since 1919 when Weed and McKibbon demonstrated that various salt and glucose solutions could lower ICP in cats. Cushing and Foley as well as Foley and Putnam obtained similar results. The first reported clinical use of hypertonic agents involved urea solutions in the 1950s [75]. Mannitol started to be used in the 1960s [76] with hypertonic saline (HTS) not being utilized until the 1990s [77].

Hyperosmolar therapy lowers ICP by creating an osmolar gradient, thereby providing a gradient for water egress out of the brain. In order for an osmolar agent to create an effective gradient, it must be impermeable to the BBB. The reflection coefficient describes the BBB permeability of a substance, ranging from 0 (complete permeability) to 1 (complete impermeability) [78]. The effectiveness of hyperosmolar therapy requires an intact BBB. In regions of the brain where the BBB is damaged, there is equilibration of molecules between blood and brain interstitial fluid. Therefore, ICP is mainly reduced via removal of water from portions of the brain with an intact BBB. The majority of the effect of hyperosmolar treatment occurs shortly after maximal osmolarity is reached. With ongoing increased serum osmolarity, the brain begins to accommodate. It has been known for decades that the brain is able to produce "idiogenic osmoles," which are now known to be polyols, amino acids, and methylamines produced by astrocytes as well as small proteins produced by neurons [79, 80]. Consequently, as serum osmolarity is decreased, rebound cerebral edema can occur given the reversal of the osmolar gradient favoring water entry into the brain.

The primary agents used to for hyperosmolar therapy are mannitol and HTS. Mannitol is a carbohydrate that increases serum osmolarity by dehydration as it acts as an osmotic diuretic. It also lowers blood viscosity and causes reactive vasoconstriction of cerebral blood vessels [81]. Mannitol is typically administered as a 20% solution with boluses of 0.25–1.0 gram/kg [82]. It can be dosed at intervals of 2–4 hours or longer, depending on the clinical situation. Mannitol exerts its effects within 10–15 minutes with a maximal effect by 20–60 minutes [83]. The effect of mannitol is typically monitored by following both calculated and measured serum osmolality. Laboratory studies including osmolality and basic metabolic profile should be drawn prior to giving a dose of mannitol. While an osmolality of greater than 320 mOsm/kg has been suggested as a cutoff for mannitol therapy, it is not an accurate measure of excess mannitol and can also be increased due to conditions such as hyperglycemia. The osmolar gap is more useful in the detection of remaining mannitol in the serum with an osmolar gap of >20 mOsm/kg indicating incomplete clearance. With incomplete clearance, mannitol can accumulate in regions of the brain with BBB permeability causing a reverse osmotic shift and rebound ICP elevation. Given its potent osmotic diuretic effect, mannitol can lead to acute kidney injury, dehydration, and hypotension. Electrolytes should also be closely monitored.

In comparison to mannitol, HTS directly increases serum osmolality rather than indirectly via diuresis [82]. It is typically administered as 2%, 3%, or 23.4% solutions. Frequent serum sodium checks should be performed for patients receiving HTS, with the goal of using the lowest dose possible. We typically monitor serum sodium every 8 hours for patients receiving 2% and every 4–6 hours for patients receiving 3% HTS. This agent results in fluid expansion and, unlike mannitol, does not contribute to significant diuresis. Furthermore, HTS has a reflection coefficient of 1.0 compared to 0.9 for mannitol and thus has a theoretically decreased risk of rebound cerebral edema [84, 85]. Given volume expansion secondary to HTS, caution should be used when treating patients with poorly controlled heart failure or pulmonary edema. The patient's baseline sodium should also be taken into consideration due to the risk of osmotic demyelination that may occur in patients with chronic hyponatremia in the context of precipitous increases in sodium concentration.

Studies have shown that hyperosmolar treatments are able to reverse transtentorial herniation [86]. However, controversy remains as to whether HTS or mannitol is more effective. Findings from one study suggested that HTS is more effective than mannitol in lowering ICP and decreasing the total number of ICU days, without having an effect on 2-week mortality [87]. Other studies have shown no difference in the average elevated ICP time or in 6-month outcomes [88].

