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Optic Nerve Sheath Diameter Sonography for Elevated IOP in TBI: Effects of dexmedetomidine and Midazolam

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Abstract: Traumatic brain injury (TBI) can be defined as the disruption in brain function, or other evidence of brain pathology, caused by an external physical force. Management of increased intracranial pressure should be tackled systematically in the emergency department. The Emergency Neurological Life Support (ENLS) created a simplified tiered approach for management. Initiating sedation and analgesia helps reduce noxious stimulation that may increase ICP. Intracranial hypertension is a widely known severe condition caused by different diseases. Disease management and diagnosis are challenging. The brain could be damaged by compressing effects on the intracranial structures or reducing the blood flow. Brain ischemia or brainstem herniation is a possible complication of intracranial hypertension, which may lead to destructive and fatal deterioration.1 Invasive intracranial devices are still the primary approach to measuring intracranial pressure (ICP). The optic nerve (ON) is a continuation of the central nervous system and is surrounded with cerebrospinal fluid (CSF) and meningeal layers that are directly contiguous with those around the brain. Therefore, when the pressure in the CSF increases, the optic nerve sheath (ONS) can distend, which makes optic nerve sheath diameter (ONSD) a potential surrogate for intracranial pressure (ICP) assessment. Transorbital ultrasonography (US) is an ideal tool for repetitive noninvasive measurements. The retrobulbar segment of ONS appeared to be the most sensitive to increases in CSF volume according to previous cadaveric studies. ONSD had been compared to invasive ICP measurements including spinal taps, external ventricular drains, and intraparenchymal transducers; ventriculoperitoneal shunt malfunction; and CT or MRI imaging findings consistent with elevated ICP. Dexmedetomidine (Dex), with its unique characteristics of sedation without respiratory depression and residual metabolites, concomitant analgesic and sympatholytic effects, and no interference in neurological assessment or weaning from mechanical ventilation, was presumably considered suitable for the sedation of TBI patients. Midazolam and propofol are the preferred drugs for sedation in the ICU as they lower the ICP by lowering the cerebral metabolism (cerebral metabolic rate of oxygen-CMRO2). Midazolam is cheaper than propofol in the doses required to achieve a high level of sedation in severe head injury and hence more appropriate in a resource-constrained environment.

Keywords: *Optic Nerve Sheath Diameter, IOP, dexmedetomidine , Midazolam*

Introduction

Traumatic brain injury (TBI) can be defined as the disruption in brain function, or other evidence of brain pathology, caused by an external physical force [1]. The yearly incidence of TBI is estimated at 50 million cases worldwide; thus, approximately half of the global population will have an episode of TBI in their life. In the UK, it is the most common cause of death and disability in those aged less than 40 years. Moreover, even higher rates of morbidity and mortality are seen in low-income and middle-income countries. Yearly, TBI costs the global economy approximately 400 billion US dollars, representing 0.5% of the gross world product [1].

TBI is a heterogeneous entity, reflecting several underlying macroscopic modes of injury (e.g., extrinsic compression from mass lesion, contusion, diffuse axonal injury [DAI]) as well as a range of mechanisms by which neuronal injury can be inflicted (e.g., 'classical' ischemia, apoptosis, mitochondrial dysfunction, cortical spreading depression [CSD], and micro vascular thrombosis) in differing proportions with resultant varying clinical courses [2].

Practically, the clinical severity of TBI has long been stratified according to post-resuscitation Glasgow Coma Scale scores into mild (GCS 14–15), moderate (9–13), and severe (3–8). Severe TBI has mortality rates of 30–40% and can cause significant physical, psychosocial, and social deficits in up to 60% of cases [3].

There has been a secular trend towards reduced incidence of severe TBI in the first world, driven by public health interventions such as seatbelt legislation, helmet use, and workplace health and safety regulations. This has paralleled improved outcomes following TBI delivered in large part by the widespread establishment of specialized neurointensive care [4].

Epidemiology

TBI continues to plague millions of individuals around the world on an annual basis. According to the Centers for Disease Control, the total combined rates for TBI-related emergency department visits, hospitalizations, and deaths have increased in the decade 2001–2010. However, taken individually, the number of deaths related to TBIs has decreased over this same period of time likely secondary in part to increased awareness, structuralizing management and guidelines, and significant technological advancements in current treatment regimens [5]. We should also acknowledge that there is a certain percentage of TBIs that never reach medical care, hence, the overall rates for TBIs are likely underreported [5].

The highest rates of TBI tend to be in a very young age-group (0–4 y) as well as in adolescents and young adults (15–24 y). There is another peak in incidence in the elderly (>65 y). The 2 leading causes of TBI overall are falls and motor vehicle accidents. As a result of an overall increased number of TBIs, but lower rate of related deaths, we have a growing population of individuals living with significant disabilities directly related to their TBI [6].

