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Benefits Of Ketamine Versus Propofol In Acute Traumatic Brain Injuries With Elevated Intracranial Pressure

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Abstract

Ketamine is a widely used medication that can be administered for the delivery of anesthesia as well as analgesia while supporting hemodynamics. A commonly taught concept based on early research is that ketamine should not be administered to those with acute brain injuries. Early research had stated that ketamine can cause a dangerous increase in intracranial pressure (ICP) and thus a decrease in cerebral perfusion and oxygenation in those with traumatic brain injuries (TBI) (Takeshita et al., 1972). More recent research has shown that ketamine may be efficacious for patients with TBIs and can decrease ICP (Dengler et al., 2022). In comparison, the use of propofol for induction is a widely accepted and much more common practice for induction with the benefits of possibly avoiding a detrimental increase in ICP (Adembri et al., 2007). This literature review was conducted to identify the benefits and safety of cerebral hemodynamics with the use of ketamine versus propofol for induction in the adult population presenting for decompressive craniotomy. A literature review of confounding evidence has been conducted, including electronic bibliographic databases, relevant articles, and several anesthesia textbooks. In searching the databases the focus was on studies using ketamine and propofol with acute brain injuries and their effects on intracranial pressure in patients presenting for decompressive craniotomies. There are currently 31 research studies and systematic reviews included. Positive clinical outcomes, such as decreased ICP, hemodynamic control, and ideal pain control, were noted in many of the studies and within the literature. It appears that the use of ketamine does not increase ICP and may be just as efficacious as propofol for those presenting with TBI (Breindahl et al., 2021).

Benefits of Ketamine Versus Propofol in Acute Traumatic Brain Injuries with Elevated Intracranial Pressure

Annually there are over 5.48 million cases of TBIs, and they account for more than half of all trauma-related deaths (Dengler et al., 2022), and are the leading cause of disability and death in young adults in the United States (Hines & Marschall, 2017). During their hospitalization, it is incredibly important to maintain cerebral hemodynamics to provide better patient outcomes. These hemodynamics changes include hemodynamic parameters such as cerebral perfusion pressure (CPP), cerebral blood flow (CBF), intracranial pressure (ICP), and cerebral metabolic rate of oxygen (CMRO2). It is noted that periods of elevated ICP combined with hypotension leads to an increase in mortality and poorer outcomes for patients with a TBI (Dengler et al., 2022).

A traumatic brain injury can result from both a closed head injury or a penetrating injury by foreign objects such as bullets. These injuries can then be further exacerbated by hypotension, defined as systolic blood pressure less than 90 mmHg or mean arterial blood pressure less than 65 mmHg (Hines & Marschall, 2017), and hypoxia. TBIs are categorized as either primary or secondary injuries. Primary injuries are directly related to trauma with a disruption in normal anatomy and physiology of the brain and are generally focal. Four categories of primary brain injuries are subdural hematoma, epidural hematoma, intraparenchymal hemorrhage, and nonfocal, diffuse neuronal injury from the disruption of axons of the central nervous system. The most common type of injury is an acute subdural hematoma, and this often warrants surgical intervention. This is the focus of this literature review as it is the most common injury seen and will be referred to as a TBI throughout the review. Acute subdural hematoma carries the highest risk of mortality. With this injury, there is an accumulation of blood from the veins between the

skull and brain, which can lead to an increase in ICP, and compression of cerebral blood flow. Secondary injuries are from preventable situations such as systemic hypotension, hypoxia, hypercapnia, and hyperthermia. These secondary injuries have a further negative impact on patients who have primary head injuries and greatly increase the risk of morbidity and mortality. Thus, they should be treated aggressively and accordingly (Butterworth et al., 2022).

The initial gold standard for assessing the seriousness of a neurological injury is the Glasgow Coma Scale (GCS). This scale assesses coma severity based on eye-opening responses, motor abilities, and verbal abilities (see Table 1). A GCS of less than eight is considered severe. Once determined that there is a significant injury it is important to measure ICP in patients who are unconscious and/or have a GCS <8. The gold standard for measuring ICP is an intraventricular catheter, which also allows for the drainage of CSF simultaneously. There is also the use of intraparenchymal, subdural, or epidural catheters. Intracranial pressure (ICP) refers to supratentorial cerebrospinal fluid pressure. A normal ICP is 5-15 mmHg in adults. This can be measured within the lateral ventricle or the subarachnoid space over the cerebral cortex (Nagelhout & Elisha, 2018). The Monro-Kelly doctrine states that the brain is not compressible and enclosed in the cranium, so any increase in intracranial volume will cause an increase in ICP (Nagelhout & Elisha, 2018). Further, the intracranial space is made up of four compartments: the brain, blood, intracellular water, and CSF. If any of these factors increase, there must be a decrease in the other factors to maintain a constant ICP. If compensatory mechanisms to decrease any of the other factors are not sufficient, ICP can rise. Elevated ICP is defined as pressures exceeding 20-25 mmHg. At this point, treatment is necessary to maintain appropriate cerebral hemodynamics and patient safety.

Table 1

Glasgow Coma Scale (GCS)

Category	Score
1. Eyes open	4.
Never	1
To pain	2
To verbal stimuli	3
Spontaneously	4
2. Best verbal response:	
None	1
Incomprehensible sounds	2
Inappropriate words	3
Patient disoriented and converse	4
Patient oriented and converses	5
3. Best motor response:	
None	1
Extension (decerebrate rigidity)	2
Flexion abnormal (decorticate rigidity)	3
Flexion withdrawal	4
Patient localizes pain	5
Patient obeys	6
	Sections 1, 2, 3 Total= 3-15

Note. Reprinted from *Anesthesiologists Manual of Surgical Procedures,* by Jaffe, 2016, p. 115. Copyright 2016 by Wolters Kluwer Health.

Treatment generally consists of surgery or a drain to decrease pressure on the brain. If that is not a possibility there is also the option to correct the positioning of the patient which can help decrease ICP by promoting venous drainage. Other options include managing temperature, ventilation, hemodynamics, and as mentioned above drainage of CSF (Nagelhout & Elisha, 2018). Surgical options for TBIs depend on the type of injury. Surgery generally involves interventions such as craniotomy for hematoma drainage, decompressive craniectomy for cerebral edema, or spinal stabilization. It is important to also remember that many of these patients present with multiple traumas and may present to the operating room for procedures for other injuries. A prirority is on efforts to optimize cerebral perfusion and avoid drugs and

techniques that could potentially increase ICP with anesthetic induction, maintenance, and emergence.

Many induction agents can be used to help maintain cerebral hemodynamics when providing anesthesia for this population. Currently, the most common choice of anesthesia for this population is propofol, a sedative-hypnotic (Bhaire et al., 2019). Propofol induces anesthesia by interacting with the $GABA_A$ receptor. When these receptors are activated, there is an increase in transmembrane chloride conductance, leading to hyperpolarization and inhibition of the postsynaptic cell membrane (Flood et al., 2014). A major advantage to propofol is its rapid onset of action, as well as a rapid return of consciousness with minimal neurological effects afterward. Negative implications to the use of propofol include dose-dependent hypotension, which can lead to a decrease in cerebral blood flow and metabolic rate of oxygen. In those with TBI, this can be detrimental.

