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Abstract

As research and science has progressed to further analyze the effects of anesthetics on cerebral physiology, the margin of safety for each anesthetic is reassessed to enhance patient outcomes and recovery. The purpose of this review is to strategically examine and provide updated information on the impact of specific anesthetics administered during the intraoperative period as it applies to patients with acute traumatic brain injury (TBI). In efforts to preserve the cerebral physiology of the patient, current research has identified benefits of administering intravenous over inhalation anesthetics to reduce secondary injuries that have been linked to chronic TBI, morbidity, and mortality. Concentrating on common anesthetics used in the United States of America, research included in this review identified desflurane, sevoflurane, isoflurane, and nitrous oxide as the most studied and accessible inhalation anesthetics for this group of patients during the intraoperative period. Comparatively, intravenous anesthetics propofol, ketamine, benzodiazepines, opioids, and etomidate were more closely evaluated. At the conclusion of this review, the nurse anesthetist will be empowered with current clinical research to make a balanced and informed decision when caring for a patient with acute TBI.

Keywords: traumatic brain injury, neuroprotection, anesthesia, intravenous, inhalational anesthetics, halogenated anesthetics

Comparing Intravenous and Inhalation Anesthetics for Intraoperative Anesthesia in Adult Patients with an Acute Traumatic Brain Injury

A patient presenting with TBI will have varying physical and physiological injuries that present challenges for the nurse anesthetist to provide stabilization or resuscitation efforts. According to Georges and Das (2022), approximately 1.7 million people sustain a TBI in the United States every year. This emphasizes the importance for well-coordinated care to evaluate, manage, and improve patient outcomes. Unique to many other injuries, TBI produces an increased risk for secondary injuries to develop. These secondary injuries may be increased intracranial pressure (ICP), hypoxia, hypotension, hypothermia, electrolyte disturbances, toxic amino acids, oxygen radicals, and more. This insult may occur from the initial injuries or in response to anesthesia or surgical interventions, which highlights the importance of decisions made in the anesthesia care plan. While patients with secondary injuries have exhibited long-term deficits, slower recovery times, and higher morbidity, the implication of this study is to focus on the impact of anesthesia to compare intravenous and inhalational anesthetics and highlight superior anesthetics that reduce these risks and improve patient recovery.

The Brain Trauma Foundation (BTF) produced guidelines to enhance patient recovery from TBI and disclosed that the guidelines were adhered to in only 30% of documented cases indicating that approximately 70% of patients may not be receiving optimal care (Khormi et al., 2020). While patients presenting with an acute TBI require a delicate balance of anesthesia and surgical interventions, considerations for perioperative management need to lessen the medication contribution to secondary injuries while under anesthesia. The long-term impacts of secondary injuries from TBI requires additional research, however studies have found that there is an increased risk for Chronic Traumatic Encephalopathy, chronic neuronal injury, seizures,

subarachnoid hemorrhage (SAH), and death (George & Das, 2022). The chronic neurological changes that occur from secondary injuries of TBI may be preventable with appropriate anesthetic management. Although the major goals of anesthesia remain patient-specific, this level of injury requires delicately tailored medications to optimize the patient's recovery. Exploring anesthetic choices through the intraoperative period, anesthetics that offer neuroprotective benefits will be considered. To focus on current available anesthetics, research was collected on propofol, ketamine, etomidate, benzodiazepines, opioids, sevoflurane, isoflurane, desflurane, and nitrous oxide and compared.