Pathophysiology

TBI pathogenesis is a complex process that results from primary and secondary injuries that lead to temporary or permanent neurological deficits. The primary deficit is related directly to the primary external impact of the brain. The secondary injury can happen from minutes to days from the primary impact and consists of a molecular, chemical, and inflammatory cascade responsible for further cerebral damage. This cascade involves depolarization of the neurons with the release of excitatory neurotransmitters such as glutamate and aspartate that lead to increased intracellular calcium. Intracellular calcium activates a series of mechanisms with the activation of enzymes caspases, and free radicals that results in degradation of cells either directly or indirectly through an apoptotic process [7].

This degradation of neuronal cells is associated with an inflammatory response that further damages neuronal cells and incites a breach in the blood brain barrier (BBB) and further cerebral edema. This entire process is up regulated and down regulated as well through several mediators. After the second injury phase follows the recovery period, which consists of reorganization in an anatomical, molecular, and functional level. The volume of the intracranial compartment is comprised of 3 separate contents: the brain parenchyma (83%), cerebrospinal fluid (CSF, 11%), and blood (6%). Each of these contents relies on one another for a homeostatic

environment within the skull. However, when intracranial volume exceeds that of its normal constituents, a cascade of compensatory mechanisms takes place [8].

An increase in intracranial volume can take place in the traumatized brain via mass effect from blood, both cytotoxic and vasogenic edema, and venous congestion. Brain tissue is incompressible. As a result, edematous brain tissue will initially cause an extrusion of CSF to the spinal compartment. Eventually, blood especially that of venous origin is also extruded away from the brain. Without proper intervention, and sometimes even with maximal intervention, the compensatory mechanisms fail and the end result is pathological brain compression and ensuing death [9].

Management of Increased Intracranial Pressure

Management of increased intracranial pressure should be tackled systematically in the emergency department. The Emergency Neurological Life Support (ENLS) created a simplified tiered approach for management. Initiating sedation and analgesia helps reduce noxious stimulation that may increase ICP. In addition, elevating the head of the bed more than 30° and keeping the neck midline assists cerebral venous drainage [10].

Hyperosmolar Therapy

Hyperosmolar therapy, including mannitol or hypertonic saline (HTS), has equally shown benefits in lowering ICP. Mannitol is given as a 0.5–1 g/kg IV bolus via a peripheral intravenous line over 5–15 min. This process can be repeated every 4–6 h. Monitoring adequate dosing can be based on the osmolar gap; a gap > 20 mOsm/kg has shown no benefit. Hypertonic saline is available from 2 to 23.4% and can be administered as a bolus alone or with mannitol. Concentrations of HTS greater than 7.5% should be given through a central venous catheter. Concentrations less than 7.5% can be bolused via a peripheral line; however, infusions should be given in a large vessel. Generally speaking, equimolar dosing is recommended during any hyperosmolar agent administration. Dosing is variable throughout many studies and institutional practices/protocols differ depending on what is available. [11].

Antiepileptic

Seizure activity (i.e., gross seizures, subclinical, and post-traumatic epilepsy) can be seen in those with increasing ICP. Seizure activity can increase cerebral metabolic demand and worsen ICP. Anticonvulsants should be considered in those with increased ICP, especially depending on the etiology. Patients with TBI, intracranial hemorrhages, subarachnoid hemorrhage, and large volume ischemic injuries would benefit from prophylactic anticonvulsant therapy. Phenytoin and levetiracetam are the most commonly used agents. Prophylaxis has been shown to prevent early seizure activity but not post-traumatic epilepsy. There is no evidence to suggest loading dose therapy is beneficial in preventing seizures or progression to epilepsy [12].

Induction Agents and Sedation

Fentanyl has been used in premedication to blunt increases in ICP related to laryngotracheal stimulation in rapid sequence intubation (RSI). In a normotensive/hypertensive patient, an intravenous bolus of fentanyl (2–3 mcg/kg) 3 min prior to induction is recommended. Fentanyl is hemodynamically neutral; however, it can decrease MAP and CPP when given in bolus doses. Etomidate is commonly used as an induction agent in patients with TBI because it can decrease cerebral blood flow and cerebral metabolic demand while preserving cerebral perfusion pressure [13].

If ICP remains a concern, increasing sedation can assist in management. Propofol can decrease cerebral metabolic demand (CMRO2) and CBV. A bolus dose of 1–2 mg/kg can be administered, followed by a continuous infusion to a maximum of 200 µg/kg/min in ventilated patients. However, propofol has an increased propensity to cause systemic hypotension. A MAP of 80 to 110 mmHg should be targeted to maintain a CPP greater than 60 mmHg. Vasopressors can be implemented to maintain cerebral perfusion pressure goals. Tier 3 of ENLS focuses on the most aggressive level of management. This tier titrates sedation to ICP goals or burst suppression on continuous electroencephalogram (cEEG). Pentobarbital can be administered and titrated to both goals (bolus 5–15 mg/kg over 30 min to 2 h, followed by a maintenance infusion of 1–4 mg/kg/h) [14].