Sedation

Sedative agents decrease ICP by lowering cerebral metabolic activity. Additionally, reduction in agitation may reduce the amount of Valsalva maneuvering and elevations in jugular venous pressure. Propofol is the most commonly

used sedative agent for ICP control. Propofol is a GABAa receptor agonist with a rapid onset and offset. While able to rapidly and effectively lower ICP, propofol has a number of side effects. Hypotension is often the first side effect encountered, and caution should be taken not to lower CPP. Propofol treatment can also lead to hypertriglyceridemia and pancreatitis, and triglyceride levels should be routinely monitored. The most common serious side effect is propofol-related infusion syndrome (PRIS), in which profound metabolic acidosis, hyperkalemia, hepatomegaly, renal failure, cardiac dysrhythmia, and heart failure occur. Propofol has been compared with morphine, with findings of decreased ICP on day 3 in the propofol group [41]. However, there were no significant differences between the two groups in mortality or GOS. In post hoc analysis, lower dose propofol treatment resulted in no difference in ICP control while being associated with significantly lower mortality [41]. The Brain Trauma Foundation gives a Level IIB recommendation to using propofol to control elevated ICP, although notes the lack of evidence regarding any improvement in mortality or 6-month functional outcomes [40]. Given the adverse side effects associated with high dose and long-term use of propofol, boluses of propofol (1–2 mg/kg IV) can be administered during periods of ICP crises in order to minimize use of continuous propofol infusions. Caution should be used and relevant laboratory values should be closely monitored in patients treated with propofol for longer than 48 hours or receiving doses greater than 5 mg/kg/hour to prevent development of PRIS.

Seizure Control

Seizure activity and especially generalized tonic-clonic seizures are associated with increased ICP [49, 89]. Increases in ICP are believed to be due to the increases in metabolism and blood flow secondary to epileptiform activity [90]. Therefore, in any patient in whom there is a concern for seizure, early treatment should be instituted in combination with continuous EEG monitoring if there is concern for subclinical seizures or status epilepticus. For patients actively seizing, the first line medication is a benzodiazepine. Lorazepam can be administered in doses of 0.1 mg/kg IV every 5–10 minutes. Alternatively, diazepam can be given at doses of 0.15 mg/kg IV every 5 minutes or midazolam can be given at doses of 0.2 mg/kg IV or IM. Patients with frequent seizures or in status epilepticus should also be loaded with fosphenytoin (20 PE/kg IV) or valproic acid (20–40 mg/kg IV). Newer studies have suggested that levetiracetam (20–330 mg/kg) is as effective in treating status epilepticus as phenytoin, and it has the advantage of fewer side effects and drug interactions [91, 92]. Patients with refractory status epilepticus may require a midazolam drip or burst suppression with pentobarbital in the most severe cases. Detailed discussion of the diagnosis and treatment of status epilepticus is provided in Chapter 2.

Hypothermia

Hypothermia is thought to decrease ICP by suppressing brain metabolism. It has been proven to be effective for the treatment of comatose survivors of cardiac arrest, where targeted temperature management has become the standard of care [93–95]. There was significant early enthusiasm for the use of therapeutic hypothermia in the treatment of increased ICP. However, there is no clear evidence regarding the benefit of hypothermia for this purpose. Furthermore, hypothermia is associated with significant side effects, including coagulopathy, immunosuppression, electrolyte imbalances, and cardiac dysrhythmia (Table 1.1).

Nonetheless, hypothermia has been used both prophylactically and for refractory intracranial hypertension. While studies have reported conflicting results regarding the prophylactic use of hypothermia, recent randomized controlled trials (RCTs) have not found a benefit. A large RCT in TBI patients in 2001 showed no difference in mortality or neurological outcomes when comparing normothermia to hypothermia [96]. A follow-up study enrolled patients within 2.5 hours of TBI but again found no difference in mortality or neurological outcomes [97]. It has been suggested that patients who received surgical hematoma evacuation and were cooled quickly benefited more than those with diffuse injury [98]. A large multicenter RCT (POLAR) is currently under way to more rigorously test the use of prophylactic hypothermia in TBI [99]. However, in light of the currently available evidence, the Brain Trauma Foundation gives a Level IIB recommendation against the use of early hypothermia [40].