Literature Review

Methodology

A computerized, systematic search of the University of New England Library database was performed to include Access Anesthesiology, Access Medicine, CINAHL Complete, Cochrane Database of Systematic Reviews, Lexicomp, MEDLINE, PubMed, Nursing & Allied Health database, Scopus, and UpToDate records. An additional search of Google Scholar was performed. This comprehensive search included keywords *traumatic brain injury, anesthesia, intravenous, inhalational anesthetics, halogenated anesthetics, neurosurgery, neuroprotection, neurotoxicity,* and *neuromonitoring*. Inclusion criteria consisted of the English language, full-text availability, adult patient population, acute TBI, and review articles published after 2012 with a focus on primary research and systematic literature review articles since 2016. Exclusion criteria consisted of studies older than 2012, languages other than English, and a pediatric patient population. A total of 24 sources were included; six consisted of primary research, six case studies, one meta-analysis, seven systematic literature reviews, two books, and two prospective

articles. Seven of the included articles were supported by data within the Cochrane Database system and cited within the work.

Total Intravenous Anesthesia

With ongoing advances in research, best practice to improve patient outcomes requires anesthesia providers to consider the advantages of specific available medications. This evidence-based decision should be based on quality, accuracy, and current data that is patient-focused and inclusive of their current injuries. The lack of consistent adherence to the BTF guidelines previously mentioned was correlated with higher rates of mortality and morbidity (Khormi et al., 2020). Consequently, the focus on knowledge of TBI considerations, neuroprotective medications, and individual patient needs necessitate broader reach to healthcare providers. As research expands, the considerations of total intravenous anesthesia (TIVA) and inhalational anesthetic choices aim to promote better outcomes for these patients. The following anesthetics were scrutinized for the safe intraoperative application with acute TBI and evaluated whether current research found improvements in anesthetic practice.

Propofol

As a widely used intravenous anesthetic, propofol has remained an essential sedative and hypnotic to provide patients with a smooth induction for general anesthesia. It is a phenol derivative emulsion and has many benefits, such as anticonvulsant, antipruritic, anxiolytic and antiemetic properties that can prevent and treat current conditions without the need for additional medications. According to Hausburg et al. (2020), propofol has antioxidant properties and reduces oxidative stress, inflammatory markers, and lipid peroxidation that may arise with general anesthesia. While this article has limited human data, the study showed evidence in a rat model that propofol exhibited evidence of increased survival rate of neurons after a cerebral

ischemic-reperfusion injury. This exhibited a reduction ischemia by 21% in the sample (Hausburg et al., 2020). Although ischemia does not specifically establish evidence of a TBI, the clinical implications are similar; whereas there is an elevated risk for ischemia following a TBI due to decreased cerebral blood flow (CBF) and resulting in secondary injuries (Vella et al., 2017).

Conversely, considerations for a patient with TBI are the side effects of propofol. Specifically, decreases in the following parameters: blood pressure (BP), mean arterial pressure (MAP), preload, contractility, systemic vascular resistance (SVR), cardiac output (CO), CBF, the cerebral metabolic rate of oxygen ($CMRO_2$), intraocular pressure (IOP), and ICP (Kannabiran & Bidkar, 2018). Given these risks, administering smaller doses to effect during induction is recommended to avoid large changes in hemodynamics, such as blood pressure, and consideration for use in conjunction with compensating medications, such as ketamine, which will be discussed later. According to Carney et al. (2017), there is evidence of morbidity when high doses of propofol have been administered. As a gamma-aminobutyric acid (GABA) receptor agonist, the onset and duration may vary depending on the neurological damage from the TBI (Carney et al., 2017).

Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that acts on mu-opioid receptors, muscarinic receptors, and sodium channels to provide patients with analgesia, hypnosis, amnesia, bronchodilation, and both positive and negative inotropic effects (Godoy et al., 2021). There are many benefits of ketamine, such as patients are more likely to retain their respiratory drive, upper airway reflexes, and spontaneous ventilation at low to moderate doses while under general anesthesia and maintaining hemodynamic stability. Evidence has shown

that ketamine aids in the prevention of secondary injuries by suppressing the spread of depolarization, which has been shown to result in delayed cerebral ischemia and long-term detrimental effects (Godoy et al., 2020; Madsen et al., 2021).