An anesthetic that can mitigate these hemodynamic effects is ketamine. Ketamine provides an excellent anesthetic, with its dissociative profile, effectiveness for managing pain, and minimal effects on hemodynamics and respiratory status. Ketamine exerts effects on *N*-methyl-d-aspartate (NMDA), opioid, monoaminergic, muscarinic, and neuronal nicotinic acetylcholine receptors (Flood et al., 2014). However, even with these qualities, the use of ketamine is still avoided in the world of neurosurgery. Ketamine has been perpetuated as a poor choice for anesthesia based on evidence from articles in the 1970s and 1980s that stated ketamine could lead to dangerous increases in ICP. Further, the FDA package insert for ketamine also cautions the use of this medication, stating that there is “an increase in cerebrospinal fluid pressure…following administration of ketamine hydrochloride” (JHP Pharmaceuticals, 2012). The FDA further states that ketamine should be used with “extreme caution in patients with

preanesthetic elevated cerebrospinal fluid pressure." (JHP Pharmaceuticals, 2012). There is limited data to support this claim, as well as studies that find ketamine to be useful for patients presenting with TBI.

The purpose of this paper is to assess the use of ketamine and propofol independently, as well as a combination of the two, as anesthetic agents for those presenting with severe TBI. A review of pharmacokinetics will be discussed utilizing the literature to ascertain their effects on hemodynamics. Analysis of each medication will be done, assessing ketamine and propofol's overall effects on ICP, CMRO2, CPP, and CBF. The purpose of the literature review is to determine if either medication provides better pain control, maintenance of cerebral hemodynamics, and overall improved patient outcomes.

Literature Review

Methods

A literature search was performed on the following databases: PubMed, Google Scholar, Scopus, and Cochrane Library. Articles including randomized control trials (RCT), systematic reviews of RCTs, as well as experimental studies that were published in the last five years were preferentially selected. Included were older articles due to their substantial evidence and influence on medical practice. Other supportive articles such as literature reviews, case studies, review articles, and quasi-experimental studies were also found. Overall, 33 articles were included in this literature review. Four articles were excluded due to low levels of evidence.

Keywords for the initial search included "ketamine for patients with elevated intracranial pressure" which yielded multiple articles demonstrating ketamine use and its effects on intracranial pressure and cerebral perfusion. Further search terms utilized were "propofol +

intracranial pressure", "ketofol", "ketamine + traumatic brain injury", and "propofol + traumatic brain injury", which lead to more specific results concerning the research question.

Several common themes were noted in the articles that were examined by the authors of the studies. Original studies regarding ketamine and its safety for those with elevated intracranial pressure (ICP) stated ketamine could lead to a further increase in ICP and was not a safe anesthetic option. Later articles stated there could be safety and neuroprotection offered with ketamine use, as well as stability for cerebral hemodynamics. Other articles included in this literature review noted that there were benefits to using a combination of ketamine and propofol ("ketofol"). Lastly, a major theme noted was that ketamine and propofol both offered beneficial properties to an anesthetic, with one agent not being preferable over the other. These themes will be explored below.

Ketamine Use Can Cause Deleterious Effects on Cerebral Hemodynamics

With the introduction of ketamine in the 1970s, many studies were conducted regarding the medication's safety and efficacy in anesthetic practices, resulting in indoctrination into practice that lasted decades. Of note, these studies are all from the 1970s to the 1990s, making them quite aged for a literature review. Although the studies are from the 1970s and 1980s they have left a large impact on the use of ketamine, so they are therefore necessary to include in this review and discussion. Of importance, there are three components of intracranial pressure as mentioned before which are: blood, cerebrospinal fluid (CSF), and brain matter. An increase in any of these with poor compensation may lead to a rise in intracranial pressure.

Initially in a study done by Evans et al. (1971), four children presenting for lumbar punctures with injections of medications were anesthetized with ketamine. In the four patients, it was noted that ICP was elevated to values of 210 to 300 mm H2O. This group argued that

ketamine should be contraindicated in neurodiagnostic procedures and in patients who are suffering from increased intracranial pressure or are presenting with an already present "space-occupying lesion" (Evans et al., 1971). This article poses a major limitation because the patients involved all had CSF outflow obstruction and ICP could not be sufficiently regulated at baseline.

A 1971 study conducted by Gardner et al. included eleven patients with an ASA status of I, aged 18-43 scheduled for general surgical procedures (i.e., hernia repair, orthopedic operations) under spinal anesthetic that volunteered for this study. Each patient had a lumbar subarachnoid catheter placed to monitor pressures throughout the procedures and were given 2 mg/kg of ketamine in combination with diazepam (to minimize the side effects of ketamine) intravenously. All the participants had an improvement in blood pressure, as well as an increase in CSF pressure (Gardner et al., 1971). A limitation of this study is that only CSF pressure was calculated, and not ICP measurements. Therefore, it could be assumed that with compensation, ICP could have been maintained after this rise in CSF pressure occurred.

In research presented by Gibbs (1972),a total of 20 patients were studied**.** In group one, 11 patients with normal CSF pathways were presenting for lumbar discectomy. In group two, nine patients had intracranial lesions present and were having a craniotomy. In both groups, they received an average of 1.1 mg/kg of ketamine, nitrous oxide, and relaxation for anesthesia for the procedures. Arterial pressures were measured, as well as cerebrospinal fluid pressures (CSFP) via a lumbar catheter. In group one, no significant elevation in CSFP was noted. In group two, however, there was a substantial increase in CSFP in six out of the nine patients, with a maximum pressure rise of 150 mm H2O. In summary, this group stated that ketamine should be used with caution in patients with intracranial lesions (Gibbs, 1972).

Two studies were assessed in the article presented by List et al. (1972). First, a four-month-old hydrocephalic infant was given 2mg/kg of ketamine for ventriculoperitoneal shunt placement. This patient initially had a flat fontanelle. After drug administration and as the patient was being draped, respirations apparently ceased, and the fontanelle was noted to be bulging. A ventricular puncture was done, draining 30-40 mL of CSF, and respirations resumed spontaneously. With follow-up concerns that patients with elevated CSFP may be sensitive to ketamine, a further study was done on seven hydrocephalic patients presenting for the same procedure. CSFP was measured via a catheter in the lateral ventricle. Once baseline values had been established, each patient was given 2.5 mg/kg of ketamine. Out of seven patients, all but one had marked increases in CSFP. Moreover, in one patient CSFP rose to greater than 800 mm H2O and CSF had to be removed for decompression. The average increase in CSFP was 247 mm H2O. The group suggested that ketamine should only be used in patients with elevated CSFP if the CSFP could be monitored continuously and rapid decompression could be provided (List et al., 1972).

In a study conducted in 1972 by Shapiro et al., the authors set out to assess the effects of intravenous ketamine on ICP**.** There were seven patients assessed, and they either received ketamine for induction or a neurodiagnostic procedure. ICP was measured via a ventriculostomy catheter in the lateral cerebral ventricle, and arterial blood pressures were measured with either a brachial cuff or a radial arterial catheter. The patients then received 2mg/kg intravenous ketamine. Four patients were noted to have an increase in ICP after receiving the ketamine. Of note, these patients had abnormal CSF flow dynamics. In this group, the ICP rose an average of 13 to 63 mmHg, or on average a 62-80% increase in cerebral blood flow. There was a minimal increase in systemic arterial pressure, in comparison. This increase in ICP was followed by a

rapid reduction after receiving thiopental and if needed manual hyperventilation via mask. Overall, Shapiro et al. asserted that the risk of acute intracranial hypertension with ketamine use was high in patients who presented with intracranial pathologies and caution its use in this population (Shapiro et al., 1972).