Midazolam has a neutral hemodynamic profile and can lower systemic blood pressure, thus reducing CPP. Another concern surrounding midazolam is its ability to accumulate in adipose tissue over time, resulting in delayed awakening. Midazolam has also been shown to increase ventilatory days, prolonged coma, and ICU length of stay. However, its anticonvulsant and anxiolytic properties can be beneficial in certain cases [13].

The use of Ketamine has been controversial in patients with head injury. It was thought that its positive effects on sympathetic stimulation might cause a rise in ICP via stimulation and exacerbate the underlying condition. However, when Ketamine is used alongside a y-aminobutyric acid (GABA) receptor agonist, the ICP rise may not occur. Ketamine may also be considered beneficial by increasing cerebral perfusion through a transient increase in systemic blood pressure [8].

Kumar and colleagues' literature review determined that Ketamine can be used safely in patients with TBI, although no large clinical trials have been done. Ketamine also positively affects intraocular pressure (IOP) in a dose-dependent fashion. Usually, doses less than 4 mg/kg decreased IOP. However, due to limitations and weaknesses, several retrospective and prospective studies have not been able to conclude a solid recommendation on ketamine use in this patient population [15].

Paralysis

There is not enough current evidence to recommend rocuronium over succinylcholine for rapid sequence intubation (RSI) in patients with TBI. Notably, it was shown that sustained paralysis with rocuronium could prevent repeat neurologic exams. Patients who receive rocuronium are also administered less sedation and analgesia post-intubation because paralysis makes it appear the patient is sedated. In addition, the rapid offset of succinylcholine allows for early neurologic exams [16].

Ventilation

While additional therapies are being implemented, a brief moment of hyperventilation (< 2 h) to a PaCO2 of 30–35 mmHg may be considered. In addition, hyperventilation for a goal of mild to moderate hypocapnia (PaCO2 25–34 mmHg) may be considered in patients who have failed other management strategies. However, hyperventilation for more than 6 h is unlikely beneficial and may exacerbate ischemic injury due to cerebral vasoconstriction. Ideally, cerebral oxygen monitors, such as jugular venous oximetry or brain tissue oxygen monitoring, should be implemented to monitor for cerebral ischemia [17].

Biomarkers

Sustained efforts have been made to identify biomarkers of the injury that results from TBI to detect ongoing injury, to stratify the need for monitoring and interventions and to provide prognostic information. Several biological compartments have been assessed including serum, cerebrospinal fluid, cerebral microdialysate from brain extracellular fluid, and brain tissue. Biomarkers are currently not performed routinely outside of clinical research contexts. Noteworthy biomarkers in TBI include glia-related biomarkers (GFAP, S100B), neuron/axon-related biomarkers (neuron-specific enolase [NSE], neurofilament light polypeptide [NFL], ubiquitin carboxy-terminal hydrolase [UCH-L1], tau, amyloid β, αII-Spectrin breakdown products among others) and other inflammation-related biomarkers (high mobility group box protein 1 [HMGB1], various cytokines and autoantibodies) [18].

Therapeutic Hypothermia

There are several plausible mechanisms by which hypothermia can mitigate the effects of TBI including reducing ICP, reducing the innate inflammatory response and reducing the cerebral metabolic rate. These need to be balanced against the risks of coagulopathy, immunosuppression, hypotension, pneumonia, renal impairment and decreased catecholamine responsiveness. Two large phase 3 randomized trials have attempted to show the putative benefit of therapeutic hypothermia. The multi-center non-blinded Randomized Controlled Trial (RCT) Eurotherm3235 (2015) is the largest trial on hypothermia for patients with intracranial hypertension (> 20 mmHg) after TBI [19].

Optic Nerve Sheath Diameter Sonography for Diagnosis of Elevated IOP in TBI

Intracranial hypertension is a widely known severe condition caused by different diseases. Disease management and diagnosis are challenging. The brain could be damaged by compressing effects on the intracranial structures or reducing the blood flow. Brain ischemia or brainstem herniation is a possible complication of intracranial hypertension, which may lead to destructive and fatal deterioration [20]. Invasive intracranial devices are still the primary approach to measuring intracranial pressure (ICP) [20].

Intracranial hypertension occurs when ICP is 20 mmHg [21]. Invasive ICP monitoring is associated with many complications such as hemorrhage or infection with a significantly high risk of bacterial colonization [22]. As a result, it is essential to find new non-invasive methods for monitoring ICP, even though several techniques are available [23]. In case of the lack of invasive intracranial devices or contraindications in some situations, there are non-invasive methods such as magnetic resonance imaging (MRI) and computed tomography (CT) scan that can be rapidly used to predict increased ICP [24]. However, these techniques are too expensive, need prolonged acquisition, are not available in all health care centers, and usually need transporting the patient, which may be limited or harmful [24].

Transcranial Doppler sonography (TCD) may give a picture representative of intracranial hypertension. The Transcranial Doppler sonography pulsatility index reveals the reduction in the cerebral perfusion pressure caused by intracranial hypertension. On the other hand, it needs an expert radiologist, as TCD is not easy to perform, even with an experienced physician [25].