While the vasodilation that occurs with ketamine increases CBF, $CMRO_2$, and cerebral perfusion pressure (CPP), the ICP is usually minimal or unchanged. This is contrary to previous research that suggested ketamine increased ICP, causing detrimental effects. According to recent research, evidence has shown that ketamine causes little to no adverse effects on patient outcomes or mortality and although it may cause temporary ICP changes, the CPP remains unchanged after ketamine administration (Godoy et al. 2020; Bhattacharya & Maung, 2016).

As the use of ketamine has broadened, it has found a place in safe intraoperative management patients. In conjunction with other medications, ketamine promotes the ability to awaken patients intraoperatively for neurological assessments, to maintain hemodynamic stability, to reduce the risk for hypotension, and to promote faster detection of worsening neurological conditions in a patient with TBI (Adams et al., 2017). Ketamine usually preserves or increases MAP and may increase the amplitude of evoked potential monitoring that may be used intraoperatively to monitor neurological electrical activity during the procedure. The effect on EMP should be considered when neuromonitoring is being implemented. There has been no evidence of ketamine affecting the latency of evoked potential monitoring (Adams et al., 2017).

While the uses of ketamine are increasing, the benefits mentioned previously may present contraindications and risks for patients with TBI. In patients with acute TBI, there may also be trauma to other organs that may affect anesthetic metabolism and excretion. Specifically, the liver and kidneys should be assessed due to many anesthetics undergoing hepatic metabolism and renal elimination. According to Godoy et al. (2020), in the presence of hydrocephalus, a

current brain aneurysm or the loss of cerebral autoregulation, ketamine could cause detrimental effects. Additionally, nausea, vomiting, dizziness, diplopia, drowsiness, dysphoria, and confusion are side effects that could impact neurological assessments and increase the neurological risk for increased ICP.

Benzodiazepines

The most common medication administered for TBI is midazolam, although diazepam and lorazepam are included in this class. The primary distinction is the faster onset and shorter duration of 30-60 minutes of midazolam in comparison to up to several hours of duration by other benzodiazepines in its class. According to Kannabiran and Bidkar (2018), midazolam offers anticonvulsant properties by increasing the seizure threshold, causing sedation, decreasing MAP, decreasing CBF, $CMRO_2$, and CBF, causing anterograde amnesia, and having little to no impact on ICP, CPP, and CO. As an adjunct to ketamine, midazolam is commonly administered to reduce the risk for emergence delirium and hallucinations associated with larger doses of ketamine. Moreover, patients with TBI have an increased risk for agitation and delirium from the neurological injury, and they require a balanced anesthetic technique to promote a safe and smooth emergence. Therefore administering midazolam offers direct and indirect benefits to these patients (Bhattacharya & Maung, 2016; Capizzi et al., 2020). Additional considerations for administering midazolam while under general anesthesia are that they may cause increased heart rate, transient hypertension, and the reduction in airway reflexes and activity that may lead to a dose-dependent transient apnea or ventilatory depression. While these effects may not be contraindicated if the patient will be mechanically ventilated and adjunct to other anesthetics, the effects may increase the risk for aspiration if a rapid sequence induction is required.

Opioids

As important adjunct medications in anesthesia, opioids utilized frequently with an acute TBI are fentanyl and remifentanil. According to Kannabiran and Bidkar (2018), both opioids were found to be equally effective when utilized with TIVA for a neurosurgery case, however, remifentanil exhibited remarkable patient recovery and cough suppression when given at greater plasma concentrations. Remifentanil reduced the risk for increased ICP and secondary injuries upon emergence from anesthesia. While exclusive opioid administration offers analgesia, sedation, and dose-dependent respiratory depression, it also reduces the sympathetic response to laryngoscopy and surgical stimulation that could result in secondary injuries. In combination with other induction medications, such as propofol, optimal surgical conditions can be achieved by the opioids providing a fast onset, short duration, and analgesic properties not provided by induction medications. Furthermore, administering opioids may also produce decreased MAP, CBF, CPP, ICP and $CMRO_2$; therefore, the current condition of the patient influences the use and doses of opioids. If EMP monitoring is used intraoperatively, opioids are generally acceptable as they do not affect the amplitude and only cause modest increases to latency (Kannabiran & Bidkar, 2018). However, patients with an acute TBI may have a more permeable blood-brain barrier (BBB) from the trauma endured which may lead to increased opioid distribution, therefore decreased doses of opioids should be considered (Adams et al., 2017).

