Chapter 11
Steroids, Diuretics, and Anticonvulsants

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Abstract Edema formation induced by increased vascular permeability worsens tissue damage and exacerbates residual neuronal function. To prevent such secondary damage, many drugs with the potential to reduce edema formation have been used and studied. However, many randomized controlled trials have shown that steroid therapy did not improve neurologic function; on the contrary, steroid therapy caused a higher incidence of side effects. Therefore, steroid administration is not recommended in acute neuronal injury, except for edema associated with brain tumor.

Diuretics are used widely in neurosurgery to reduce brain volume and intracranial pressure. Mannitol is effective at doses of 0.25–1 g/kg body weight. Loop diuretics are used as combination drugs with mannitol to facilitate urination.

Any cortical damage or irritation associated with brain injury, including that induced by brain surgery, has the potential to induce seizures. Diazepam and phenytoin are widely used to stop seizures. Intravenous anesthetics have anticonvulsant effects.

Keywords Methylprednisolone • Mannitol • Benzodiazepine • Propofol

11.1 Introduction

Edema formation worsens brain damage and exacerbates residual neuronal function. To prevent such secondary damage, several drugs including steroids and diuretics (mannitol and loop diuretics) have widely been used during a preoperative period for neurosurgery. In addition, any cortical damage or irritation associated with brain injury, including that induced by neurosurgery, has the potential to induce seizures. In this chapter, we will focus on benefits of usage of such drugs during the preoperative period for neuroanesthetic management. We will also discuss about adverse effects of such drugs.

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11.2 Steroids

Steroids have been used to assist in the control of cerebral edema in patients with brain disease. Steroids are thought to restore altered vascular permeability or increased blood–brain barrier permeability resulting from tissue damage [1]. However, steroid therapy has a high incidence of side effects such as infection, gastrointestinal bleeding, and hyperglycemia [2–5]. Therefore, steroid administration is not recommended in acute neuronal injury, except for edema associated with brain tumors [6, 7].

11.2.1 Brain Tumor, Metastatic Brain Tumor

The effectiveness of steroids in reducing cerebral edema associated with brain tumors is well known. Administration of steroids before elective surgery has the potential to reduce edema formation and improve neuronal function before craniotomy. Administration of steroids in patients with symptoms of increased intracranial pressure (ICP), such as consciousness disorder, headache, vomiting, and motor dysfunction, is standard care. Starting doses of dexamethasone are 4–16 mg/day [6, 7].

11.2.2 Traumatic Brain Injury

Administration of steroids in adult patients with head injuries has been abandoned as a result of controlled trials showing deleterious effects. The majority of these trials showed that steroids did not improve outcome or lower intracranial pressure in patients with severe traumatic brain injury (TBI). On the contrary, a high dose of methylprednisolone was associated with increased mortality [2]. The use of steroids is also not recommended in the treatment of severe TBI in pediatric patients [3].

11.2.3 Acute Spinal Cord Injury

The efficacy of steroids for SCI has been investigated in a number of studies, the most widely recognized of which is the National Acute Spinal Cord Injury Study (NASCIS). In the NASCIS2 trial (1990) [8], methylprednisolone was administered at an initial loading dose of 30 mg/kg within 8 h of injury, followed by administration at 5.4 mg/kg/h for 23 h. The results showed that neurological function was improved by methylprednisolone in the acute phase of SCI. However, in NASCIS3 (1997) [9], it was shown that methylprednisolone induced severe pneumonia and

sepsis. The harmful side effects of methylprednisolone administration include infection, hyperglycemia, gastrointestinal hemorrhage, and myopathy. In guidelines on the management of acute SCI published in 2013, it was concluded that there was no consistent or compelling medical evidence to justify the administration of methylprednisolone for acute SCI [5].

11.3 Diuretics

Diuretics are used widely in neurosurgery to control brain volume and intracranial pressure by reducing the intracellular and extracellular fluid compartments. Osmotic diuretics are preferentially used in perioperative situations because of their speed of action and efficacy. Loop diuretics used as combination drugs with mannitol can be effective in facilitating urination.