Fundus examination is widely used as an assessment tool in cases of cerebral edema because it is noninvasiveness, easy to be repeated, and experienced ophthalmologists can be readily available as this technique has been used for decades. However, it has some disadvantages as follows: it is operator-dependent, and the need to prepare the patient to examine the form of mydriatic drops may interfere with assessing pupil responses and cause blurred vision. Also, it is a qualitative assessment; therefore, it is challenging to monitor the changes accurately [26].

Ultrasonographic (USG) measuring of optic nerve sheath diameter (ONSD) shows increased interest in the last years. This is because ultrasonography has become a bedside and simple tool commonly used in emergencies. The equipment needed is usually cheap and available. The ICP can be indirectly evaluated through the measurement of the optic nerve, anatomically occurring in the subarachnoid space and wrapped with a sheath derived from the meninges, extending towards the orbit. This communication allows CSF to transfer, transmitting the changes between ICP and infraorbital subarachnoid spaces pressure [27].

The Value and Limitations of ONSD Measurement

The optic nerve (ON) is a continuation of the central nervous system and is surrounded with cerebrospinal fluid (CSF) and meningeal layers that are directly contiguous with those around the brain. Therefore, when the pressure in the CSF increases, the optic nerve sheath (ONS) can distend, which makes optic nerve sheath diameter (ONSD) a potential surrogate for intracranial pressure (ICP) assessment. Transorbital ultrasonography (US) is an ideal tool for repetitive noninvasive measurements. The retrobulbar segment of ONS appeared to be the most sensitive to increases in CSF volume according to previous cadaveric studies. ONSD had been compared to invasive ICP measurements including spinal taps, external ventricular drains, and intraparenchymal transducers; ventriculoperitoneal shunt malfunction; and CT or MRI imaging findings consistent with elevated ICP [28].

US of the ONSD have shown to have moderate to high sensitivity for the detection of elevated ICP, ranging from 86% to 97% [29]. However, ONSD has still not found widespread acceptance in the clinical practice, as studies uncover several issues including wide heterogeneity in measurements with ranging from 50.6% to 97.3% [29], large variations in ONSD cutoffs used for determination of elevated ICP, ranging from 4.2 to 6.5 mm with wide confidence intervals [29], limited reporting of the effect of age and gender on measurements [29], variations in transducers and frequencies used [29], different measurement planes [29], variable requirements for averaging multiple measurements from the same eye or both eyes [29], different patient positioning during

measurement [29], using different training requirements or definitions of experts [29] and large interobserver variations [29].

In addition, some studies performed ONSD measurements incorrectly measuring the ON instead of ONSD, or not including the entire ONSD in the sample measurement image. These inconsistencies in ONSD image acquisition and measurement are implicated as a potential cause of large heterogeneity in the results of ONSD studies. This scoping review aims to identify and classify existing ONSD measurement quality criteria (QC) and describe variations in transorbital US technique. Variations in descriptions of anatomy and the definitions of IB, SHB, and OB are shown in Figure1 [30].

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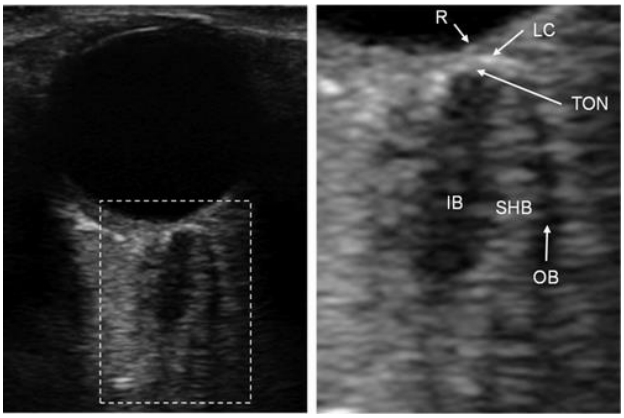

Figure 1: Anatomic definitions [30].

Addressing this category is challenging because of three main issues: poor anatomic differentiation, little agreement on the ONS anatomic structures on ultrasound, and the use of two main measurement methods, referred to here as internal ONSD (ONSDint) and external ONSD (ONSDext). Poor anatomic differentiation, where the ON cannot be differentiated from the ONS, can be due different factors including incorrect transducer placement, inability to capture the central cross-section of the ONS, or use of low transducer frequency with lower resolution which can lead to incorrect measurements [31].

When a good anatomic differentiation was present, three sonographic areas were noted: the inner hypoechoic band corresponding to the ON, surrounded by the stripped hyperechoic band, which in turn, was surrounded by an outer hypoechoic band [32]. ONSD can be measured in two different ways: ONSDint, where ONSD is measured at the border between the SHB and OB, and ONSDext, where ONSD is measured outside the OB. One study showed that ONSDext had mean values higher by 0.67 (range: 0.2-1.2) mm compared to the ONSDint. ONSDint also had a higher effect size between elevated ICP and normal controls (1.5 mm difference) when compared to the ONSDext (0.9 mm difference) [33].