The study by Crumrine et al. (1975) assessed a group of 26 children, aged 4.5-16 years. These 26 children all had hydrocephalus with present shunts or external ventriculostomies that needed revisions. Ventricular fluid pressures (VFP) were measured in the lateral ventricle, as well as baseline vital signs and arterial blood gases. During the anesthetic, once the VFP reached its peak value, an ABG was drawn and analyzed. Patients remained breathing spontaneously throughout. They were grouped into three separate groups. Group I, with six patients, received ketamine 2.5 mg/kg intravenously within 20 seconds of induction. Group II, with six patients, received ketamine 10 mg/kg intramuscularly in the anterior thigh. Group III, with 14 patients, was premedicated with either droperidol 0.1mg/kg intramuscularly (five patients), secobarbital 2mg/kg intramuscularly (four patients), or diazepam 0.2 mg/kg intramuscularly (four patients) one hour before anesthesia. They were then anesthetized with 10 mg/kg of ketamine intramuscularly. In all groups, every patient but one (that was not premedicated) had an increase in VFP after receiving ketamine. There were no statistical differences noted in the amount of increase in ICP between the intravenous group and the intramuscular group. In both groups, VFP increased by two to eight times the control value after receiving ketamine and the authors stated there may be significant rises in VFP that can lead to an increased risk of brain herniation (Crumrine et al., 1975).

Overall, these studies have demonstrated valuable information on the use of ketamine in patients requiring anesthesia. Although, it is clear all these studies were based on generally small

population sizes, as well as a large portion of patients who were already suffering from some type of cerebrospinal outflow tract abnormality. Furthermore, and most importantly, none of the studies listed had any comparison of ketamine to any other anesthetic and the differences that could have been noted in patients who received different anesthetics.

Ketamine May Be Beneficial for Cerebral Hemodynamics

Bourgoin et al. (2005) conducted a prospective randomized study on 30 patients with severe head injuries (post-resuscitation). Patients were randomized to receive either sufentanil combined with midazolam, or ketamine combined with midazolam for sedation while in intensive care. Each had an arterial line and ICP measurements were obtained via a ventricular catheter, from which CPP was also calculated. Concurrently an EEG was used and BIS was computed to assess levels of sedation. The authors found ICP and CPP values did not vary significantly between the two groups. When given double the concentration of the medication, there was no major alteration in any of the cerebral hemodynamics when compared to baseline values. The group concluded that an infusion of ketamine-midazolam was just as sufficient as sufentanil-midazolam for controlling ICP/CPP in patients with severe traumatic brain injuries (Bourgoin et al., 2005).

A systematic review of prospective RCTs was completed by Zeiler et al. (2014) compounding studies that attributed to the safe use of ketamine for those at risk for deleterious effects of increasing ICP. They included multiple articles that led to a population size of 101 adults and 55 pediatric patients. All articles included in the systematic review documented ICP measurements in patients with severe traumatic brain injury (TBI) while utilizing ketamine. ICP did not increase in any of the studies included, and three studies demonstrated a significant decrease in ICP with ketamine boluses. Overall, no deleterious effects on ICP were noted when

ketamine was used in such populations. Limitations to this systematic review included concomitant use of other background sedative medications and the group identified there was significant heterogeneity within the studies.

A 2014 meta-analysis of RCTs conducted by Wang et al. led to a study population of 198 patients from five different trials. The main outcome this group searched to study was ICP levels within the first 24 hours of ketamine administration. The secondary outcome searched for was an alaysis of MAP and CPP levels. The main conclusion was that ketamine does not increase ICP and assists with maintaining hemodynamic status. It should not be ruled out as an anesthetic agent due to ICP concerns, and the ICP and MAP levels were similar in groups with the use of opioids. Further, there are listed advantages of ketamine versus opioids, as ketamine will assist in maintaining CPP and hemodynamics, no withdrawal symptoms, and decreased risks of nausea and vomiting. The authors listed a few limitations to their meta-analysis. One of the studies the authors included was based on ketamine bolus dosing while the other four were based on infusions. One of the studies was also based on pediatrics while the others were based on studies on adults. Secondly, the RCTs included took place over 17 years so there were concerns that nonexperimental aspects of patient care may have differed over the years and altered outcomes (Wang et al., 2014).

A randomized trial conducted by Mayber et al. (2014) was a staple in leading the way for research on ketamine use in patients with elevated ICP. This RCT included 30 conscious patients that had supratentorial tumors or intracranial aneurysms and were presenting for craniotomy. Patients were induced with thiopental and isoflurane combined with nitrous oxide in oxygen. They were then given 1 mg/kg ketamine intravenously before surgical stimulation began. Data collected included: middle cerebral artery blood flow velocity (Vmca) via transcranial doppler,

MAP, HR, and ICP or CSFP every minute for 10 minutes following ketamine administration. The RCT demonstrated that after ketamine administration there was no increase in ICP, instead ICP and Vmca decreased. Mayber et al. (2014) postulated that ketamine can safely be administered to patients with mildly increased ICP who are anesthetized and mechanically ventilated without fear of altering cerebral hemodynamics (Mayber et al., 2014).

In 2012 an exploratory retrospective multicenter analysis was conducted by Hertle et al. (2012) regarding the effect of analgesics and sedatives on spreading depolarizations that accompany an acute brain injury. Spreading depolarizations refers to the breakdown of ion gradients across cellular membranes in conjunction with brain injury. Large amounts of glutamate are released, while there is a massive influx of sodium ions into the neurons, leading to cytotoxic edema (Telles et al., 2021). The occurrence is possibly associated with a poor prognosis. 115 patients were included, each having a craniotomy to treat a TBI, relieve compression after a malignant hemorrhagic stroke, for an aneurysm clip, or to remove blood clots from subarachnoid hemorrhage (SAH) or intracerebral hemorrhage (ICH). Patients' electrocorticographic recordings were initiated after the craniotomy in the intensive care unit (ICU). The patients received varying doses of different medications including propofol, midazolam, fentanyl, sufentanil, ketamine, and morphine. Ketamine was the only medication shown to reduce the occurrence of spreading depolarizations and no other medication exhibited such. Hertle et al. concluded that this finding demonstrated that ketamine offers a degree of neuroprotection and can be beneficial (Hertle et al., 2012).

Dengler et al. (2021) directed a retrospective observational study with a population size of 46 neurocritical adults. Included were patients who received ketamine, sustained a severe TBI, had an ICP monitor in place, received osmotherapy, were adequately sedated, received analgesic

infusions, and were mechanically ventilated. Data was collected in the medical record and evaluated retrospectively. They sought to assess on an hourly basis the proportion of ketamine boluses that lead to an improved ICP and CPP. It was discovered that 46% of ketamine boluses resulted in an improved ICP and CPP and the group concluded that ketamine boluses were associated with a reduction in ICP and an improvement in CPP. Limitations included: ICP values were only measured hourly and may not have directly correlated with ketamine administration timing, there were no control groups; lack of a formal protocol for ketamine administration; and lack of RASS values, PaCO2, and sodium values at the time of administrations not considered (Dengler et al., 2021).