Etomidate

As a GABA-mimetic hypnotic medication, etomidate is an induction anesthetic that offers sedation with a rapid onset of less than 30 seconds and provides little to no cardiac depression with induction of anesthesia. This can be beneficial for a patient who cannot tolerate mild hypotension. Etomidate is a common anesthetic administered for a more balanced

induction of anesthesia (Bhattacharya & Maung, 2016). The benefits of etomidate include decreased oxygen consumption, ICP, IOP, and $CMRO_2$. With a duration of less than ten minutes, etomidate causes minimal respiratory depression, which reduces the risk for hypoventilation, hypercapnia, ischemia, and hypoxia. With other induction medications, these effects can cause cascade of effects that can lead to secondary injuries (Georges & Das, 2022).

Etomidate will significantly decrease amplitude and moderately increase the latency of neuromonitoring if EMP is being used and should be considered (Kannabiran & Bidkar, 2018). The short duration of etomidate may deem this side effect inapplicable and further research into neuromonitoring may be necessary to consider this an intraoperative concern. Additional considerations for a patient with TBI are a history of Addison's disease, porphyria, or evidence of sepsis, as etomidate can exacerbate these symptoms of adrenal insufficiency.

Important to the patient with TBI, etomidate causes decreased CBF, cerebral metabolic rate, oxygen consumption, increased CPP, nausea and vomiting, adrenal suppression, and myoclonus that can appear seizure-like (Kannabiran & Bidkar, 2018). This effect may be minimized by pre-medicating with midazolam and fentanyl.

Inhalational Agents

Desflurane

Even as the fastest inhalational anesthetic in use, desflurane is not always the first-line agent for anesthesia despite its low blood-gas and oil-gas partition coefficient. While it offers both neurological and cardiac protection, the disadvantages of desflurane can be detrimental for patients with TBI. As an airway irritant, this pungent agent can induce coughing, breath holding, laryngospasm, copious secretions, and hypoxia that increase the risk for secondary injuries. Additionally, reflex tachycardia and hypertension were also noted to occur from the sympathetic

stimulation of desflurane, all of which present severe consequences for a patient with an acute TBI (Nagelhout & Sass, 2018). According to Kannabiran and Bidkar (2018), desflurane has been shown to decrease MAP and $CMRO_2$ and increase CBF, CPP, and ICP. Nonetheless, research has shown evidence of desflurane providing neurovascular protection in cases of neurological trauma by protecting against decreased cerebral ischemia. While the protective mechanisms remain unclear, research by Jayaraman et al. (2021) supported additional data on these neuroprotective benefits. While this study revealed favorable strengths for desflurane administration for patients with TBI, it is noted that the mechanisms of action, therapeutic window, and long-term neurological effects of desflurane on this group of patients are not clearly understood and remains a weakness for safe clinical application.

Sevoflurane

Sevoflurane is a common inhalation agent with a moderate blood-gas and oil-gas partition coefficient with a rapid onset and offset. As a non-pungent inhalation anesthetic, it is a worthy option for inhalation induction and patients with reactive airway disease, providing beneficial bronchodilation and the least amount of airway irritation among its counterparts. Furthermore, research data has shown sevoflurane to decrease MAP and $CMRO_2$ and increase CBF, CPP, and ICP (Kannabiran & Bidkar, 2018). Like desflurane, sevoflurane also helps attenuate large vessel vasospasms and thrombosis induced by SAH.