11.3.1 Mannitol

Mannitol is a widely used osmotic diuretic. It passes the glomerular filter, is not reabsorbed, and is excreted in an unchanged form, resulting in facilitation of urination via its osmotic effect [2–4, 10]. Mannitol is administered at a dose of 0.25–1 g/kg over a period of 15–20 min [10]. The mechanisms by which mannitol reduces ICP are thought to be as follows [2]:

- Mannitol has been shown to control ICP by reducing blood viscosity. This results from viscosity-mediated reflex vasoconstriction, which allows cerebral blood flow to be maintained, despite a reduced level of cerebral blood volume.
- Mannitol administration reduces ICP by an osmotic effect as a result of fluid movement from the brain parenchyma into the intravascular region. This effect takes 15–30 min and persists for up to 6 h.

Acute hyponatremia and hyperkalemia are side effects of intraoperative mannitol administration. Rebound swelling is another side effect of mannitol administration. Mannitol accumulates in injured brain tissue, and fluid movement occurs from the intravascular space to the brain parenchyma, resulting in exacerbation of brain edema. Mannitol administration with serum osmolarity levels >320 mOsm poses the risk of the development of acute tubular necrosis and renal failure.

11.3.2 Glycerol

Glycerol is also an osmotic diuretic. Glycerol is metabolized and enters the glycolytic pathway [10]. Glycerol is used to control increased ICP caused by severe

stroke. Administration of glycerol in severe stroke patients with ICP elevation improved 14-day survival [11]. *10 % glycerol is administered at a dose of 1–1.2 mL/kg*.

11.3.3 Loop Diuretics

Loop diuretics inhibit sodium and chloride reabsorption by acting as a Na-K-2Cl cotransporter at the loop of Henle, thus promoting urine excretion. Hypokalemia and metabolic alkalemia are side effects of loop diuretic administration [10]. Furosemide is administered intravenously at a dose of 5–20 mg.

11.4 Anticonvulsants

Seizures are caused by irritation of the cerebral cortex. Seizures rarely occur under general anesthesia; however, in awake craniotomy, seizure is one of the most serious complications. If seizures occur, surgery should be discontinued immediately, and the appropriate treatment discussed between the anesthesiologists and the neurosurgeons. Propofol is widely used for treating seizures during operative periods. Phenytoin, midazolam, and thiopental are also used. If a single injection is insufficient to stop the seizure, continuous infusion should be considered.

11.4.1 Post-neurosurgery

There are still no guidelines on post-neurosurgical prophylactic anticonvulsants.

11.4.2 Traumatic Brain Injury

Anticonvulsants decrease the incidence of early posttraumatic seizures (PTS) (within 7 days of injury). Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS [2–4].

11.4.3 Subarachnoid Hemorrhage

The use of prophylactic anticonvulsants may be considered in the immediate posthemorrhagic period. Routine long-term use of anticonvulsants is not

recommended but may be considered in patients with known risk factors for delayed seizure disorder such as prior seizure, intracerebral hematoma, intractable hypertension, infarction, or aneurysm in the middle cerebral artery [12, 13]. Although recommended drugs and doses are not stated in the guidelines, phenytoin is widely used in subarachnoid hemorrhage.

11.4.4 Benzodiazepines (Diazepam, Midazolam)

Benzodiazepines increase the affinity of gamma-aminobutyric acid (GABA) for GABAa receptors by binding to this receptor complex and promoting opening of chloride ion channels, resulting in the inhibition of neuronal excitation [14]. In seizures, diazepam is administered at a dose of 10 mg and midazolam at a dose of 0.1–0.3 mg/kg [15].

11.4.5 Phenytoin

Phenytoin stabilizes the inactive state of voltage-gated sodium channels and decreases sodium influx into neurons [16]. In seizures, phenytoin is administered at a dose of 5–20 mg/kg [15]. Recently, fosphenytoin has also been used as a prodrug of phenytoin.

11.4.6 Barbiturates (Thiopental, Phenobarbital)

Barbiturates increase the effect of GABA or directly open chloride ion channels by binding to $GABA_A$ receptors [14]. In seizures, phenobarbital is administered at a dose of 15–20 mg/kg. The dose of thiopental in seizures is the same as that in general anesthesia [15].

11.4.7 Propofol

The mechanism of action of propofol is still unclear; however, propofol is considered to be a GABA agonist and to suppress seizures via GABA-mediated inhibition [17]. The dose of propofol in seizures is the same as that in general anesthesia [15].

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