A 2014 systematic review by Cohen et al. tallied up a large population of 953 patients across different studies. Studies included were those with reported data on the effect of IV ketamine as a bolus versus infusion in those who had previously been intubated/were being intubated in a data collection. The primary outcome being assessed was cerebral perfusion pressure. Secondary outcome measures included neurological outcomes, mortality, and ICU length of stay. Cohen et al. concluded that the available data suggests that ketamine does not adversely affect ICP, CPP, neurological outcomes, or mortality when compared to other anesthetic agents (Cohen et al., 2014).

Carlson et al. (2019) conducted a prospective, randomized, multiple crossover trial on a population of 10 patients observed in the ICU post-craniotomy. Those included had either aneurysmal SAH or a severe TBI with an injury that required invasive monitoring and craniotomy. The 10 patients were placed on an alteration of ketamine or another sedation agent on every six-hour schedule and the occurrence of spreading depolarization (SD) was assessed. The treatment order was randomized. Hours that patients did not receive any ketamine or when

they received a dose of <1.15 mg/kg/hr were associated with a greater risk of spreading depolarizations compared to those who were on a ketamine infusion and at a rate of >1.15 mg/kg/hr or more. Limitations listed were that they had an imbalance in groups, there were heterogenous groups with two patients having a TBI, they did not perform a pharmacokinetic analysis, and they did not perform analysis per patient because of the multiple crossovers. Though the group finalized their stance that ketamine inhibits spreading depolarization over a wide range of dosages and an improvement in ICP was seen with higher doses of ketamine (Carlson et al., 2019).

Finally, Oddo et al. (2016) presented a literature review that sought to assess how to optimize sedation in patients with acute brain injuries. Patients included were those with either a severe TBI, poor-grade subarachnoid hemorrhage, severe ischemic/hemorrhagic stroke, comatose cardiac arrest, or status epilepticus. The group provided a summary of the cerebral physiologic effects of sedatives and analgesics and comparative notes on each in patients with acute brain injuries (ABI); they were particularly curious about ketamine. From the literature review, it was determined that ketamine should be considered for patients who recently suffered ABI as new studies have shown it does not increase ICP and offers analgesia. In patients that received ketamine, it was shown they had the lowest incidence of spreading depolarizations when compared to those that received midazolam or propofol.

Propofol Use and Effects on Cerebral Hemodynamics

In total, there were limited articles found that showed that propofol had a deleterious effect on ICP, possibly resulting in its favored use in critical neuroanesthesia. With its rapid recovery profile, it also has some neuroprotection offered with its ability to decrease cerebral metabolic rate for oxygen (CMRO2) as well as a decrease in ICP and cerebral blood flow which

improves operating conditions (Adembri et al., 2007). The articles listed here will discuss further findings attesting to propofol's benefits in anesthesia for maintaining CPP and ICP in those with acute TBI when used as an induction agent/maintenance agent. Unfortunately, many of the articles presented in this section do not specifically compare propofol with ketamine which presents a limitation to this literature review.

In the RCT conducted by Bastol et al. (2015), 75 patients were included who were presenting for craniotomies for supratentorial tumor resection. The patients were randomized to one of three groups that would either receive sevoflurane, desflurane, or propofol for anesthetic maintenance. Brain relaxation was subjectively assessed by the neurosurgeon at three different points during the procedure. Per this study, propofol, sevoflurane, and desflurane have similar effects on the relaxation of the brain and all are acceptable for use in neurosurgery. The limitation of this study is that there were only subjective measurements of brain relaxation and there were no ICP measurements obtained to compare (Bastol et al., 2015).

A randomized prospective study was directed by Peters et al. (2003) on 117 patients with supratentorial tumors presenting for craniotomy. Patients were randomized to receive either propofol-fentanyl, isoflurane-fentanyl, or sevoflurane-fentanyl anesthesia. Subdural ICP, MAP, CPP, and arteriovenous oxygen difference (AVDO2) were monitored before and after 10 minutes of hyperventilation. The tension of the dura was also monitored. Peters et al. noted that ICP and AVDO2 were lower and CPP was higher in the group of patients who were anesthetized with propofol compared to the other two groups during hyperventilation. The authors concluded that propofol, compared with sevoflurane or isoflurane, is the ideal option for operating conditions for cerebral tumors as there is a lower subdural ICP, cerebral swelling is less pronounced, and CPP is higher (Peters et al., 2003).

Khallaf et al. (2019) presented a prospective RCT on 60 patients in which they evaluated cerebral hemodynamics and ICP changes with the administration of dexmedetomidine versus propofol anesthesia via an ICP monitor. Of note, they did assess that hypotensive episodes were more likely to be seen in the propofol-only group versus the group that received dexmedetomidine as well as a higher rate of delirium, but the hypotension assessed was transient. Khallaf et al. (2019) concluded that propofol is an effective agent for patients with TBI and that the addition of dexmedetomidine may be a beneficial additive. Weaknesses presented in this study are the lack of ketamine in the research, potential for generalizability because it was based out of a single center, and inadequate assessment of sedation as it was assessed via loss of agitation and not a scoring system such as the Richmond Agitation-Sedation scale (Khallaf et al., 2019).

Finally, in a systematic review produced by Chui et al. (2014), databases were searched for RCTs, and 14 studies were included with 1,819 patients in total. The group searched for RCTs that compared anesthesia that was maintained with propofol versus volatiles for those undergoing elective craniotomies. The primary outcome measure was an intraoperative brain relaxation score. Secondary outcomes that were measured were cerebral hemodynamics, cardiovascular alterations, recovery postoperatively, postoperative complications, and outcomes clinically. A meta-analysis was completed. From the 14 studies, Chui et al. (2019) concluded that propofol-maintained anesthesia led to fewer hypotensive events intraoperatively; it maintained higher CPP values and lower ICP values compared to the volatile-maintained anesthesia groups. Chui et al. (2019) listed some limits to the review. There was significant clinical and methodological heterogeneity in the primary studies, and they were unable to combine all the outcome variables for the recovery profiles. Also, factors such as autoregulation and carbon

dioxide reactivity were not included. Chui et al. concluded propofol anesthesia resulted in lower ICP values and higher CPP values than seen with volatile-based anesthesia in those presenting for craniotomy (Chui et al. 2014).

Combination of Ketamine and Propofol (Ketofol)

The following articles will analyze the use of ketamine and propofol (ketofol) consecutively on induction, the administration of ketofol infusions, and the many benefits noted with this combination by RCTs.

In 2012 a randomized, double-blind trial was conducted by Andolfatto et al. (2012) to assess the use of ketofol versus propofol alone for emergency procedural sedation. Ketofol was mixed as a 1:1 ratio of 10 mg/mL of ketamine and 10 mg/mL of propofol in a 20 mL syringe, resulting in five mg of ketamine and five mg of propofol in one mL. The patients receiving ketofol received a dose of 0.375 mg/kg (Andolfatto et al., 2012). 284 patients were included with 142 patients per group. The primary outcome being assessed was the number and proportion of patients who experienced an adverse respiratory event; secondary outcomes included sedation consistency, efficacy/time, induction time, and adverse events. It was noted that deep sedation was achieved in both groups, and the timing/number of doses required to reach this was similar in both groups. Ketofol led to a more consistent depth of anesthesia, and propofol lead to a higher incidence of intraprocedural agitation, while the ketofol group agitation was more common during the recovery phase. Overall, the limitations of the study included the difference in clinicians' opinions, as different clinicians may have intervened at different thresholds in the phase of a possible adverse event. Also, a variety of procedures were performed so the weight-based dosing schedule for different procedures may have affected the incidence of adverse events. Further, for this literature review specifically, this study does not have any correlation to

critical neuroanesthesia and ICP/CPP management. Conclusively, Andolfatto et al. (2012) stated that sedation depth was more consistent with ketofol and there was no increase in adverse events for procedural sedation with ketofol vs propofol for procedural sedation (Andolfatto et al., 2012).