The neuroprotective benefits of sevoflurane make it an ideal inhalational anesthetic for patients with TBI. According to Wang et al. (2021), sevoflurane exhibited evidence of neuroprotection as it suppressed TBI-induced neuronal apoptosis, delayed neuronal changes, and reduced excessive autophagy that can produce hypoxic-ischemic brain injuries. Furthermore, increased BBB permeability and increased brain water that occurred with an acute TBI were

observed, and these effects improved or reversed by administration of sevoflurane in the sample of rats used in this clinical study. While this research tested sevoflurane administration at different concentrations, the limitations include the non-human samples and lack of identifiable influences on secondary injuries during the recovery period. It was not evident what minimum alveolar concentration (MAC) was considered therapeutic or ideal to achieve these results.

Isoflurane

Chemically similar to desflurane, isoflurane is minimally metabolized, but its effect has a slower onset and offset attributed to being more soluble than the other inhalation anesthetics; the blood-gas and oil-gas partition coefficients of isoflurane are higher than many other inhalation agents. Isoflurane has shown evidence of neurovascular protection in cases of neurological trauma by protecting against delayed cerebral ischemia (Jayaraman et al., 2021). Isoflurane has also shown evidence of reducing or preventing neuronal apoptosis, BBB disruption, and inflammation through neuroprotective mechanisms in studies with mice models. According to Bhattacharya and Maung (2016), isoflurane was also recognized to inhibit cellular apoptosis via the cytokine cascade. While shown to increase membrane fluidity, it also exhibited limited effects on ischemic or hypoxic events following a SAH. Although the mechanism of action appears to be similar between isoflurane and sevoflurane, the evidence requires additional investigation (Altay et al., 2020). This data has been exhibited during a predictable brain injury with ischemia for pre-operative treatment, which would not be a typical application for anesthesia although this application has shown isoflurane to modulate excitotoxicity.

Nitrous Oxide

As a rapid onset inhalation anesthetic, nitrous oxide has a low blood-gas and oil-gas partition coefficients and intraoperatively has a relatively fast onset and offset. While it provides

analgesic properties, data revealed that it was not the ideal inhalation agent to be used for these patients. Specifically, the research identified nitrous oxide to cause cerebral dilation and increase the risk for patients with acute TBI to experience increased ICP, creating precarious conditions to develop secondary injuries. In fact, it was suggested that due to these risks, nitrous oxide should not be administered (Bhattacharya & Maung, 2016). Nonetheless, nitrous oxide had little or no effect on MAP, decreases CBF and CO, increases CBF, HR, and SVR, and has variable effects on $CMRO_2$. Additionally, data showed that nitrous oxide decreased amplitude in EMP monitoring, but did not affect latency (Kannabiran & Bidkar, 2018; Nagelhout & Sass, 2018).

Increased Risk Factors Associated with TBI

While the medications researched in this review are administered every day in anesthesia, the margin of safety is variable as it applies for each patient, condition, and setting in which it is given. For this review, each anesthetic was assessed through a unique focus on how safe it is for use intraoperatively for patients experiencing an acute TBI. Consequently, many of the common anesthetics are not ideal. Although the neurological insult from a TBI can be difficult to manage, the priority for the nurse anesthetist is to return or maintain hemodynamic stability and prevent secondary injuries from occurring. Additional known secondary injuries associated with are hemorrhage, edema, reduced CBF, ischemia, stroke, and permanent neuronal deterioration (George & Das, 2022). Although conditions and risks are as unique as the patient, mechanisms that increase the risk for ischemia have been identified as the main source of secondary injuries. In fact, studies have shown that ischemic injuries will expand if reperfusion does not occur within four-to-six hours from the initial insult (Hausburg et al., 2020). According to Jayakumar et al. (2021), this is circumvented by decreasing ICP, promoting brain relaxation, and promoting

a situation for hemodynamic balance. The sequelae from TBI can also be avoided with adjunctive interventions to follow.

