Choice of Anaesthesia, Drugs and Medications

35

Christian Sigvald Langfrits and Bent Lob Dahl

Recommendations

Level I

There are insufficient data to support a Level I recommendation for this topic.

Level II

Prophylactic administration of barbiturates to induce burst suppression EEG 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.

Propofol is recommended for the control of ICP but not for improvement in mortality or 6-month outcome. High-dose propofol can produce significant morbidity.

Level III

There are many Level III recommendations for the topics dealt with in this chapter.

35.1 Overview

The most important in the treatment of patients with brain injury is to maintain oxygenation and blood pressure while securing airway and circulation in order to ensure the best outcome for the patients.

All procedures should be aimed at preserving a normal ICP, cerebral circulation and oxygenation. Use the drugs that you are familiar with. Titrate drugs carefully to avoid hypotension and changes in PaO_2 and $PaCO_2$. Head should be in neutral position and elevated 10–15° to increase cerebral venous drainage without compromising CBF. It must be checked whether the venous drainage is compromised by a cervical collar.

Sedatives and analgesics are widely used to treat pain and agitation in prehospital setting as well as during operative procedures and intensive care. The most widely used drugs are:

C. S. Langfrits (✉)
Department of Anesthesia and Intensive Care, Aalborg University Hospital, Aalborg, Denmark
e-mail: c.langfrits@rn.dk

B. L. Dahl
Department of Anesthesia and Intensive Care, Silkeborg Regional Hospital, Silkeborg, Denmark
e-mail: bentdahl@rm.dk

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Sedatives	Thiopental, propofol, midazolam, dexmedetomidine, ketamine, etomidate, clonidine
Analgesics	Morphine, fentanyl, remifentanil, sufentanil, alfentanil
Volatile anaesthetics	Sevoflurane, isoflurane, nitrous oxide
Muscle relaxants	Succinylcholine, mivacurium, atracurium, cisatracurium, vecuronium, rocuronium
Inotropics	Dopamine, dopexamine, noradrenaline, phenylephrine, epinephrine, adrenaline
Weak analgesics	Ketorolac, paracetamol (acetaminophen)

Tips, Tricks and Pitfalls

- Use the drug you are most familiar with.
- A decrease in blood pressure, or an unexpected high or low CO_2, may create more havoc in the injured brain than the use of a suboptimal anaesthetic drug since the differences between the drugs detected in clinical trials are minor.
- Titrate your drugs to avoid hypotension and changes in PaO_2 and $PaCO_2$. Remember many of the severely head-injured patients have additional injuries and are prone to be hypovolemic and will require smaller doses of drugs.
- The acute patient has decreased intracranial compliance and hence decreased compensative ability for even minor changes in ICP. Anaesthesia and intubation should be performed according to this. All procedures should aim at maintaining normal ICP. The head should be in neutral position and elevated 10–15° to increase cerebral venous drainage without compromising CBF. It must be checked whether the venous drainage is compromised if a cervical collar is used.
- For acute intubation in a cardiorespiratory stable patient, propofol or thiopental can be used for sedation. Ketamine or etomidate can be used in cardiorespiratory unstable patients. All analgesics can be used. If relaxation is needed, succinylcholine can be used for rapid sequence intubation, unless there is recent spinal cord injury or severe burns. Mivacurium, atracurium, cisatracurium and vecuronium or rocuronium can also be used according to local instructions.
- 'Inotropics' such as norepinephrine, dopamine, dopexamine, phenylephrine and ephedrine can be used according to the clinical situation. Most TBI patients have a normal to increased cardiac output and vasodilatation and may benefit from norepinephrine infusion (0.02–0.20 μg/kg body weight/min).

35.2 Background

35.2.1 Propofol

Propofol has become widely used because of its rapid onset and short duration, facilitating neurologic examination. Propofol has been shown to reduce cerebral metabolism and oxygen consumption, thereby providing a potential neuroprotective effect. One double-blind randomized controlled clinical trial (RCT) comparing morphine and propofol failed to show a significant difference in GOS or mortality. In a post hoc analysis, a significant increase in neurological outcome was observed in patients receiving high-dose propofol (Kelly et al. 1999).

Propofol infusion syndrome is a safety concern. The clinical features are hyperkalaemia, hepatomegaly, lipaemia, metabolic acidosis, myocardial failure, rhabdomyolysis and renal failure resulting in death. Doses exceeding 5 mg/kg/h, or any dose for more than 48 h, should be avoided.

35.2.2 Midazolam

Midazolam, a relatively short-acting benzodiazepine, is frequently used in neurointensive care units. Its use carries a significant risk of a decrease

in MAP and a sustained increase in ICP resulting in a decrease in CPP. Midazolam can be reversed by flumazenil.