Use of hypothermia for treatment of increased ICP has been less well tested. Early, small studies suggested that hypothermia was able to reduce ICP and improve outcomes [46]. In the more recent Eurotherm3235 trial, hypothermia did not result in improvement in ICP or better outcomes in patients with TBI and sustained elevations in ICP above 20 mmHg [100]. However, there is ongoing debate as to whether hypothermia may play a role in patients with refractory ICP with sustained elevations above 25 mmHg despite maximal medical therapy when CPP is adequately optimized.

The available evidence suggests that prophylactic use of hypothermia is not beneficial; and while able to lower ICP, it is unclear whether outcomes are improved when hypothermia is used in cases of refractory high ICP. Therefore, hypothermia should still be considered when other options have failed if it is felt that the benefits outweigh the risks.

Decompressive Craniectomy

As discussed above, cerebral edema can lead to increased ICP causing brain tissue to herniate into adjacent compartments. A wide craniectomy with duroplasty aimed at decompressing the frontal, parietal, and temporal lobes has been shown to be beneficial in reducing ICP. While numerous studies have shown that decompressive craniectomy is effective in lowering ICP [101, 102], the optimal timing remains to be established. The DECRA study compared early decompressive craniectomy for patients with standard medical therapy in patients with diffuse TBI [103]. In the craniectomy group, 70% of patients had an unfavorable outcome compared with 51% of patients in the standard medical therapy group. However, criticism of the DECRA study focused on the fact that the threshold for surgery (ICP >20 mmHg for >15 minutes) did not reflect typical clinical practice, where decompressive hemicraniectomy is typically reserved for ICP refractory to all medical interventions. The surgical group also likely had more severe TBI, and the study design allowed for a high rate of crossover from the standard medical therapy arm to the surgical arm [104].

More recently, the RESCUEicp trial evaluated the effectiveness of decompressive hemicraniectomy on clinical outcomes in TBI patients with elevated ICP (>25 mmHg) refractory to aggressive medical therapy [105]. The trial aimed to simulate clinical practice more closely as patients had to fail both stage 1 and 2 treatments before being considered for decompressive hemicraniectomy. Stage 1 treatments included sedation, analgesia, head elevation, and mechanical ventilation, while stage 2 treatments included osmolar therapy, ventriculostomy, and hypothermia. Barbiturates use was not allowed until failing stage 1 and 2 therapies and either being randomized to surgery or continued medical management. While hemicraniectomy improved mortality at 6 months, the proportion of patients with moderate disability and good outcomes were not improved [105]. Therefore, there are Level IIA recommendations from the Brain Trauma Foundation that craniectomy does not improve 6-month outcomes, though the procedure is able to effectively reduce ICP and may reduce the number of days spent in the ICU [40].

Another important issue is the size of decompressive craniectomy. A larger craniectomy is thought to more effectively decompress the intracranial contents and lower ICP. A small bone opening carries with it the potential risk of brain herniating through the opening with a mushroom cap appearance causing constriction and venous ischemia [106]. Studies have shown better outcomes for patients with larger decompressive craniectomies; however, the inclusion criteria and procedures varied [107, 108].

The role of decompressive craniectomy in patients with malignant MCA infarcts is more established. Several large RCTs have demonstrated the benefit of decompressive craniectomy in this population. Over 10 years ago, the DECIMAL and DESTINY trials showed that early decompressive craniectomy reduced mortality and resulted in more patients with moderate disability [43, 109]. The HAMLET trial confirmed the benefit of decompressive craniectomy within 48 hours of stroke onset [110]. The American Heart Association and American Stroke Association therefore recommend that there is Class I evidence for decompressive craniectomy in patients with unilateral MCA infarctions who deteriorate within 48 hours despite medical therapy [111]. DESTINY II showed that early decompressive craniectomy was also beneficial in stroke patients 61 years of age and older [43]. Of note, hemicraniectomy seems to be most beneficial for stroke patients when performed early, when the edema is likely predominantly cytotoxic. Relieving pressure by hemicraniectomy improves tissue perfusion and thus improves the energetic balance, allowing restoration of ionic gradients. If performed late, when patients have already developed vasogenic edema, hemicraniectomy will decrease tissue pressure resulting in a larger hydrostatic pressure gradient driving the efflux of plasma proteins and contributing to more cerebral edema [112, 113].