Adjunct Interventions to Aid Anesthesia Choice

While the knowledgeable provider will be ready to manage anesthetic choices for these patients, specific interventions have been adapted into practice with positive results to reduce secondary injuries from acute TBI. These interventions include ventilator settings, head elevation, temperature control, CT imaging, ventricular drainage, intermittent hyperosmolar therapy, mannitol/furosemide administration, plasma administration, neuromonitoring, maintaining blood glucose levels under 200 mg/dL, and invasive hemodynamic monitoring, such as an arterial line, CPP, ICP, and advanced cerebral monitoring (Carney et al., 2017; Bhattacharya & Maung, 2016). Robba et al. (2021) identified that lung injuries are a common secondary injury following a TBI. Although many of these patients require mechanical ventilation, it is unclear in this study whether it is due to ventilator settings or the inflammatory response from the trauma. Wettervik et al. (2019) provided additional research that mild hyperventilation resulted in improved pressure autoregulation, cultivating improved conditions for the patient to recover. Although these interventions are not the focus of this review, considering these strategies to reduce secondary injuries may aid in guiding the anesthetic choices. During the acute phase of care patients with TBI are usually most susceptible to secondary injuries and anesthetic decisions include whether it is in the best interest to postpone diagnostic or elective procedures (Abcejo et al., 2017).

Intravenous vs. Inhalation Anesthetics

As anesthesia impacts vital signs and hemodynamics in a healthy patient, maintaining balance and reducing the harmful effects of anesthetic choices are important goals in anesthesia.

Additionally, acute TBI can often alter the MAP, CPP, ICP, CBF, $CMRO_2$, and inflammatory response. Consequently, the risks and benefits of intravenous and inhalation anesthetics were compared.

Intravenous Anesthesia. A case report evaluated the post-operative status of a patient with acute TBI complaining of an unexplained severe headache relieved by local anesthetics (Robb, 2018). While the anesthetics used intraoperatively and postoperatively were not disclosed, the results exhibited positive results for the patients and can influence the important use of local anesthetics for neurotrauma. In comparison to inhalational anesthetics, TIVA has shown to have an abundance of benefits in managing anesthesia for patients with acute TBI as shown in Table 1 (Kannabiran & Bidkar, 2018). With the use of controlled infusions, effects are titrated to relax the brain with unawareness, analgesia, and hypnosis. Without the influence of ventilator settings and respiratory function, TIVA provides more target-controlled anesthesia to maintain the necessary sedation, analgesia, and amnesia to support safe surgical conditions for both the patient and the surgical team.

Table 1

Intravenous Agent Effects on Hemodynamics

Intravenous agent	MAP	CBF	CPP	ICP	$CMRO_2$
Propofol	⇓⇓⇓	⇓⇓⇓	⇑⇑	⇓⇓	⇓⇓⇓
Etomidate	0 - ⇓	⇓⇓⇓	⇑⇑	⇓⇓⇓	⇓⇓⇓
Ketamine	⇑⇑	⇓⇓⇓	⇓	⇑⇑⇑	⇑
Benzodiazepines	0 - ⇓	⇓⇓	⇑	0	⇓⇓
Opioids	0 - ⇓	⇓	0 - ⇓	0 - ⇓	⇓

Note: This table demonstrates the physiological changes that was collected from research data on intravenous anesthetics neurosurgery procedures. Adapted from Kannabiran, N., & Bidkar, P. U. (2018). Total intravenous anesthesia in neurosurgery. *Journal of Neuroanaesthesiology and Critical Care*, *5*(03), 141-149.

Furthermore, the side effects of intravenous anesthetics, such as cough suppression, reduce the risks for secondary injuries (Kannabiran & Bidkar, 2018). While a detrimental side effect of inhalation agents is a dose-dependent cerebral vasodilation that results in increased ICP, a balanced TIVA will facilitate adequate hemodynamics to maintain perfusion and reduce risks for bleeding and secondary injury. As data revealed that TIVA provided higher quality of hemodynamic management in comparison to inhalation anesthetics, specific intravenous agents, such as propofol, provide a dose-dependent decrease in ICP, CBF, and $CMRO_2$ (Jayakumer et al., 2021). Additionally, propofol demonstrated renoprotection, immunomodulation, and protection against cellular apoptosis and ischemia.