Bhardwaj et al. (2022) conducted an RCT comparing the use of ketofol and propofol anesthesia during aneurysmal clipping. It was a double-blinded controlled trial that took place between July 2017 and June 2018 consisting of 40 participants aged between 18-75 years who presented for aneurysm neck clipping after an aneurysmal SAH. Only patients with normal ICP and that were conscious were included. Two random groups were made with 20 people in each. Group P patients received propofol for induction and maintenance, and group KP received a combination of ketamine and propofol instead. An intraventricular catheter was inserted to measure ICP and measured based on a scoring system. Substantial conclusions were made, firstly that intraoperatively the group KP needed much less propofol to maintain sedation throughout the procedure. Next, fentanyl and muscle relaxation consumption were similar in the two groups. Further, there was a significant decrease of MAP during induction for group P; but during the rest of the surgery, the two groups remained comparable, although the article did record that ketofol maintained hemodynamics more effectively. Finally, ICP measured was an average of 11.64 mmHg in group KP and 11.47 in group P, demonstrating no significant difference in ICP between the two. Brain relaxation scores between the two groups were similar as well. Overall, when ketofol is administered with a controlled end-tidal carbon dioxide (EtCo2) between 35-45, the group concluded that it provides better hemodynamic stability compared to propofol alone for induction and maintenance of anesthesia without deleterious effects on ICP (Bhardwaj et al., 2020).

A study directed by Luthra et al. (2019) consisted of 40 patients participating in a randomized, double-blinded, controlled trial to see the difference in cerebral oxygenation in neurosurgical patients receiving either ketofol or propofol. The participants were randomized to either receive ketofol or propofol using a computer-generated randomized table; the investigator/patient did not know which drug was being administered. A jugular venous oxygen saturation (SjVO2) catheter was inserted postinduction, and a baseline was obtained, then assessed one hour, two hours, and six hours after surgery. The group also recorded intraoperative hemodynamics and brain relaxation scores. Of importance, the study concluded that SjVO2 values remained higher in the ketofol group at each recording. In the propofol group, there was a significant fall in SjVO2 at the two-hour mark; further, 75% of the patients in the propofol group had a >20% fall in their MAP, and 55% of them needed phenylephrine. In the ketofol group, only 15% of the group had a fall of >20% in their MAP. Fentanyl requirements were much less in the ketofol group compared to the propofol group. Brain relaxation scores were similar in both groups. Overall, Luthra et al. (2019) presented that in neurosurgical patients presenting for clipping of aneurysm after SAH ketofol anesthesia provides a much more stable hemodynamic profile and cerebral oxygenation than propofol anesthesia (Luthra et al., 2019).

Smischney et al. (2016) lead a randomized, double-blinded, placebo-controlled trial consisting of 85 patients. Patients included were aged 18-60 with an American Society of Anesthesiology (ASA) physical status of I and II presenting for surgical procedures with general anesthesia. The group sought to assess whether induction with ketofol or propofol made a difference in hemodynamics. Patients received either a weight-based dose of propofol of 2 mg/kg or ketofol at a weight-based dose as a mixture of 0.75 mg/kg of ketamine and 1.5 mg/kg of propofol. Hemodynamics were assessed with a NICOM (four adhesive patches that monitor

cardiac output, total peripheral resistance, and stroke volume) as well as standard monitors. The primary endpoints being assessed were a drop in systolic blood pressure (SBP) of >20% from the patient's baseline at five minutes, 10 minutes, and 30 minutes. Secondary endpoints included changes in the measurements obtained via the NICOM. In all, the propofol group had more patients with a >20% decrease in SBP at five minutes and 10 minutes. But there was no difference in the use of intraoperative vasoactive medication use between the two groups. Smischney et al. did state that the dose ratio used was "not ideal". Overall, the group believed that ketofol shows better hemodynamic stability when compared to propofol alone for induction (Smischney et al., 2012).

A randomized, double-blind study was produced by Sharma et al. (2016). The authors sought to assess whether there were any major differences when a patient received a ketofol of fentanyl-propofol (fentofol) infusion for a short orthopedic procedure. The study group was of 100 patients, all with ASA scores of I or II. Hemodynamics were measured for the patients that received either the ketofol or fentofol for induction and then maintenance with the infusion as well. It was assessed that there was a decrease in pulse rate, SBP, and DBP intraoperatively and postoperatively in the fentofol group; the ketofol group had a significant increase in pulse rate, SBP, and DBP. The total amount of propofol consumed was lower in the ketofol group. There were no major adverse effects in the ketofol group that was assessed, while the fentofol group had a significantly prolonged recovery time in comparison. In conclusion, Sharma et al. (2016) stated that a total intravenous anesthetic (TIVA) of ketofol compared to fentofol provided better sedation, analgesia, stability of hemodynamics, and a better recovery profile (Sharma et al., 2016).

Limitations

As listed in the above sections, there are some important limitations in the included articles. In the earlier studies, many patients included in the groups had CSF outflow tract abnormalities which could have affected cerebral hemodynamics at baseline. This makes it difficult to assume that these results could transfer the results to patients who have effective CSF drainage. Further, many of the studies have small sample sizes of fewer than 100 patients. Also, a majority of the studies do not have a strict comparison of just propofol or ketamine, and many compare propofol to other medications, or ketamine to other medications, without the other being included. Finally, there are limited studies on the application of these medications on patients specifically presenting for decompressive craniotomies for elevated ICP. These limitations make it difficult to apply these results to the population in the research question. Further and more specific RCTs with larger population sizes are needed to better understand the cerebral hemodynamic effects of ketamine versus propofol for patients presenting for decompressive craniotomy with elevated ICP.

Discussion

The Origins of the Concerns About Ketamine

As an anesthesia provider, one of the many things that is important is to remain up to date with current literature and research. It is quite suprising that many providers and authors of textbooks are not current with the literature on ketamine and propofol and their effects on ICP for patients presenting with acute TBI. It appears that many of the original studies showing that ketamine may have deleterious effects on ICP and should not be used in those with acute TBIs are not strong studies and cannot be applied to the general population of those with brain injuries, which will be further discussed.

Firstly, many of these original articles showed that there were increases in ICP in patients who had CSF outflow obstructions. It cannot be surmised whether the ketamine caused an increase in ICP, or if it was simply because there was an obstruction that caused the increase in ICP. In current medical practice, many patients with TBI will have a drain placed that can facilitate CSF drainage and prevent increases in ICP. Therefore, it could be assumed that these articles stating ketamine is not safe for patients with increased ICP cannot be applied to those with competent CSF outflow tracts.

These articles have another limitation. Unfortunately, they all are based on small case-control studies and were poorly designed and controlled. Of the articles listed in the literature review above, their sample sizes were as follows: one infant (List et al, 1972), four children (Evans et al., 1971), seven adults (Shapiro et al., 1972), 11 adults (Gardner et al., 1971), 20 adults (Gibbs et al., 1972), 26 children (Crumrine et al., 1975). These are all relatively small sample sizes, making it difficult to apply them to practice as legitimate sources. Many research textbooks state that sufficient sample size is 30 or more participants to provide sufficient evidence.

