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Effect of Sedation on Cerebral Metabolic Rate of Oxygen in Traumatic Brain Injury Patients

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Abstract

Several different classes of sedative agents are used in the management of patients with traumatic brain injury (TBI). These agents are used at induction of anaesthesia, to maintain sedation, to reduce elevated intracranial pressure (ICP), to terminate seizure activity and facilitate ventilation. The intent of their use is to prevent secondary brain injury by facilitating and optimizing ventilation, reducing cerebral metabolic rate ($CMRO_2$) and reducing ICP. There is limited evidence available as to the best choice of sedative agents in TBI, with each agent having specific advantages and disadvantages. Propofol is a commonly used sedative in the management of patients with TBI, primarily due to its ability to reduce ICP and $CMRO_2$. Propofol exerts a dose-dependent effect on cerebral metabolism; at lower doses (<4 mg/kg/h), it maintains the coupling of cerebral blood flow (CBF) with $CMRO_2$, preserving cerebral oxygenation. However, at higher doses, propofol can lead to burst suppression on electroencephalography (EEG), which significantly reduces $CMRO_2$, potentially benefiting patients by minimizing secondary brain injury. Dexmedetomidine, a α2-adrenergic receptor agonist, is another sedative used in TBI patients, particularly for its neuroprotective properties. Unlike propofol, dexmedetomidine has a more modest impact on $CMRO_2$, often leading to only a mild reduction. This is due to its sedative effect, which occurs without causing deep anesthesia or burst suppression on EEG. As a result, dexmedetomidine preserves CBF while slightly reducing $CMRO_2$, which can be advantageous in maintaining cerebral oxygen balance in TBI patients. Other agents like benzodiazepines, barbiturates, narcotics, ketamine and etomidate will be discussed, and we offer evidence-based guidance to the appropriate context in which each agent may be used.

Keywords: Sedation, Dexmedetomidine, Propofol.

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1. Introduction

There are two main categories of traumatic brain injuries: primary and secondary. TBI occurs when kinetic energy is transferred to brain tissue. Hypoxemia, hypotension, hypo- or hyper-carbia, hypo- or hyper-glycemia, hypo- or hyper-thermia, seizures, and other complications can worsen traumatic brain injury (TBI) during the next few minutes to hours. This is called secondary brain injury. The principal goal of therapeutic measures after TBI is to prevent further brain injury. This is best handled by an anesthesiologist, ideally a neuro-anesthesiologist [1]. Care of a TBI patient should begin at site of the injury, with an aim to secure the patients' airway and maintain adequate ventilation and circulation [1]. Urgent transportation to a tertiary care facility equipped for neurosurgery is necessary for patients suffering from moderate to severe TBI. Results in TBI patients can be affected by how the patient is transported, how long it takes for the patient to be transported, and whether a doctor or a paramedic is in charge of response team. Hypoxia and hypotension prevention should be the main aims of care due to the fact that even a single episode of hypotension is linked to double death rate and increased morbidity risk [1]. Administering sedatives to patients with TBI involves utilizing many medication classes.

As analgesics or anticonvulsants, for instance, some of these agents might have other benefits. This research examines and contrasts various agents, providing evidence-based recommendations for when to employ each one. It is critical to define sedatives and the situations in which they are administered in the context of TBI. Sedative compounds are defined in this document as medications that reduce awareness and have therapeutic uses in treating TBI. It is common to need airway protection and breathing management after a primary brain injury. Endotracheal intubation can be safely facilitated with the use of induction sedative drugs, which are different from muscle relaxants. This helps to minimize haemodynamic instability and consequent brain injury. In order to optimize breathing, CMRO2, CBF, and ICP, maintenance of sedation is integrated into the overall therapy of TBI. To lower ICP, sedative medications are crucial for refractory, increased ICP in severe TBI. Refractory acute posttraumatic epilepsy is

another condition that can be treated with sedative hypnotics. Sedatives have the same anxiolytic effects on mechanically ventilated patients as they do on all patients [1]. Brain edema, intracranial haematoma, increased ICP, decreased cerebral perfusion pressure (CPP), and cerebral ischaemia are all symptoms of TBI. The secondary insults of hypoxia, hypercapnea, systemic hypotension, and intracranial hypertension are the primary targets of therapeutic efforts. Several of these difficulties are addressed by sedatives. They lower CMRO2, which in turn lowers CBF and cerebral blood volume (CBV), and they enable breathing optimization to avoid hypoxia and reach normocapnea (and hypocapnea during short periods of elevated ICP. Nevertheless, they come with a risk of lowering systemic blood pressure, which in turn lowers CPP, in addition to other side effects.