Inhalation Anesthesia. While the blood-gas and oil-gas partition coefficients vary between inhalation anesthetics, the significant delay in emergence creates additional challenges when neurological assessments are pertinent to assess for secondary injuries. In consideration

for using inhalation anesthesia, the ideal MAC for inhalation anesthetics was evaluated. Subsequently, data supporting neuroprotection to inhibit cell injury was found with 2% isoflurane and 3% sevoflurane inspired (Altay et al., 2020). The data in this study revealed that isoflurane increased apoptosis at 1% yet had no unfavorable effect in the mice sample at 1.5-2%. However, 3% isoflurane caused BBB cessation. Additionally, this research determined that the volume of infarct tissue was decreased at 1.0 and 2.0 MAC of sevoflurane. However, there was no evidence of neuroprotection when sevoflurane was delivered at 0.5 MAC. While this study showed little to minimal effects of isoflurane and sevoflurane on CBF, researchers acknowledged that this model experiment should be explored further (Altay et al., 2020).

In consideration of the effects of each inhalation anesthetic in use today, isoflurane, sevoflurane, desflurane, and nitrous oxide all impacted cerebral dynamics distinctively as shown in Table 2 (Kannabiran & Bidkar, 2018). Altay et al. (2020), Kannabiran & Bidkar (2018) and Chauhan et al. (2020) found that patient response time after anesthesia was prolonged with the administration of inhalation anesthetics, specifically sevoflurane, in comparison to intravenous anesthetics. Nonetheless, data showed superior benefits of sevoflurane when the patient is undergoing inadequate oxygen or cerebral hypoperfusion. This is due to sevoflurane increasing cerebral spinal fluid (CSF) in the lumbar region and jugular bulb oximetry; however intracranial hypertension may counteract these side effects of sevoflurane (Hassan et al., 2017).

Table 2

Inhalation Agent Effects on Hemodynamics

Inhaled agents	MAP	CBF	CPP	ICP	$CMRO_2$
Isoflurane	⇓⇓	⇑	⇓⇓	⇑	⇓⇓⇓
Sevoflurane	⇓⇓	⇑	⇑	0 - ⇑	⇓⇓⇓
Desflurane	⇓⇓	⇑	⇑	⇑	⇓
Nitrous Oxide	0 - ⇓	⇑ - ⇑⇑	⇓	⇑⇑ ⇑	⇓⇑

Note: This table demonstrates the physiological changes collected from research data on inhalational anesthetics administered in neurosurgery procedures. Adapted from Kannabiran, N., & Bidkar, P. U. (2018). Total intravenous anesthesia in neurosurgery. *Journal of Neuroanaesthesiology and Critical Care*, *5*(03), 141-149.

While safe anesthetic management for these patients is challenging, the use of inhalation anesthetics has shown beneficial evidence of neuroprotective mechanisms that warrant additional research. The research is emerging, and the arising quality data demonstrate important considerations for the anesthesia provider. In fact, short durations of xenon gas have revealed advantages for patients to regain cognition, reduce neurological damage, and improve rates of survival. As an NMDA receptor agonist, xenon is thought to inactivate agitated receptors in the brain that become hyperactivated from TBI (Common anesthetic, 2019). However, more research is necessary to evaluate the safety administration for these patients.

Literature Limitations and Strengths

As each study provided quality data and evidence-based research to guide anesthetic choices for patients with acute TBI, each study had limitations within their work to be considered. Specifically, Jayakumar et al. (2021) noted that chronic neurological results were not investigated and could have impacted the data and outcomes comparing intravenous and inhalation anesthesia for a patient with an acute subdural hematoma undergoing an emergency

craniotomy. The inclusion of chronic neurological results was also limited noted in Chauhan et al. (2020) and Hassan et al. (2017). Additionally, Jayakumar et al. (2021) disclosed data that may have been missed in their clinical report that compared the effects of sevoflurane and propofol on cerebral oxygenation with an acute TBI.