Further, in many of the articles from the 1970s, the patients did not have controlled ventilation. It could be argued that many of them most likely ended up hypoventilating, leading to hypercarbia which can be deleterious to cerebral hemodynamics. In the study by List et al. (1972) the patient was not being appropriately ventilated. Per the article, the patient received a large dose of ketamine and respirations had stopped, which could have led to very serious hypercarbia and cerebral vasodilation. Crumrine et al. (1975) had a similar situation, in which the group of 26 children were all spontaneously breathing throughout the study. It could be argued that this could have been the variable that could have triggered the significant increase in

VFP (ventricular fluid pressure) and it does not seem possible that it could have only been the ketamine contributing to this finding. Further noted, Shapiro et al. (1972) utilized hyperventilation to treat and decrease the elevated ICP, which also suggests that hypercarbia could have been the cause of the elevated ICP, not the medication.

Finally, many of these studies were conducted with only the administration of ketamine, and no other anesthetic. In the current practice of anesthesia, many medications are used to provide anesthesia and analgesia. It would be a very rare situation in which the provider would solely be using ketamine. In all seven of the studies from the 1970s that lead to the concerns about ketamine, the patients all simply received ketamine and no other form of analgesia or sedation for their procedures.

In conclusion, it is apparent that these seven studies have led to very firm, yet poorly supported, concerns that ketamine can cause an increase in ICP in those with acute severe TBIs. Due to their small sample sizes, poorly controlled variables, minimal use of other medications, and uncontrolled ventilation, it seems fair to waive these concerns from these studies that ketamine can have deleterious effects on cerebral hemodynamics. Overall, it certainly warrants newer investigations into why ketamine, propofol, and ketofol may be ideal choices for patients in this population.

Ketamine Has Been Proven to be Beneficial to Patients with Acute TBI and/or Increased ICP

Fortunately, there has been an increase in studies assessing the safety of ketamine in patients with brain injuries. The studies from the 1970s and 1980s have left a prolonged impact on the practice of anesthesia, so it could be assumed it will take quite some time for these fears to be diminished. Many newer studies conducted from the 1990s and onward have started to try and

change this narrative. Of note, the research is still limited, and much more is needed to continue to understand the safety and efficacy of ketamine versus propofol in patients with TBIs.

Ketamine Can Decrease ICP

There are multiple RCTs and systematic reviews available in the current literature to support the use of ketamine over other anesthetics for patients with brain injuries who require anesthesia. As noted by Zeiler et al. (2014), out of 156 patients in multiple RCTs, it was noted that there were no deleterious effects on ICP with the use of ketamine. Even better, three of the studies showed a decrease in ICP with ketamine boluses (Zeiler et al., 2014). Wang et al. (2014) found similar outcomes in their meta-analysis, and these authors stated that ketamine had better maintenance of cerebral hemodynamics than a narcotic-based anesthetic. The level I study by Mayber et al. (1995) again affirmed the safety of ketamine. This study showed there was a small decrease in ICP and that there is no correlation between increases in ICP and ketamine (Mayber et al., 1995). Dengler et al. (2022) produced their retrospective observational study with a study group of 46 patients in a neurocritical care unit, they stated that ketamine boluses are associated with a reduction in ICP and an increase in CPP. The authors also stated that ketamine had a greater effect on lowering ICP when the ICP was greater than 20mmHg, which shows there may be a possibility ketamine could be used as a treatment for elevated ICP in some populations (Dengler et al., 2022). Finally, two studies conducted by Bourgoin et al. and Cohen et al. had similar conclusions and both articles stated that ketamine does not produce adverse patient outcomes regarding ICP and CPP in patients with acute TBIs. These articles all show positive aspects of ketamine use in patients with TBIs and it is hard data to ignore.

In conclusion, many studies to date show promising use of ketamine for lowering ICP in a dose dependent manner, not increasing it. It is monumental that these studies have been

completed and are helping destroy the old notion of inaccurate warnings of ketamine. More research is certainly needed to affirm these conclusions. With this research being continued hopefully more practitioners can feel safe in administering ketamine to patients with elevated ICP so their patients can also receive the benefits this medication can offer them.

Ketamine Causes Decreased Spreading Depolarizations Which Offers Additive Neuroprotection

Another key component to the benefits of ketamine is the discovery of decreased spreading depolarizations in concurrency with ketamine use. As mentioned above, spreading depolarizations refers to the physiologic breakdown of ion gradients across cellular membranes after a brain injury. Glutamate, an excitatory neurotransmitter, is released as well as a massive influx of sodium into the neurons. This results in cytotoxic edema, which could be dire for a patient with a brain injury. Per Gregers et al. (2020), spreading depolarizations are linked to poor neurological outcomes in patients with a TBI. Therefore, anything that can assist in decreasing them can provide great benefit for a patient. Also, a key point noted by Himmelseher et al. (2005) stated that ketamine offered neuroprotection due to its ability to block the activation of NMDA receptors, which appears to place a key role in the injury cascade produced by glutamate leading to cell death.

Conducted studies thus far, as mentioned prior, have shown evidence that ketamine can decrease spreading depolarizations in a dose-dependent fashion. Most important were the studies done by Hertle et al. (2019) and Carlson et al. (2019), as they showed promising results for decreasing spreading depolarizations. Carlson et al. (2019) studied different analgesics and sedatives and they felt that spreading depolarizations can be modified in humans, with ketamine being the most influential of all anesthetics at decreasing them. This is very important to

practice, as it demonstrates that ketamine, which many anesthetists are fearful of, is the safest option in these regards as it offers neuroprotection (Hertle et al., 2012). Carlson et al. (2019) had similar conclusions, stating that ketamine can inhibit the spreading depolarizations over a wide range of dosages. Overall, these studies indicate that ketamine may offer neuroprotection, not neurological damage, to patients with TBI. Further studies are needed to assess ketamine's ability to decrease spreading depolarizations and the safest dose ranges for such properties.

Ketamine Can Decrease Opioid Requirements

The opioid pandemic across the United States was very eye-opening to the numerous negative effects of narcotics. While of course beneficial and certainly necessary at times for treating acute pain, there are also deleterious effects associated with them as well. Firstly, there is the risk of opioid withdrawal, as a patient who receives large amounts of narcotics and then is withdrawn from them may experience elevated blood pressure in response to pain, which can in turn increase ICP. Further, the use of opioids could lead to hypoventilation, which will lead to vasodilation from increased CO2, resulting in an elevated ICP. These factors make narcotics sound less than ideal as the primary option for pain management in patients with TBI. Multiple studies conducted have shown that ketamine use can decrease the need for narcotics in patients with TBIs, while further assuring that they are safe for this population. Wang et al. (2014) conducted a large meta-analysis of five trials, and the main finding was that ketamine had better maintenance of CPP and hemodynamics with the least withdrawal symptoms compared to other anesthetics. Bhardwaj et al. (2022) and Luthra et al. (2019) also stated that there was a decreased consumption of fentanyl in patients who received an infusion of ketamine for surgery.