Barbiturates

Barbiturates have long been known to decrease ICP secondary to decreasing cerebral metabolism [114] in addition to decreasing coughing, movement, and Valsalva maneuvering. It has also been suggested that barbiturates inhibit oxygen radical-mediated lipid peroxidation, which may also contribute to lowering ICP [115–117]. Pentobarbital is the most commonly used barbiturate. Thiopental has also been used for ICP control. Some evidence suggests that treatment with thiopental results in better control of ICP as well as decreased risk of death at 6 months [118]. However, it is currently unavailable for clinical use in the United States. Pentobarbital is typically administered as a bolus of 5–15 mg/kg IV every 15–30 minutes until the ICP has been controlled. Thereafter a continuous infusion of 1–4 m/kg/hour can be initiated. During pentobarbital administration, continuous EEG should be recorded with a goal of achieving burst suppression with 6–8 seconds between bursts [50] Pentobarbital has been used both prophylactically and for refractory ICP. When compared with standard treatment, prophylactic use of pentobarbital resulted in no significant difference in mortality or GOS at 1 year, and 54% of patients in the pentobarbital group vs. 7% of controls developed hypotension [119]. Thus, the Brain Trauma Foundation has given a Level IIB recommendation against the prophylactic use of barbiturates for preventing increased ICP [40]. In 1988, Eisenberg et al. studied the use

of pentobarbital for refractory ICP [120]. The trial demonstrated that pentobarbital was effective in lowering ICP, and that those patients whose ICP responded had improved survival (92% vs, 17%). However, the utility of pentobarbital remains limited by its side effects. While pentobarbital decreases ICP, it lowers blood pressure, thereby lowering CPP. This may account for why treatment with pentobarbital does not result in any improvement in functional outcomes in patients being treated for increased ICP [116]. Additional side effects of pentobarbital treatment include cardiac suppression and ileus. We consider using pentobarbital for ICP control in patients refractory to other interventions provided they can be kept hemodynamically stable, in line with the Level IIB recommendations issued by the Brain Trauma Foundation [40].

Steroids

Glucocorticoids have both genomic and nongenomic effects. After diffusing through plasma membranes, glucocorticoids bind to their cytoplasmic receptor, which results in the exposure of its nuclear localization signals allowing the movement of the glucocorticoid-receptor complex into the nucleus. Glucocorticoids bind to glucocorticoid response elements (GREs) in order to regulate the transcription of nuclear DNA. This results in the transcriptional downregulation of several key inflammatory cytokines such as IL-1β, IL-4, IL-5, and IL-10 [121]. Glucocorticoids also exert anti-inflammatory effects by interfering with NF-κB signaling [122]. As mentioned above, vasogenic edema occurs in the context of increased vascular permeability. Steroids are thought to reduce the permeability of capillaries surrounding tumors [123–125]. Steroids affect the ability of molecules to transfer across the BBB, and have been shown to decrease the amount of peritumoral water without affecting perfusion [126, 127].

Steroids have long been known to be of benefit in the perioperative management of patients with brain tumors [128, 129], and still play an important role in neurocritical care. Steroid treatment remains invaluable in the treatment of increased ICP secondary to tumor-related edema. Dexamethasone is the most commonly used corticosteroid due to its long half-life and low mineralocorticoid activity. Typically, dexamethasone is administered in a 10–20 mg intravenous dose at presentation with tumor-related neurological symptoms in the brain or spinal cord. The dose can be increased up to 100 mg per day with daily maintenance doses usually ranging from 4 to 24 mg in divided doses [130].