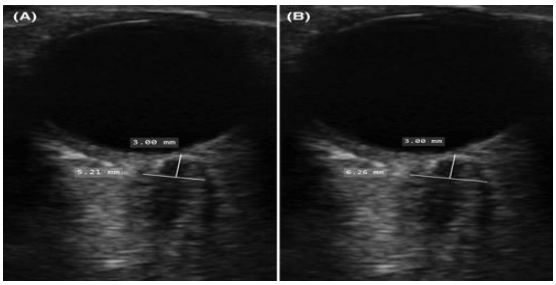

Figure 2: ONSD measurement methods. The two main measurement methods reported in the literature measure the stripped hyperechoic band (SHB) alone by placing the measurement caliper at the boundary between the SHB and the surrounding outer hypoechoic band (OB), referred to here as the “internal ONSD” (A); alternatively, the calipers are placed outside the OB, referred to here as the “external ONSD” (B) [34].

In conclusion, Measurements of ONSD may be a valuable noninvasive surrogate marker for elevated ICP. Transorbital US is widely used for this purpose, being a noninvasive bedside tool with an excellent safety profile [34].

Dexmedetomidine

Dexmedetomidine, a potent and highly selective α-2 adrenoceptor agonist, has been described as a unique sedative with analgesic, sympatholytic, and respiratory-preserving properties. It has been approved by the U.S. Food and Drug Administration for short-term sedation (< 24 h) of initially intubated and mechanically ventilated adult patients in the intensive care unit (ICU) and for sedation of non-intubated patients during surgical and other procedures. Although dexmedetomidine is now widely used for the above indications in the ICU and the operating room, its clinical applications have been greatly expanded in recent decades due to many favorable physiological effects [35].

Effects of dexmedetomidine

- **Sedative effects**

Dexmedetomidine induces a unique sedative response, known as "arousal sedation" or "cooperative sedation", which shows an easy transition from sleep to wakefulness, thus allowing a patient to be cooperative and communicative when stimulated. This sedative property of dexmedetomidine is similar to natural sleep. Dexmedetomidine is known to suppress noradrenergic neuronal firing of the locus ceruleus in the brain stem, which leads to a loss of wakefulness via activation of an endogenous sleep-promoting pathway. Although patient cooperation can be achieved using other sedatives, with careful dose titration, dexmedetomidine may promote cooperative sedation more easily within the recommended dosage range [36].

It was demonstrated that healthy volunteers sedated with dexmedetomidine (0.2 or 0.6 μg/kg/h after a bolus dose of 1 μg/kg) could be easily aroused when asked to perform various tests, but then returned to a sedative state when left alone. Dexmedetomidine shows dose-dependent sedative effects. If large enough doses are administered, dexmedetomidine produces deep sedation or even general anesthesia, which suggests that dexmedetomidine, has the potential to become part of a total intravenous anesthesia strategy. However, the cardiovascular effects of dexmedetomidine may limit this application, especially in less healthy patients. Despite dose-related sedation, memory and cognitive functions are not severely impaired with dexmedetomidine administration [37].

Dexmedetomidine may provide adequate sedation in critically ill patients. In early clinical trials, dexmedetomidine showed a similar level of sedation to propofol, and the mean times to extubation were also comparable. When compared with the propofol group, mean heart rates were mostly lower, but not less than 60 beats/min, and opioid requirements were significantly lower in the dexmedetomidine group. Furthermore, a recent study demonstrated that dexmedetomidine decreases the duration of mechanical ventilation [38].

- **Analgesic effects**

The analgesic properties of dexmedetomidine are mediated by several mechanisms, including spinal, supraspinal, and peripheral actions. However, the analgesic efficacy of dexmedetomidine is controversial. A ceiling effect has been shown in an ischemic pain model in healthy volunteers at doses > 0.5 μg/kg. However, in a cold pressor test, a dose-dependent analgesic effect was noted over a wide range of plasma concentrations from 0.5–8.0 ng/ml [39].

The opioid-sparing effect of dexmedetomidine has been well documented in several clinical trials. Even as a sole analgesic, a 0.4 μg/kg dose of dexmedetomidine can be effectively used for pain relief after laparoscopic tubal ligation, although accompanying drowsiness and bradycardia may be undesirable side effects during the recovery period. A recent meta-analysis of 21 randomized trials demonstrated that intraoperative dexmedetomidine administration for general anesthesia was superior to remifentanil administration, with

lower pain scores during the first 24 postoperative hours and with less hypotension, shivering, and postoperative nausea and vomiting [40].

Dexmedetomidine has anti-nociceptive effects on both somatic and visceral pain when administered via the neuraxial route. A recent meta-analysis including 16 randomized controlled trials showed that neuraxial dexmedetomidine administration significantly decreases postoperative pain intensity and prolongs analgesic duration but with an increased risk of bradycardia [41].