A strong predictor of prognosis following TBI is even a single episode of hypotension [2-3]. Specific sedative medications should be chosen with caution in TBI due to a lack of accessible evidence. No sedative drug was shown to be significantly better than the other in a recent comprehensive evaluation of TBI outcomes [4]. Further restricting the applicability of these findings is the fact that several of these studies covered decades and involved patients with milder traumatic brain injuries. When many sedatives are administered at once, it becomes difficult to determine how effective each one is. The Brain Trauma Foundation's guidelines also note that, with the exception of barbiturates for refractory raised ICP, there is insufficient high-quality information to suggest a specific sedative drug. Notwithstanding this, doctors should weigh the benefits and drawbacks of each medication when determining which one to use in a given TBI scenario [5].

1.2. Propofol

Propofol is a phenol derivative with high lipid solubility and a rapid onset of action. It has a very low water solubility egg phosphatide, glycerol, and soybean oil produce an emulsion. Consciousness can be reliably restored even after protracted administration thanks to the relatively fast plasma clearance, which allows for easier neurological testing. Prolonged infusions do raise the context-sensitive half time, but not nearly as much as with other sedatives. [6] The usage of propofol as an induction agent and maintenance sedative in the neurointensive care unit has grown substantially since its introduction in 1986. Propofol has positive benefits on the brain, according to multiple research [7]. Propofol has been demonstrated to decrease ICP, CBF, and CMRO2 [8]. Lack of sufficient fluid resuscitation and vasopressors might lead to a decrease in the CPP due to a drop in mean arterial blood pressure (MAP). Propofol has been linked to a quicker recovery of consciousness upon withdrawal of sedation and better quality of sedation when compared to midazolam in medical and surgical intensive care unit patients [9-10].

In regions of the brain that experience high levels of oxidative stress, mitochondrial malfunction and cell death are becoming more and more recognized in the scientific literature [11-12]. One mechanism by which propofol might protect neurons is via reducing oxidative stress. Utilizing various cerebral biomarkers as endpoints in the acute phase of traumatic brain injury, a randomized controlled trial compared sedation with midazolam and propofol utilizing cerebral microdialysis catheters [13]. The lactate to pyruvate ratio, an indicator of cerebral oxidative stress, did not differ between the two groups after 72 hours. Although the study's sample size was limited and the propofol concentrations may not have been high enough to detect an antioxidant effect, this is an intriguing and new avenue for investigation. There may be additional side effects linked to the lipid formulation of propofol, in addition to a decrease in MAP and the necessity for higher vasopressor dosages to maintain CPP. When propofol infusion syndrome (PRIS) first emerged, it was in the context of case studies involving children who had been anesthetized with the drug.

Afterwards, reports of its usage in adults emerged, both as a general anesthetic and for long-term infusions in intensive care unit patients. Several clinical symptoms, such as lactic acidosis, heart failure, and Brugada-like changes in electrocardiograms (see Figure 1), can indicate the impending occurrence of malignant arrhythmias [14]. Rhabdomyolysis, kidney failure, and cardiac arrest are possible outcomes. Multiple routes contribute to incompletely understood pathophysiology of PRIS. Hypothesized mechanisms include an imbalance between mitochondrial energy consumption and demand and its consequences on lipid metabolism. Crucially, people with TBI are believed to have a higher prevalence of PRIS. Only seven out of sixty-seven adult neurosurgical ICU patients who had symptoms of PRIS ultimately survived, according to a retrospective cohort study. Higher dosages associated with a higher incidence of PRIS [15]. PRIS may be more prevalent in TBI due to ability to reduce increased ICP with substantial doses of propofol [16].