Given its success in treating neurological symptoms in patients with brain tumors, steroids have been studied for use in ICP control in other disease processes. The available evidence in TBI suggests that steroids are not beneficial. An RCT consisting of 957 patients with severe TBI conducted in 1998 demonstrated that treatment with tirilazad mesylate (a synthetic 21-amino steroid) had no benefit with respect to death or outcomes [131]. In 2004, the Corticosteroid Randomization After Significant Head Injury Trial (CRASH) studied treatment with either 2 g intravenous methylprednisolone followed by 0.4 mg/hour for 48 hours or placebo. There was an increase in mortality at 2 weeks (21.1% vs. 17.9%, relative risk (RR) 1.18%) and 6 months (25.7% vs 22.3%, RR 1.15) when comparing corticosteroid vs. placebo, respectively [132, 133]. There was also a higher percentage of patients with severe disability at 6 months in the corticosteroid group (38.1% vs 36.3%), although this did not reach statistical significance [132, 133]. The Brain Trauma Foundation has therefore issued a Level I recommendation against the use of steroids in TBI for either improving outcomes or ICP [40].

While not shown to be of benefit in TBI, the use of steroids has become more popular in the treatment of SDH. Localized inflammation occurs after SDH promoting angiogenesis, and perioperative steroid use results in higher survival and lower risk of SDH recurrence [134]. The Steroids in Chronic Subdural Hematomas (SUCRE) trial is a double-blind, randomized trial currently under way that will help to elucidate the role of steroids in the management of SDH [135]. While steroid use remains controversial after aneurysmal SAH, there is some evidence to suggest that dexamethasone treatment may improve outcomes [136], especially in those patients who undergo microsurgical clipping but not endovascular coiling [137].

Care should be taken when using steroids given the large number of potential side effects, which are typically associated with the dose and length of steroid treatment [138]. However, the most common side effects encountered with acute use of steroids in the ICU are insulin resistance leading to hyperglycemia and myopathy [139]. Additional systemic side effects are various and include development of a cushingoid appearance, truncal obesity, hirsutism, acne, impaired wound healing, easy bruising, hypertension, immunosuppression, cataracts, gastrointestinal bleeding, and osteoporosis, among others [139]. Additionally, dexamethasone has several important drug interactions. By inducing CYP3A4, phenytoin increases the clearance of dexamethasone and decreases its plasma half-life by up to 50% [140–142]. Carbamazepine and phenobarbital may also induce metabolism of dexamethasone [143].

Paralysis

Paralysis with neuromuscular blocking agents has been used for ICP control. Paralysis facilitates the lowering of ICP by preventing shivering and coughing and also by decreasing overall energy expenditure [144–148]. It also facilitates mechanical ventilation, allowing for optimization

of pCO_2 and oxygenation [149]. Paralytics may decrease the pro-inflammatory effects of mechanical ventilation [150]. Paralytic agents work by interrupting signal transmission at the neuromuscular junction and can be depolarizing (succinylcholine) or non-depolarizing (all others). Succinylcholine is depolarizing as it mimics the action of acetylcholine, while the other agents are competitive acetylcholine antagonists. Interactions can occur with drugs that inhibit plasma cholinesterase activity. Given that there is no effect on consciousness, adequate sedation and analgesia must always be used in patients receiving paralytics. Suggested dosing is listed in Table 1.1.

Strong evidence does not exist for the use of paralysis in ICP control. Of concern, two studies have shown that use of succinylcholine can lead to increases in ICP [151, 152] Two retrospective studies assessing prolonged used of paralytics found no improvement in outcomes and demonstrated an increased frequency of complications such as pneumonia [153, 154]. In addition to the risk of pneumonia, use of paralysis is also associated with development of critical illness neuropathy and myopathy [155, 156]. Other side effects include anaphylaxis, cardiac arrest and arrhythmias, malignant hyperthermia, hyperkalemia, jaw rigidity, rhabdomyolysis, and myalgias. Given the associated side effects and lack of evidence regarding ICP control and outcomes (summarized in a recent meta-analysis [157]), we generally do not advocate for the use of paralytics. Consideration can be given to a bolus of a paralytic for patients with ongoing ICP crises refractory to all other medical interventions. Paralytics may also play a role in the treatment of refractory shivering in patients being cooled.

Conclusions

Diagnosis and management of ICP crises are cornerstones of neurocritical care. Herein we have summarized key clinical features characterizing increased ICP and outlined our algorithm for ICP management. The relevant literature regarding each step in management is discussed. While several trials have been published in recent years, high-quality data are lacking for most methods of ICP control. We recommend a step-wise treatment approach for the management of ICP and call for additional RCTs to better define the utility and role in management of different methods for ICP treatment.

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