The Benefits of Propofol for Patients with Acute TBI and/or Increased ICP

Currently, multiple studies have been conducted that show the safety and efficacy of propofol for patients with TBI and elevated ICP. Unfortunately, many of the studies do not compare propofol and ketamine separately as anesthetic agents for these populations. But overall, the studies offer valid insights into the usefulness and safety of propofol use in patients presenting with TBIs.

All of the studies included in the literature review, other than those from the 1970s and 1980s, state that propofol is an ideal anesthetic option for patients with elevated ICP because it can offer a certain amount of neuroprotection as it inhibits cellular pathways activated after brain injury (Adembri et al., 2007). As one can surmise, this is a useful aspect of a propofol anesthetic. Bastol et al. (2015), Chui et al. (2014), and Peters et al (2003) all conducted large RCTs demonstrating propofol's safety for patients with TBIs and/or elevated ICP. Even though propofol generally demonstrates some vasodilation and brief hypotension with large doses, it does not appear to have any disastrous effects on ICP and is generally brief. A major limitation of these studies is that there are no articles that compare just propofol and ketamine alone. Generally, all these articles include other anesthetics such as volatile gasses and Precedex.

These studies all showed that propofol, largely in comparison to sevoflurane anesthetic, is the ideal option when operating on patients with any increased/risk of an increased ICP. These articles provide useful information and will help this literature review finalize the idea that ketofol, a combination of ketamine and propofol, may be the current best anesthetic choice for sedation of patients with elevated ICP and TBIs.

Why Two is Better Than One: Ketofol Shows to be the Most Ideal Option

After conducting this literature review it appears that a combination of ketamine and propofol as an infusion (ketofol) is the most ideal option for patients presenting with acute TBI. RCTs that were conducted demonstrated a few key aspects of ketofol infusions such as more stable hemodynamics, decreased consumption of propofol and narcotics, and better recovery profiles. Using ketofol has been shown to provide adequate sedation and analgesia while also decreased total doses of each drug (Sharma et al., 2016).

Ketofol Proves to Provide Better Hemodynamics

As discussed previously, propofol can cause a dose dependent decrease in blood pressure. While on the other hand, ketamine can provide an increase in heart rate and blood pressure. In understanding this, it seems plausible that the two medications can counteract one another and provide a satisfactory hemodynamic balance. Multiple RCTs showed that there were significant decreases in MAP during induction with propofol, although these findings were transient. There was also noted decreases in stroke volume in patients who received propofol only (Smischney et al., 2012). And in comparison, the other subjects who received ketofol had improved/stable hemodynamics and no evidence of increased ICP. As discussed before, the randomized trial by Luthra et al. (2019) demonstrated that 55% of the patients who received propofol only required phenylephrine boluses, while the ketofol group only 15% required phenylephrine boluses. This appears to be quite promising for the use of ketofol and it would be interesting to see more cases done researching this idea.

Ketofol Decreases Narcotics and Total Amount of Anesthetic Consumed

The final summation demonstrated by multiple articles was that ketofol infusion can reduce the amount of narcotics and propofol consumed intraoperatively when used as an

anesthetic for patients with acute TBIs. Sharma et al. (2016) stated that patients who received ketofol infusions required less narcotics as well as decreased amounts of propofol during a TIVA anesthetic. Importantly, attempts to decrease narcotic intake can be very useful to this population. Specifically to this population, many studies have shown that fentanyl/ other narcotic boluses can lead to decreased cardiac output, MAP, and respiratory rate (Sharma et al., 2016). Again, a decrease in respiratory rate could pose a substantial safety risk for a patient with a TBI postoperatively. If there are decreased respirations, there could be potential hypercarbia and further cerebral vasodilation. This is something that needs to be avoided at all costs. Unfortunately, more research is needed to assess this, as there is a limited amount of these studies available, which poses a major limitation to this idea.

Conclusion

Recommendations

Further research is needed in relation to this topic. While great advancements have been made in the understanding of ketamine's safety for patients with TBI, there are not enough comparative studies currently out there that relate the use of ketamine to propofol. Numerous articles do not address any of the cerebral protective properties of ketamine (except those addressing decreasing spreading depolarizations). Instead, they address that ketamine is not contraindicated in patients with elevated ICP, not that ketamine has an advantage over other anesthetics. More research should be conducted to address this with larger, multicentric studies to assess the effects and advantages. Further, another important aspect that has not been addressed is patients' recovery postoperatively. Ketamine does have an increased risk of delirium due to its pharmacologic profile. With increased postoperative delirium there is prolonged hospitalizations and increased risk of mortality. It would be useful to see if ketamine

has any effect on postoperative delirium for patients with acute TBI. Studies should be conducted to identify this information.

Overall, there have been great advancements in the understanding of ketamine and propofol as anesthetics for patients presenting with acute TBI. Most importantly, it appears that change has started to occur in utilizing ketamine for patients with acute TBI and/or elevated ICP. But still, it is continued to be a taught concept that ketamine should not be given to this population. After the studies in the 1970s and 1980s imprinted this strong belief into anesthesia, there has been a stubbornness in anesthesia culture regarding ketamine's use for patients with increased ICP and/or acute TBI. Fortunately, there is an increased interest in the topic with promising results, and hopefully there will be plenty more to come. With the use of ketamine and propofol appropriately, anesthesia providers can provide safe, stable hemodynamics, maintain adequate cerebral perfusion, and overall have a large impact on determining factors that will benefit a patient's long-term outcome and prevent mortality.

References

Adembri, C., Venturi, L., & Pellegrini-Giampietro, D. E. (2007). Neuroprotective effects of propofol in acute cerebral injury. *CNS Drug Reviews*, *13*(3), 333–351. https://doi.org/10.1111/j.1527-3458.2007.00015.x

Albanese, J., Arnaud, S., Rey, M., Thomachot, L., Alliez, B., & Martin, C. (1997). Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. *Anesthesiology*, *87*(6), 1328–1334. https://doi.org/10.1097/00000542-199712000-00011

Alkhachroum, A., Der-Nigoghossian, C. A., Mathews, E., Massad, N., Letchinger, R., Doyle, K., Chiu, W. T., Kromm, J., Rubinos, C., Velazquez, A., Roh, D., Agarwal, S., Park, S., Connolly, E. S., & Claassen, J. (2020). Ketamine to treat super-refractory status epilepticus. *Neurology*, *95*(16), e2286–e2294. https://doi.org/10.1212/wnl.0000000000010611

Andolfatto, G., Abu-Laban, R. B., Zed, P. J., Staniforth, S. M., Stackhouse, S., Moadebi, S., & Willman, E. (2012). Ketamine-Propofol combination (ketofol) versus propofol alone for emergency department procedural sedation and analgesia: A randomized double-blind trial. *Annals of Emergency Medicine*, *59*(6), 504-512.e2. https://doi.org/10.1016/j.annemergmed.2012.01.017

Bastola, P., Bhagat, H., & Wig, J. (2015). Comparative evaluation of propofol, sevoflurane, and desflurane for neuroanaesthesia: A prospective randomised study in patients undergoing elective supratentorial craniotomy. *Indian Journal of Anaesthesia*, *59*(5), 287. https://doi.org/10.4103/0019-5049.156868

Bell, J. D. (2017). In vogue: Ketamine for neuroprotection in acute neurologic injury. *Neuroscience and Neuroanesthesiology*, *124*(4), 1237–1243. https://doi.org/10.1213/ANE.0000000000001856