A concern has been raised regarding the potential impact of PRIS on the efficacy of propofol as a sedative for TBI, especially at larger dosages. Pancreatitis and an increase in pancreatic enzymes are two more possible side effects of propofol [17]. Some worry that propofol provides an ideal environment for the growth of microbes [18], but this may be less of an issue with more recent formulations. When doing nutritional assessments, it is important to consider propofol's high calorie content. As a sedative that can lower CMRO2 and ICP, propofol is often prescribed to individuals who have suffered TBIs. At lower doses (<4 mg/kg/h), propofol preserves cerebral oxygenation via maintaining the coupling of CBF with $CMRO_2$. Patients may benefit from a reduction in secondary brain injury because to propofol's burst suppression on electroencephalography (EEG) at larger doses, which considerably lowers $CMRO_2$. While propofol does a good job of lowering $CMRO_k$, it's important to use caution while administering it because it might cause hypotension. Hypotension lowers CPP, which in turn compromises the supply of cerebral oxygen.

Another concern that comes with using propofol for a long time is propofol infusion syndrome (PRIS), which is extremely rare but can have serious consequences, including death [18]. There was some concern in the beginning that propofol would make vulnerable individuals more active during seizures [19]. Uncertainty surrounds the question of whether this behavior reflected normal muscle tone or actual seizure activity [20]. On flip side, propofol is effective in treating status epilepticus and has been shown to raise threshold for seizures. Case series showing seizure activity cessation with propofol infusions provide bulk of evidence for its treatment in refractory status epilepticus [21]. Although propofol significantly reduces cardiac index and mean arterial pressure, it has shown to achieve and maintain

burst suppression [22]. Another benefit of propofol is it helps with neurological evaluations because of how quickly it starts working and how quickly it stops. When administering doses more than 4 mg/kg/hour for more than 48 hours, clinicians should exercise caution to avoid PRIS [23].

A decrease in MAP and, by extension, CPP, may occur as an induction agent; however, this can be minimized with careful administration of vasopressors and fluid boluses. When other treatments for status epilepticus fail, propofol may be necessary. There is a risk that it can affect hemodynamics if used as a tool to achieve burst suppression. Propofol is a commonly used sedative in the management of patients with TBI, primarily due to its ability to reduce ICP and $CMRO_2$. Propofol exerts a dose-dependent effect on cerebral metabolism; at lower doses (<4 mg/kg/h), it maintains the coupling of CBF with $CMRO_2$, preserving cerebral oxygenation. However, at higher doses, propofol can lead to burst suppression on electroencephalography (EEG), which significantly reduces $CMRO_2$, potentially benefiting patients by minimizing secondary brain injury Despite its beneficial effects on reducing $CMRO_2$, propofol must be used cautiously due to its potential for causing hypotension, which can reduce cerebral CPP and subsequently compromise cerebral oxygen delivery. Additionally, long-term use of propofol is associated with risks such as propofol infusion syndrome (PRIS), a rare but severe complication that can be fatal [25].

1.3. Benzodiazepines

Patients with TBI often get benzodiazepines as a sedative. They increase conductance of chloride ions, which in turn enhances action of GABA (γ-aminobutyric acid) at GABAA receptors; they are nonselective CNS depressants. They are able to reduce anxiety, improve memory, and prevent seizures. In the United Kingdom, midazolam was sedative of choice for TBI prior to introduction of propofol [24], whereas in the United States, lorazepam was drug of choice. When it comes to benzodiazepines for sedation in TBI, midazolam is best option because it has a shorter context sensitive half-life (t1/2) of 2-2.5 hours and a faster start and stop of action compared to lorazepam (t1/2) of 10-20 hours or diazepam (t1/2) of 20-40 hours [26]. Because imidazole ring is closed, it is highly soluble in lipids at physiological pH and has a fast onset. Some of its metabolites are active and build up with lengthy infusions, but its fast offset of effect is due to its fast hepatic metabolism [27]. For certain people, such elderly or those with liver problems, this can mean that sedation won't go away even after drug stopped. Bolus dosages of benzodiazepines considerably lower MAP and CPP in severe TBI, while these drugs also raise seizure threshold and decrease cerebral blood flow, CMRO2, and ICP [28]. When compared to barbiturates or etomidate extent to which benzodiazepines can reduce CMRO2 is lower, and burst suppression is not conceivable with these drugs [29-34]. Thus, benzodiazepines can be used to sedate individuals in situations where a neurological evaluation is not urgently needed. Buildup of metabolites, tolerance development with extended infusions, delirium risk are all major drawbacks.