Having non-human samples and small sample sizes limited the application of the data findings and different anesthetic responses included in the studies (Jayakumar et al., 2021). However, Hausburg et al. (2020) and Capizzi et al. (2020) disclosed that the ethical limitations for human trials slow these developments, but also applied in assessing propofol's effects on TBI. Robba et al. (2021) identified that although the strength in their observational study included detailed strategies collected from large multicenter facility, the limitations were based on the study's design to be observational, restricting the data to what the facility can provide. This was noted by supplemental researchers (Abcejo et al., 2017; Kannabiran & Bidkar, 2018).

Kim et al. (2019) found that in reviewing clinical data, methodology, event reporting, and results to drug treatments, the accessibility and applicability were often inconsistent and unattainable to assess. Hassan et al. (2017) found limitations that their study did not consider the impact of preoperative patient management, such as hyperosmolar, barbiturate, and cerebral hemodynamic management. Carney et al. (2017) provided BTF guidelines that suggested limited data in some areas to make recommendations for TBI, specifically, accessing quality randomized-controlled trials.

According to Kim et al. (2019), minimal quality research was available to determine the best medicinal options for patients with TBI. In fact, this was found in searching for quality articles to include in this review which suggests the need for additional research for anesthesia management of acute TBI. According to Bhattacharya and Maung (2016), equipment quality

and data limited the research findings, specifically jugular venous oximetry. Further deficits included some of the supportive data included in the determination of anesthesia for patients with TBI who presented questions and limitations. It is unclear why this source of data was included in their study with these presented concerns.

Nonetheless, the validity of the sources used for this review was thoroughly assessed and quality references were used in each article or book. Robba et al. (2021) expanded their research across the world and included different regions, cultures, incomes, and varying health issues to assess the effects of mechanical ventilation on TBI patients. Additionally, seven articles included data support from the Cochrane Library database considered to be the gold standard of evidence-based research (Adams et al., 2017; Bhattacharya & Maung, 2016; Jayakumar et al., 2021; Kannabiran & Bidkar, 2018; Kim et al., 2019; Madsen et al., 2021; Vella et al., 2017). Kim et al. (2019) included in this research, had two independent data extractors, and utilized the AMSTAR rating scale to assess the quality of the systematic reviews used in their study to maintain strength to their research. Madsen et al. (2021) utilized this quality research profile and used Trial Sequential Analysis, the GRADE methodology, and the associated eight-step assessment to strengthen their research. Consequently, the foundation of each research article utilized in this review was determined to be sufficient to support the data.

Conclusion

Although there is expanding research that both inhalational and intravenous anesthetics share risks and benefits to manage patients with an acute TBI, there are distinct differences that separate them and should be considered when administering anesthesia. While research around inhalational anesthetics has shown promising evidence of neuroprotection and considerable reduction in secondary injuries, the lack of adequate brain relaxation and challenging

intraoperative assessments can increase the risk for patients with TBI for chronic effects and poor consequences. The data included in these studies supported that each method could provide an acceptable balance of hemodynamics when used appropriately, the overall presentation and effects on the patients favored TIVA. Additionally, the negative impacts on cerebral physiology were slightly more detrimental utilizing inhalational anesthetics alone (Kannabiran & Bidkar, 2018). While it is apparent that a multimodal anesthetic approach using adjunct medications can provide optimal stability during the intraoperative period, TIVA exhibited data a delicate balance of anesthesia and hemodynamics to ease the effects of surgical stimulation and accelerate the restoration in neurological function (Bhattacharya & Maung, 2016). In comparison, TIVA was found to reduce ICP, provide brain relaxation, reduce excitatory receptors, and protect CPP better than studies involving inhalation anesthetics.

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