The potential application of dexmedetomidine for the treatment and prevention of neuropathic pain has also been investigated. Local injection of dexmedetomidine was shown to produce an antiallodynic effect in spinal nerve ligation-induced neuropathic pain in a rat model. Moreover, the use of pre-emptive intravenous dexmedetomidine reduces post-thoracotomy pain syndrome after coronary artery bypass surgery [42].

- **Neurosurgery**

Dexmedetomidine, with or without the addition of remifentanil, has emerged as the most useful agent in providing safe and acceptable conditions during neurosurgical procedures in awake patients. In particular, in awake craniotomy, which requires sophisticated neurological assessment, several studies have demonstrated that dexmedetomidine has many advantages. Cooperative sedation by dexmedetomidine may permit neurological assessment, while avoiding tachycardia and hypertension. Furthermore, dexmedetomidine has potential neuroprotective effects, including decreasing intracranial pressure and dose-dependently reducing cerebral blood flow and cerebral metabolic rate [43].

A possible explanation for these neuroprotective effects is the modulation of neurotransmitter release in the central and peripheral sympathetic nervous systems. A recent randomized controlled trial showed that the quality of intraoperative brain mapping and the efficacy of sedation with dexmedetomidine were similar to those of propofol-remifentanil during awake craniotomy. Moreover, adverse respiratory events were fewer in the dexmedetomidine group. The successful use of dexmedetomidine for awake craniotomy in children has also been reported [44].

Safety

Most of the adverse events associated with dexmedetomidine occur during or shortly after a loading infusion. A loading infusion often results in hypertension, hypotension, or bradycardia, which are closely related to the loading dose and infusion rate. The incidence of these adverse events can be prevented by slow bolus loading or by omitting bolus loading. In fact, many clinicians tend to avoid the administration of a loading dose, especially in critically ill patients. A slow titration to maintain the infusion rate of dexmedetomidine can also be helpful in preventing adverse events. It was demonstrated that the incidence of hypotension was significantly reduced by increasing the time interval between dosage adjustments in the surgical ICU [45].

Although the incidence of severe bradycardia is low, there are some case reports of dexmedetomidine-related cardiac arrest. Cardiac conduction disorders, including left anterior fascicular block and first-degree AV block, and the co-administration of amiodarone and dexmedetomidine are potential factors contributing to the development of asystole, especially during general or regional anesthesia. In addition, caution should be taken when administering dexmedetomidine to patients with volume depletion or vasoconstriction. Adequate selection of patients and dosage is most important for the safe use of dexmedetomidine [46].

Recently, numerous studies have focused on assessing the influence of anesthetic management on cancer recurrence or metastasis. It was reported the impact of clinically relevant doses of dexmedetomidine on the metastatic burden in rodent models of stress and surgery, which are similar to perioperative settings. They found that tumor cell retention and the growth of secondary tumors increased with moderate and high doses of dexmedetomidine. They also reported that these effects were mediated through α-2 adrenergic receptors, although the specific mechanism of action was not elucidated. These negative findings from animal experiments do not necessarily predict similar results in human trials and, thus, further mechanistic, translational, and clinical studies are warranted [47].

In conclusions: Dexmedetomidine is a useful and attractive drug, with great potential in many clinical situations. However, certain extended applications of dexmedetomidine require further evaluation. To ensure the safe use of dexmedetomidine, it is necessary to carefully select patients and to determine the appropriate dosage [48].

Effects of dexmedetomidine on outcomes of TBI

Traumatic brain injury (TBI) is a critical public health problem worldwide. Globally, approximately 69 million individuals suffer TBI from all causes each year. TBI leads to disability and death and places a substantial socioeconomic burden on every country. Therefore, guidelines based on clinical research were designed by different medical communities and associations to provide high-quality care to TBI victims and improve their outcomes [49].

Among the strategies included in these guidelines, sedatives and analgesics was recommended to reduce intracranial pressure (ICP) and the cerebral metabolic rate of oxygen (CMRO2), to control seizures and facilitate compatible mechanical ventilation. Dexmedetomidine (Dex), with its unique characteristics of sedation without respiratory depression and residual metabolites, concomitant analgesic and sympatholytic effects, and no interference in neurological assessment or weaning from mechanical ventilation, was presumably considered suitable for the sedation of TBI patients. However, although many basic studies have suggested Dex's neuroprotective effects in TBI patients, the available clinical evidence is insufficient to prove its benefits on TBI outcomes [50].

A previous study demonstrated that Dex significantly improved the survival of TBI patients. Regarding the TBI complication, hypotension was not significantly higher in the Dex group than that in the control group. It was suggested that hypotension is an adverse reaction to be aware of, but can be avoided or reduced when used in selected patients. Additionally, Dex usage was the only independent protective factor for patient outcome [51].

Although many studies have previously examined the effects of Dex on TBI, none of them ascertained the survival-facilitating effect of Dex in the clinical context. Studies carried out in murine TBI models suggested Dex's protective effects. It was showed that Dex prevented the injured brain from tissue lesions and cell death, and reduced axonal injury and synaptic degeneration if used at a dose of 100 μg/kg. It was demonstrated that Dex exerts its protective effects through anti-inflammatory properties via suppression of NF-κB and NLRP3 inflammasome activation through the attenuation of endoplasmic reticulum stress-induced apoptosis [52].