1.4. Narcotics

Although their sleepy effects are sometimes seen as a side effect, opioid drugs are mostly used for their analgesic effects. To assure analgesia and lower hypnotic dose requirements, patients with TBI are sedated with a variety of opioids, typically in combination with hypnotic drugs. There are benefits to using analgesia-based protocols instead of hypnotic sedative regimens that include propofol and midazolam [35–39]. Opioids such as morphine, fentanyl, sufentanil, and, more recently, remifentanil are administered intravenously. For TBI, remifentanil has emerged as a promising option to opioid sedatives. Remifentanil is fast hydrolyzed by tissue and plasma esterases, which distinguishes it from other synthetic opioids. Remifentanil is a powerful opioid receptor agonist. Because there is little buildup and the metabolism is quick, people with TBI can be evaluated neurologically and woken up more quickly [39].

When compared to hypnotic-based techniques (such as propofol or midazolam), analgesia-based sedation with remifentanil provided a more predictable and shorter time to evaluation of neurological function in neuro-intensive care patients, according to a randomized controlled trial [40]. In addition, compared to morphine, remifentanil was well-tolerated by TBI patients, and the duration to extubation was substantially shorter in the former group [40]. When used in conjunction with other sedatives, such as propofol, opioids can provide an additional level of sedation. Opioid administration via bolus injection can cause an increase in ICP, especially if it results in a decrease in mean arterial pressure (MAP). The reduction in cerebral metabolic rate of oxygen (CMRO2) induced by opioids, generally between 15–25%, is advantageous for enhancing cerebral protection [41].

1.5. Barbiturates

Sedation of patients with traumatic brain injuries has historically relied heavily on barbiturates, especially thiopentone and pentobarbital [42–43]. Thiopentone once widely used as an induction agent, but never, less harmful drugs have limited its usage to treating status epilepticus, refractory increased ICP, and similar conditions. Central nervous system (CNS) is affected by barbiturates, which cause drowsiness and general anesthesia depending on dosage, by stimulating γ-aminobutyric acid (GABA) receptors and inhibiting α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [44]**.** With many doses or infusions, drug will accumulate significantly because of extended context-sensitive half-life and fact that its elimination kinetics change from first order to zero order at plasma levels more than 30 mg/L. Targeting a therapeutic aim of burst suppression on EEG is necessary to treat refractory ICP or status epilepticus (SED), which requires plasma levels >40 mg/L. The massive doses of thiopentone needed to accomplish this make neurological evaluations impossible for a few days [45]**.** After taking all necessary precautions, thiopentone can be utilized as an induction drug in TBI if hypotension is not an issue already. Not for use as maintenance sedative after TBI. Barbiturates can reduce CMRO2 by up to 50% in some cases, making them highly effective in situations where cerebral protection needed, such as in neuroanesthesia or treatment of elevated ICP [46].

1.6. Etomidate

When hemodynamic instability is present, the intravenous induction agent most often utilized is etomidate, a carboxylated imidazole derivative. With the exception of ketamine, it is the only sedative that produces less hypotension and cardiovascular depression in this

environment [44]. A dose of 0.3 mg/kg causes anesthesia to begin within 10 seconds and last for three to five minutes; further benefits include a short elimination half-life of 2.6 hours [45]. Decreases in cerebral blood flow and ICP have been reported [46], and it has shown to inhibit EEG bursts [47–49]. Also, a relatively mild effect on CMRO2 compared to barbiturates. It is known to decrease CMRO2 by 30–40%, similar to benzodiazepines [50]. However, ketamine provides many of the same benefits without the hazards of adrenal suppression, therefore etomidate should be carefully examined as an induction drug rather than a continuous sedation medication that should be avoided in TBI [51].