35.2.3 Barbiturates

Barbiturates have been used in two different situations: prophylactically and for treatment of refractory intracranial hypertension. Prophylactic use of barbiturates was investigated in two RCTs (Schwartz et al. 1984; Ward et al. 1985), which failed to demonstrate significant clinical benefit. In patients with diffuse injury, Swartz et al. observed a mortality of 77% compared with 43% in the mannitol control group. In both studies, an undesirable decrease in blood pressure was observed. Prophylactic use of barbiturates is not recommended.

The use of barbiturates for treatment of refractory intracranial hypertension was investigated by Eisenberg et al. (1988) in an RCT. The likelihood of survival for those patients whose ICP responded to barbiturates was 92% compared to 17% in non-responders. In patients with hypotension before randomization, barbiturates provided no benefit.

A Cochrane review (Roberts and Sydenham 2012) concluded: 'There is no evidence that barbiturate therapy in patients with acute severe head injury improves outcome. Barbiturate therapy results in a fall in blood pressure in one of four treated patients. The hypotensive effect will offset any ICP lowering effect on cerebral perfusion pressure'.

35.2.4 Ketamine

Ketamine has previously been contraindicated because of fear of increase in CBF and ICP as shown in older studies (Sharma and Vavilala 2012). However, this effect may have been caused by an increase in $PaCO_2$, since all recent studies show no relevant signs of increased ICP during or after ketamine infusion. Some studies even show signs of a decrease in ICP and increase in CPP after ketamine administration (Zeiler 2014). Also the major difference between older and more recent studies is the fact that older studies were based on sedated patients with spontaneous respiration, whereas all later studies are made on anesthetized, mechanically ventilated patients.

It is important to maintain blood pressure and oxygenation in these patients. The advantage of ketamine is that blood pressure and ventilation are better preserved.

In the prehospital and emergency department settings, ketamine has been compared to etomidate for rapid sequence intubation (RSI), with no difference in mortality or patient outcome. Ketamine can, for this reason, be used in patients with TBI, with a recommended dose of 1–2 mg/kg for RSI, but is not recommended for sedation without mechanical ventilation.

35.2.5 Dexmedetomidine

Dexmedetomidine is an alpha-2 adrenergic receptor agonist with rapidly titratable sedative, sympatholytic and some analgesic effects (both per- and postoperative), but only minor respiratory depression. Dexmedetomidine produces a decrease in CBF. The effect on cerebral metabolism in humans is unknown (Pasternak and Lanier 2009). In a small series of healthy persons, an uncoupling of supply and demand in the brain was not found (Drummond et al. 2008). How it influences the injured brain is unknown. The possible benefit of attenuating the sympathetic response (decrease in heart rate and blood pressure to noxious stimuli and reduction in stress response and pulmonary vascular permeability) remains to be investigated.

Recent meta-analysis found a reduction of inflammatory mediators and neuroendocrine hormones postoperatively with dexmedetomidine compared to placebo. However, due to the heterogeneity of the studies, the actual outcomes as regards to brain protection are inconclusive (Jiang et al. 2017).

When compared to propofol, dexmedetomidine has shown a noninferiority as regards to cerebral blood flow velocity and brain oxygenation (Farag et al. 2017).

35.2.6 Etomidate

Etomidate is a short-acting intravenous anaesthetic agent whose primary effects of sedation and amnesia are mediated through the γ-aminobutyric acid (GABA) inhibitory neurotransmitter system. Beneficial effects on the CNS include a decrease in cerebral metabolic rate for oxygen, in cerebral blood flow and in ICP.

A great concern with etomidate is the inhibition of the enzyme 11-β hydroxylase and thereby reduction in cortisol production. Etomidate is not to be used as a continuous infusion, but is largely used in several countries as an induction agent in the prehospital setting and in the ICU, due to its rapid onset and favourable hemodynamic effect.

According to Cochrane (Bruder et al. 2015), there is no evidence of increased mortality, ICU lengths of stay or time with mechanical ventilation related to a single-dose administration. It does however increase the risk of adrenal gland dysfunction.

35.3 Analgesics

35.3.1 Spontaneous Ventilation

Morphine and analogue drugs should be administered with extreme caution in the spontaneously breathing patient with exhausted intracranial compliance. Careful monitoring of conscious state, respiration, blood pressure and eventually arterial blood gas analysis (PaO_2, $PaCO_2$), or capnometry/oximetry, is mandatory. Even a small dose of morphine (e.g. 3 mg IV) might provoke a decrease in $AVDO_2$, suggesting a state of hyperaemia.