It was proved that different doses of Dex all attenuated neuroinflammation. However, although Dex had long been considered "promising" in the "Lund concept" put forward by Lund University, Sweden, clinical investigators were cautious in validating its survival-facilitating effect [53].

Recently, it was found to be associated with a reduction in paroxysmal sympathetic hyperactivity and agitation in TBI patients. Although opposite opinions exist considering Dex's side effects of reducing blood pressure and heart rate, researchers agreed that more studies would be necessary to evaluate Dex's effects on TBI patients. In ICU practice, there are several choices for sedation. Those most frequently used for TBI include propofol, midazolam, ketamine, and Dex [54].

As Dex is not the only choice, and it has not been confirmed to be beneficial to TBI patients, it is not used as widely as some of the other sedatives. In our study, the use of other sedatives was balanced between groups using propensity score analysis. Other baseline characteristics included in the analysis (age, gender, the APS III score, the CCI score, the GCS score, and pupillary response) are parameters that are usually considered in prognosis judgement. APS III and CCI scores were calculated to reflect the disease severity and chronic health status, respectively. They are substitutes for the APACHE III score, which also includes an APS III part and a chronic health status part. Although fewer items on chronic health status are included in the APACHE III scoring system, they could not be wholly collected from the MIMIC database [55].

The CCI contains more items (17) on chronic health status, which can be easily obtained. It is common for TBI patients to have other combined injuries. Still, these injuries must cause organ dysfunction or occur in frail people to result in mortality, which can be evaluated by the APS III and CCI. [56].

With the propensity score matching and weighting method, the imbalance of baseline characteristics was basically corrected, for the SMD of the covariates between groups were controlled within 0.1 at large. This would make the following regression analysis conclusions more tenable. It was warranted that the use of Dex in TBI patients. It may improve the survival of TBI patients, and brings no apparent adverse reaction of hypotension, infection, or seizure. Hypotension may influence 6-month mortality, so it is advisable to keep aware of it in using Dex [51].

- **Decompressive craniotomy**

Decompressive craniectomy (DC) is a method of removing a substantial portion of the skull vault to reduce ICP and reduce the consequent deleterious sequelae. Randomized Controlled Trial (RCT)-based recommendations of trauma DC flap size in refractory raised ICP due to severe TBI suggest the use of 12 × 15-cm flaps is associated with lower mortality (26% vs 35%) and higher Extended Glasgow Outcome Scale (GOS-E) scores when compared to smaller flap sizes. DC can be classified as primary—after evacuation of a hematoma during the acute TBI phase and secondary—independently of hematoma evacuation for ICP control [57].

Midazolam

Intravenous midazolam is used for the induction of anesthesia and also in the management of acute seizures. Because of its water-soluble nature, midazolam has a rapid onset of action and can be used to manage status epilepticus when intravenous administration of other medications is not feasible. Midazolam has a high rate of tolerance, and the dose can be increased to maintain the therapeutic effect. Because of its easy mode of administration through the buccal and intranasal routes, it is a viable option in children to manage seizures. For its use in anesthesia, the response to the induction dose is more variable compared to thiopental. Midazolam can be used for anxiolysis and hypnosis during the maintenance phase of general anesthesia and is also superior to thiopental in the maintenance of anesthesia because of the less need for adjunct medications. Midazolam is an adjunct medication to regional and local anesthesia for a wide range of diagnostic and therapeutic procedures and has greater patient and physician acceptance [58].

Mechanism of action

Midazolam has poor oral absorption and has an elimination half-life of 1.5 to 2.5 hours. Midazolam converts into its active metabolite alpha-1 hydroxy midazolam, which contributes to 10% of drug action. Midazolam metabolism occurs via hepatic CYP450 enzymes and glucuronide conjugation. The mechanism of action of midazolam indirect and is related to GABA accumulation and its affinity to the benzodiazepine receptors. Two separate receptors for GABA and benzodiazepine couple to a common chloride channel. It increases the frequency of chloride channel opening [59].

Occupation of both the receptors cause membrane hyperpolarization and neuronal inhibition. The anticonvulsant activity of midazolam is related to the excess GABA action on motor circuits in the brain. Midazolam acts on glycine receptors and produces a muscle-relaxing effect. Almost all the pharmacologic effects, including sedation, anxiolysis, and anterograde amnesia, and anticonvulsant effect, can are explainable through its action on GABA receptors. Age-related deficits, hepatic, and renal insufficiency, also affect the pharmacokinetics of midazolam. Midazolam has both hydrophilic and lipophilic properties, depending upon the pH [60].