1.7. Ketamine

The N-methyl-D-aspartate receptor can be blocked by ketamine. Due to concerns that it may raise ICP, it has usually been avoided in the treatment of patients with TBI. Its epileptogenic potential is also a matter of theoretical concern. In fact, recommendations for the treatment of TBI pay scant attention to it [1]. Some have contended that since ketamine does not lower blood pressure like other commonly used sedatives, it may actually maintain cerebral perfusion pressure. Some have suggested that ketamine's hemodynamic stability makes it a safe induction agent for patients with TBI [52–57]. When it comes to whether ketamine causes seizures, the results are mixed. Seizure activity may be reduced by preventing calcium from entering neurons through NMBA receptor inhibition. Additionally, there is a wealth of information regarding the adjunctive use of ketamine in the treatment of status epliepticus [58]. One possible protective effect in patients with traumatic brain damage is the reduction of cytotoxic glutamate release caused by NMDA receptor antagonism [59]. For this reason, ketamine is most often used as an induction drug in cases of TBI and hemodynamic instability. Refractory seizure activity could be impacted by it. In addition, ketamine can lead to a slight increase in cerebral metabolic activity in certain regions of the brain due to its dissociative effects, although it generally has little to no effect on global CMRO2. Ketamine's ability to increase CMRO2 is thought to be due to its stimulatory effects on the limbic system and thalamus, while cortical regions may not be as affected [60].

1.8. Dexmedetomidine

Dexmedetomidine, in contrast to propofol and the benzodiazepines, works as a highly selective agonist at a different receptor than the GABA receptor. Calming and anxiety-reducing effects are due to its strong affinity for alpha-2 receptors, which is seven to eight times higher than clonidine. Intravenous titration can be performed because the elimination half-life is only two hours. One study found no statistically significant change in respiratory rate or oxygen saturations between individuals given dexmedetomidine and those given a placebo, suggesting that dexmedetomidine did not induce respiratory depression [61-62]. When administering a loading dose of dexmedetomidine, most prevalent adverse effects include bradycardia and hypotension. This is why some experts say that those with traumatic brain injuries shouldn't take a loading dose. Several trials have examined the use of dexmedetomidine sedation in ICU patients. To compare the safety and effectiveness of dexmedetomidine and midazolam sedation, Riker et al. conducted a prospective, double-blinded RCT in patients undergoing medical or surgical procedures in intensive care unit [63].

There was a marked decrease in hypertension, tachycardia, and ventilator time in the dexmedetomidine group. When comparing the two groups, 42.2% of patients given dexmedetomidine and 18.9% of patients given midazolam sedation suffered bradycardia. Decreasing the occurrence or severity of delirium is one possible benefit of dexmedetomidine. The risk of delirium is increased by many regularly used sedatives, such as benzodiazepines and opioids. A sedative regimen based on morphine or dexmedetomidine was administered to patients undergoing cardiac surgery in one prospective, double-blinded RCT [64]. Patients in the group that received dexmedetomidine had delirium last less time, although the delirium incidence rate was not significantly lower. Research on the efficacy of dexmedetomidine in TBI patients is limited. Aryan et al. [65] detailed its usage in patients undergoing neurosurgery procedures. On average, among the 39 patients they looked at, cerebral perfusion pressure went up and intracranial pressure went down. The results are limited by the study's retrospective design and small sample size

The authors call for more research to determine the best dosing schedule for patients undergoing neurosurgery. On a neurosurgical intensive care unit, Grof et al. conducted a prospective observational study of patients given dexmedetomidine [66]. Traumatic brain damage was present in most of these patients. An effort was made to wean patients of previous sedative regimes by using dexmedetomidine. The appropriate amount of sedation could only be achieved with relatively high dosages of dexmedetomidine, up to 2.5 mcg/kg/hour. The authors speculate that the necessity for greater doses of dexmedetomidine in this group of patients might be explained by substantial alterations in neurotransmitter systems in TBI. Both general intensive care unit (ICU) patients and patients with TBI require further high-quality RCTs to assess efficacy of dexmedetomidine as a sedative. The purpose of SPICE pilot project is to determine whether it is feasible to compare standard sedative procedures with those that include dexmedetomidine in a large-scale, multi-center experiment.