35.3.2 Controlled Ventilation

35.3.2.1 Morphine, Fentanyl and Remifentanil

In the ventilator-treated patient, morphine and fentanyl do not increase CBF or ICP. On the contrary, a decrease in ICP is observed. This is caused by the sedative effect giving rise to a decrease in CO_2 production and a decreased level of circulating catecholamines. An additive effect of hypnotics and analgesics on cerebral oxygen uptake may also play a role.

35.3.2.2 Sufentanil and Alfentanil

Comparative studies of fentanyl, alfentanil and sufentanil in patients subjected to craniotomy indicate that the use of the two latter drugs was accompanied by a decrease in CPP and an increase in CSF pressure. Cerebral autoregulation may play a role because correction of blood pressure normalized ICP. Both sufentanil and alfentanil elicit a decrease in blood pressure. As a consequence, a decrease in CVR and an increase in CBV may occur. Under these circumstances, an increase in ICP is observed.

In a systematic review (Roberts et al. 2011) of agents used for postoperative sedation (propofol, etomidate, ketamine, opioids, benzodiazepine, α-2 agonist and antipsychotics), no differences in neurological outcome or mortality between drugs were found.

35.4 Volatile Anaesthetics

Neuroprotection vs. brain cell apoptosis is discussed, but mainly in infants, volatile anaesthetics are widely used.

35.5 Muscular Relaxation

Muscular relaxation can be necessary for intubation and to facilitate ventilatory support, but the latter should be restricted because of a risk of hypoxaemia in case of extubation, masking of seizures, association to myopathy and increased length of stay in ICU.

The neuromuscular blockade of rocuronium and vecuronium can be reversed by sugammadex.

In experimental as well as human studies, succinylcholine increases ICP shortly. The rise in ICP is caused by activation from peripheral impulses from the muscles. Nondepolarizing agents such as rocuronium, vecuronium, mivacu-

rium, atracurium and cisatracurium do not increase ICP during controlled ventilation.

Succinylcholine should not be used for patients with major burns or spinal cord injury from 24 h after injury to at least 6 months due to upregulation of acetylcholine receptors and risk of life-threatening hyperkalaemia.

Nondepolarizing neuromuscular blockers may have advantages on short-term effects on ICP as compared to succinylcholine, but no evidence of differences in long-term outcome are found (Sanfilippo et al. 2015).

35.6 Inotropics

A sufficient blood pressure is important for outcome. If hypotension is observed and hypovolemia is excluded or treated, inotropics should be used. The effect of inotropics on CBF, $CMRO_2$ and ICP is not fully understood as there seems to be relatively few such receptors in cerebral vessels. The effect might depend on whether the BBB is broken or not. Inotropics can be used according to the clinical situation.

35.7 Weak Analgesics

Paracetamol (acetaminophen) might decrease the demand for morphine, and it lowers the body temperature. Ketorolac might also decrease the need for morphine. Often, it is not used because of adverse effects (bleeding and inhibition of bone healing). In a study by Casanelli et al. (2008) of 25 patients undergoing spine surgery, no bleeding was observed in the ketorolac group as compared to 3 patients in the placebo group.

Indomethacin decreases CBF and ICP very effectively and should be used very cautiously for pain management. It is regarded as an experimental drug for reduction of ICP (Sader et al. 2015).

35.8 Specific Pediatric Concerns

Propofol anaesthesia is widely used for paediatric patients. Adverse effects of propofol (increased mortality and the propofol infusion syndrome) have restricted the use of propofol for sedation and ICP control in paediatric patients with or without TBI, which are not recommended by the US FDA. Propofol for anaesthesia can be used according to local rules.

Ketamine has, in a single study, shown a decrease in ICP and increase in CCP after a single-dose administration, in a paediatric population with increased ICP and unresponsiveness to first- and second-tier interventions.

In a small study of paediatric patients with traumatic brain injury and ICP over 20 mmHg, a decrease in ICP and CPP was found without a decrease in MAP (Bramwell et al. 2006). Single dose of etomidate is to be used with caution as regards to children due to the possible worsening of outcome in the septic child.

Sedatives, analgesics and neuromuscular blockers are widely used in children and infants with TBI. Apoptotic effects of anaesthesia and surgery observed in animals are discussed, and an association between anaesthesia and an increased risk of brain damage in human infants is found. However, the evidence is considered inconclusive due to methodological difficulties. Further research of dosing thresholds, (age, number and duration of anaesthesia) is necessary (Noguchi et al. 2017).

There are few studies on the paediatric consequences of sedatives, analgesics and neuromuscular blockers. For this reason, their use is left to the treating doctor (Adelson et al. 2003; Ketharanathan et al. 2017; Kochanek et al. 2019). The use of bolus doses of midazolam and/or fentanyl during ICP crisis should be avoided due to the risk of cerebral hypoperfusion (Kochanek et al. 2019).

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