Administration

Midazolam administration can be through oral, intranasal, buccal, intravenous, and intramuscular routes. For the perioperative use of midazolam, the induction dose is 0.15 to 0.40 mg/kg via the intravenous route. For the premedication, the dose is 0.07 to 0.10 mg/kg with the intramuscular route. For intravenous sedation, the dose is titrated at 0.05 to 0.15 mg/kg. For children 1 to 5 months old, the recommended intranasal dose is 0.2mg/kg. For children six months and older, 0.2 to 0.3 mg/kg intranasal dose is the recommendation. Since elderly patients metabolize benzodiazepines more slowly and are more prone to adverse effects, caution is advised when administering the drug in that patient population [61].

Adverse effects

The common adverse effects associated with midazolam use are hiccoughs, cough, nausea, and vomiting. Thrombophlebitis, thrombosis, and pain on injection are other adverse effects. The incidence of thrombophlebitis is less than with diazepam but similar to that of thiopental. Midazolam causes anterograde amnesia, drowsiness, ataxia, falls, and confusion in the elderly. Residual hangover effect can happen with nighttime administration of midazolam, which can impair the cognitive and psychomotor abilities, which can result in falls in elderly and impaired coordination during driving. Hypotension and tachycardia can occur with rapid intravenous administration. A higher dose can result in midazolam infusion syndrome and respiratory depression [62].

Instances of midazolam infusion syndrome require continuous ventilator support. Paradoxical effects of midazolam are possible in individuals with a history of alcohol abuse and aggressive behavior, potentially leading to involuntary movements, verbalization, uncontrollable crying, and aggressive behavior. Respiratory depression can happen with a dose of 0.15 mg/kg, and the risk increases when used along with fentanyl. Concomitant use of midazolam with other CNS depressants can result in severe respiratory depression and death even at therapeutic doses [63].

Long-term use of midazolam is associated with lasting memory deficits, which are only partially reversible after discontinuing the drug. For pregnant women, the administration of the drug in the third trimester causes benzodiazepine withdrawal syndrome in the neonate resulting in hypotonia, cyanosis, and apnoeic spells. Neonates may suffer from diarrhea, tremors, and hyperexcitability. About one-third of individuals receiving midazolam can suffer from tolerance after using the drug for four weeks. Withdrawal syndrome can occur if the dose tapers too rapidly. Symptoms due to the withdrawal of benzodiazepine include irritability, clonus, hypertonicity, nausea, vomiting, diarrhea, tachycardia, and hypertension. Sudden discontinuation of midazolam can result in status epilepticus [64].

Contraindications

Contraindications for the use of midazolam include acute angle-closure glaucoma, hypotension, and shock. Careful dose adjustment is necessary in cases of kidney and liver diseases, alcohol, and drug-dependent individuals. Caution is necessary for pregnant individuals, children, and individuals with comorbid psychiatric conditions. Administration in elderly individuals and acutely ill patients requires caution to prevent the accumulation of active metabolites. Extra precautions should be taken in critically ill individuals as dose accumulation can occur [65].

Monitoring

Frequent monitoring of blood levels of midazolam and its metabolites is a requirement during the treatment of midazolam overdose. Levels of midazolam and its metabolites can are measurable in blood, plasma, and serum. Monitoring is essential for elderly individuals and individuals with liver and kidney disease. The elimination of both the drug and its metabolite decreases with renal insufficiency. Monitoring is also necessary for drug interactions with erythromycin, clarithromycin, diltiazem, sertraline, protease inhibitors, rifampin, phenytoin, phenobarbital, carbamazepine, opioids, antipsychotics, and alcohol. Induction and inhibition of CYP450 3A4 play a role in decreased and increased drug levels in the circulation. Grapefruit juice reduces the activity of the CYP 450 enzyme and increases the level of the drug. St. John's worth induces the enzyme and reduces the blood level of midazolam [66].

Toxicity

Toxicity with midazolam is rare but can happen when combined with other CNS depressants like alcohol, opioids, and other tricyclic antidepressants. The risk increases with intravenous administration and in elderly individuals with COPD. Symptoms of overdose include ataxia, nystagmus, hypotension, slurred speech, slurred speech, impaired motor coordination, coma, and death. Impaired reflexes, impaired balance and dizziness, dysarthria, and vasomotor collapse can also occur. Flumazenil is the antidote for midazolam toxicity. Supportive treatment is the initial therapy course. Activated charcoal is an option within 1 hour of intoxication. In many instances, flumazenil is not prudent, as it can precipitate seizures when used in a mixed overdose of

CNS depressants. Rapid intravenous infusion in elderly individuals having COPD can also result in an overdose [67].

Effect of midazolam on IOP in severe TBI

The present guidelines state that early management in a severe traumatic head injury for intubated patients in the intensive care unit (ICU) is to be accomplished with sedation alone and that neuromuscular blockade (NMB) is to be reserved for patients with raised intracranial pressure (ICP) that requires escalation of treatment intensity [68].

Midazolam and propofol are the preferred drugs for sedation in the ICU as they lower the ICP by lowering the cerebral metabolism (cerebral metabolic rate of oxygen-CMRO2). Midazolam is cheaper than propofol in the doses required to achieve a high level of sedation in severe head injury and hence more appropriate in a resource-constrained environment [69].

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