For the treatment of delirium and agitation, the DahLIA study is comparing dexmedetomidine to a placebo in a prospective, double-blinded RCT that is presently recruiting participants. Thus, as a sedative drug, dexmedetomidine may have several benefits in TBI. Because it does not have any respiratory depressive effects, it can be administered in patients who do not have an intubation, and there is some evidence that it can decrease delirium [66]. Dexmedetomidine, a α2-adrenergic receptor agonist, is a sedative used in TBI patients, particularly for its neuroprotective properties. Unlike propofol, dexmedetomidine has a more modest impact on $CMRO_2$, often leading to only a mild reduction. This is due to its sedative effect, which occurs without causing deep anesthesia or burst suppression on EEG. As a result, dexmedetomidine preserves CBF while slightly reducing $CMRO_2$, which can be advantageous in maintaining cerebral oxygen balance in TBI patients. Moreover, dexmedetomidine's minimal impact on respiratory function and its ability to provide sedation without significant hemodynamic instability make it a favorable option in TBI management, especially in the patients at risk of hypotension [67].

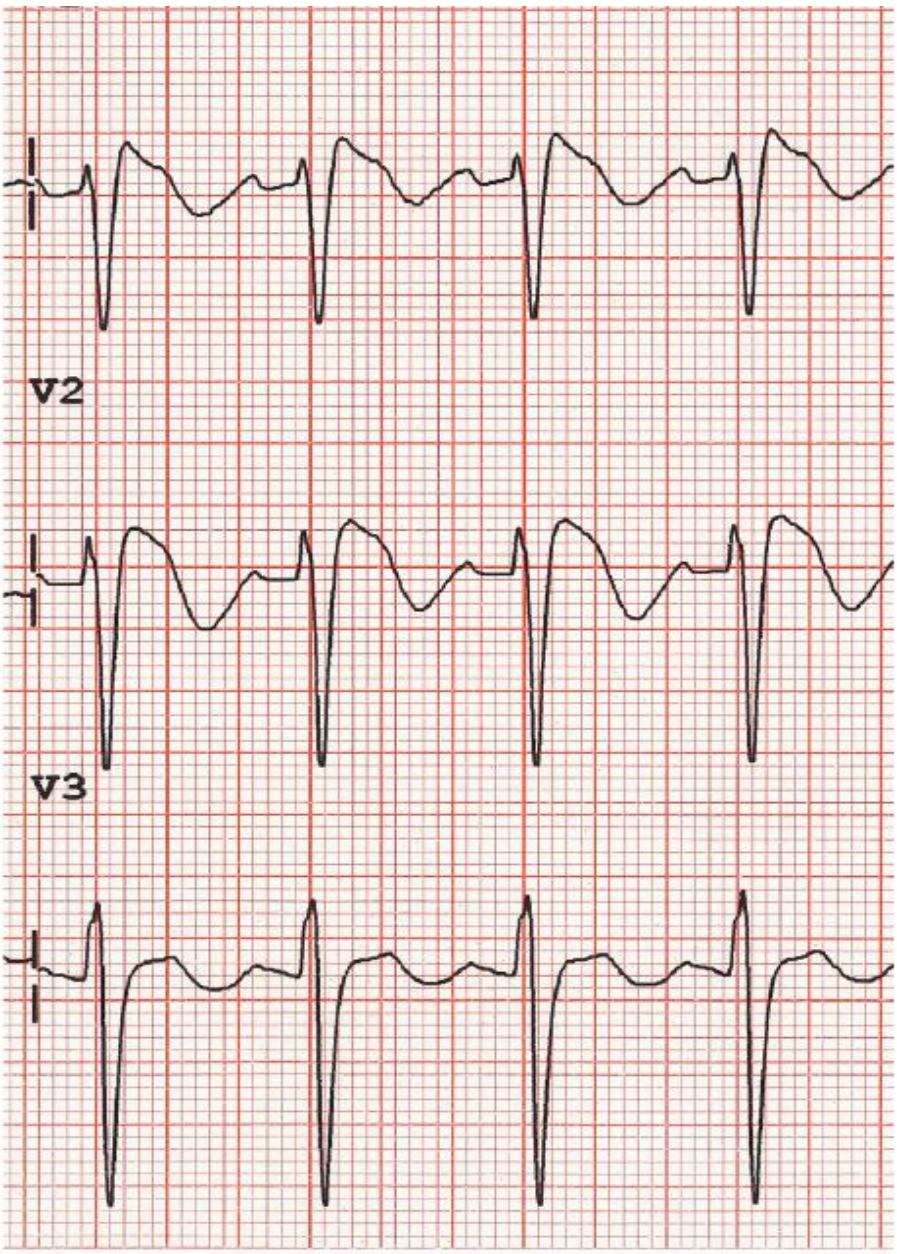

FIGURE 1: Brugada-like ECG changes that may be seen in propofol infusion syndrome. Coved ST elevation, at least 2 mm J point elevation and descending ST segment followed by a negative T wave (see [67]).

Table 1. Propofol Sedative Effects

Propofol	
Group	Phenol Derivative
Mechanism of Action/Pharmakodynamics	Potentiation $GABA_A$ receptors Na^+ channel blocker
Neuroprotective effects	Reduces CBF, $CMRO_2$ and ICP Reduces MAP, therefore variable effect on CPP Increases seizure threshold
Pharmacokinetics	Rapid hepatic metabolised, with extra-hepatic metabolism $t_{1/2}$ 2–24 hours, but rapid peripheral distribution Short context sensitive $t_{1/2}$
Advantages	Favourable effects on CBF, $CMRO_2$ and ICP Rapid onset of action Relatively short context sensitive $t_{1/2}$ facilitating neurological assessment
Disadvantages and major side effects	Hypotension may worsen CPP High lipid load Associated with elevated liver enzymes & pancreatitis Potential for PRIS, particularly with prolonged, high dose infusions Formulation may support bacterial and fungal growth Contraindicated if allergic to egg or soybeans
Dosage	Induction: 1–2.5 mg/kg, 0.5–1.5 mg/kg in elderly or limited cardiovascular reserve Maintenance of sedation: 1.5–4.5 mg/kg/hour, titrated to desired effect
Other significant facts	Increased risk of PRIS at infusions >4 mg/kg/h for >48 h
Appropriate roles in TBI	Induction agent, caution in hypotension Continuous infusion to provide sedation in TBI Refractory elevated ICP Refractory seizures

Table 2. Dexmedetomidine Sedative Effects

Dexmedetomidine	
Group	Selective α2 adrenergic agonist
Mechanism of Action/Pharmacodynamics	Peripheral α2A, brain & spinal cord α2B, α2C adrenoreceptor subtypes
Neuroprotective effects	Reduces CBF and ICP
Pharmacokinetics	Hepatic metabolism Distribution $t_{1/2}$ 6 minutes Elimination $t_{1/2}$ 2 hours
Advantages	Minimal respiratory depression Reduction in delerium
Disadvantages and major side effects	Hypotension (28%) Bradycardia Arrhythmias including atrial fibrillation Relatively high cost
Dosage	Loading dose: 1 mcg/kg Infusion: 0.42–1.0 mcg/kg/hour
Other significant facts	Minimal effect on respiratory function
Appropriate uses in TBI	Maintenance sedation agent pre & post extubation Management of agitated delirium

2. Conclusions

Sedation is a vital component of the management of patients with TBI. Consequently, a wide variety of agents and dosages are used. Propofol and dexmedetomidine offer distinct advantages in managing $CMRO_2$ in TBI patients. Propofol significantly reduces $CMRO_2$ and ICP. On the other hand, dexmedetomidine provides a more moderate reduction in $CMRO_2$ with better preservation of hemodynamic stability, making it suitable for patients when maintaining CPP is critical. Barbiturates can reduce CMRO2 by up to 50% in some cases, making them highly effective in situations where cerebral protection is needed, such as in neuroanesthesia or treatment of elevated ICP. Ketamine makes a slight increase in cerebral metabolic activity in certain regions of the brain due to its dissociative effects, although it generally has little to no effect on global CMRO2.There is a need for further prospective, randomized controlled trials, examining both physiological and clinical outcomes, to assess these agents in the context of TBI.

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