Bhardwaj, A., Panda, N., Chauhan, R., Bloria, S. D., Bharti, N., Bhagat, H., Bhaire, V., Luthra, A., Chhabra, R., & Mahajan, S. (2020). Comparison of ketofol (combination of ketamine and propofol) and propofol anesthesia in aneurysmal clipping surgery: A prospective randomized control trial. *Asian Journal of Neurosurgery*, *15*(03), 608–613. https://doi.org/10.4103/ajns.ajns_346_19

Bourgoin, A., Albanèse, J., Léone, M., Sampol-Manos, E., Viviand, X., & Martin, C. (2005). Effects of sufentanil or ketamine administered in target-controlled infusion on the cerebral hemodynamics of severely brain-injured patients. *Critical Care Medicine*, *33*(5), 1109–1113. https://doi.org/10.1097/01.ccm.0000162491.26292.98

Breindahl, N., Baekgaard, J., Christensen, R. E., Jensen, A. H., Creutzburg, A., Steinmetz, J., & Rasmussen, L. S. (2021). Ketamine versus propofol for rapid sequence induction in trauma patients: A retrospective study. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, *29*(1). https://doi.org/10.1186/s13049-021-00948-5

Butterworth, J., Mackey, D., & Wasnick, J. (2022). *Morgan and Mikhail's Clinical Anesthesiology, 7th Edition* (7th ed.). McGraw Hill / Medical

Caricato, A., Tersali, A., Pitoni, S., De Waure, C., Sandroni, C., Bocci, M., Annetta, M., Pennisi, M., & Antonelli, M. (2013). Racemic ketamine in adult head injury patients: use in endotracheal suctioning. *Critical Care*, *17*(6), R267. https://doi.org/10.1186/cc13097

Carlson, A. P., Abbas, M., Alunday, R. L., Qeadan, F., & Shuttleworth, C. W. (2019). Spreading depolarization in acute brain injury inhibited by ketamine: A prospective, randomized,

multiple crossover trial. *Journal of Neurosurgery*, *130*(5), 1513–1519. https://doi.org/10.3171/2017.12.jns171665

Chang, L. C., Raty, S. R., Ortiz, J., Bailard, N. S., & Mathew, S. J. (2013). The emerging use of ketamine for anesthesia and sedation in traumatic brain injuries. *CNS Neuroscience & Therapeutics*, *19*(6), 390–395. https://doi.org/10.1111/cns.12077

Chui, J., Mariappan, R., Mehta, J., Manninen, P., & Venkatraghavan, L. (2014). Comparison of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis. *Canadian Journal of Anesthesia/Journal Canadien D'anesthésie*, *61*(4), 347–356. https://doi.org/10.1007/s12630-014-0118-9

Cohen, L., Athaide, V., Wickham, M. E., Doyle-Waters, M. M., Rose, N. G., & Hohl, C. M. (2015). The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: A systematic review. *Annals of Emergency Medicine*, *65*(1), 43-51.e2. https://doi.org/10.1016/j.annemergmed.2014.06.018

Cornelius, B. G., Webb, E., Cornelius, A., Smith, K. W., Ristic, S., Jain, J., Cvek, U., & Trutschl, M. (2018). Effect of sedative agent selection on morbidity, mortality and length of stay in patients with increase in intracranial pressure. *World Journal of Emergency Medicine*, *9*(4), 256. https://doi.org/10.5847/wjem.j.1920-8642.2018.04.003

Dengler, B. A., Karam, O., Barthol, C. A., Chance, A., Snider, L. E., Mundy, C. M., Bounajem, M. T., Johnson, W. C., Maita, M. M., Mendez-Gomez, P. M., Seifi, A., & Hafeez, S. (2022). Ketamine boluses are associated with a reduction in intracranial pressure and an increase in cerebral perfusion pressure: A retrospective observational study of patients

with severe traumatic brain injury. *Critical Care Research and Practice*, *2022*, 1–8. https://doi.org/10.1155/2022/3834165

Filanovsky, Y., Miller, P., & Kao, J. (2010). Myth: Ketamine should not be used as an induction agent for intubation in patients with head injury. *CJEM*, *12*(02), 154–157. https://doi.org/10.1017/s1481803500012197

Flood, P., Rathmell, J. P., & Shafer, S. (2014). *Stoelting's Pharmacology & Physiology in Anesthetic Practice* (Fifth). Lippincott Williams & Wilkins.

Froese, L., Dian, J., Batson, C., Gomez, A., Unger, B., & Zeiler, F. A. (2020). Cerebrovascular response to propofol,fentanyl, and midazolam in moderate/severe traumatic brain injury: A scoping systematic review of the human and animal literature. *Neurotrauma Reports*, 100–112. https://doi.org/10.1089/neur.2020.0040100

Godoy, D. A., Badenes, R., Pelosi, P., & Robba, C. (2021). Ketamine in acute phase of severe traumatic brain injury "an old drug for new uses?" *Critical Care*, *25*(1). https://doi.org/10.1186/s13054-020-03452-x

Green, S. M., Andolfatto, G., & Krauss, B. S. (2015). Ketamine and intracranial pressure: No contraindication except hydrocephalus. *Annals of Emergency Medicine*, *65*(1), 52–54. https://doi.org/10.1016/j.annemergmed.2014.08.025

Gregers, M. C. T., Mikkelsen, S., Lindvig, K. P., & Brøchner, A. C. (2020). Ketamine as an anesthetic for patients with acute brain injury: A systematic review. *Neurocritical Care*, *33*(1), 273–282. https://doi.org/10.1007/s12028-020-00975-7

Hertle, D. N., Dreier, J. P., Woitzik, J., Hartings, J. A., Bullock, R., Okonkwo, D. O., Shutter, L. A., Vidgeon, S., Strong, A. J., Kowoll, C., Dohmen, C., Diedler, J., Veltkamp, R., Bruckner, T., Unterberg, A. W., & Sakowitz, O. W. (2012). Effect of analgesics and

sedatives on the occurrence of spreading depolarizations accompanying acute brain injury. *Brain*, *135*(8), 2390–2398. https://doi.org/10.1093/brain/aws152

Himmelseher, S., & Durieux, M. E. (2005). Revising a dogma: Ketamine for patients with neurological injury? *Anesthesia & Analgesia*, *101*(2), 524–534. https://doi.org/10.1213/01.ane.0000160585.43587.5b

Hines, R. L., & Marschall, K. E. (2017). *Stoelting's Anesthesia and Co-Existing Disease* (7th ed.). Elsevier.

Jaffe, R. A. (Ed.). (2014). *Anesthesiologist's manual of surgical procedures* (5th ed.). Lippincott Williams & Wilkins.

Khallaf, M., Thabet, A. M., Ali, M., Sharkawy, E., & Abdel-rehim, S. (2019). The effect of dexmedetomidine versus propofol in traumatic brain injury: Evaluation of some hemodynamic and intracranial pressure changes. *Egyptian Journal of Neurosurgery*, *34*(1). https://doi.org/10.1186/s41984-019-0041-z

Kolenda, H., Gremmelt, A., Rading, S., Braun, U., & Markakis, E. (1996). Ketamine for analgosedative therapy in intensive care treatment of head-injured patients. *Acta Neurochirurgica*, *138*(10), 1193–1199. https://doi.org/10.1007/bf01809750

Luthra, A., Bhaire, V., Panda, N., Chauhan, R., Rajappa, D., & Bhagat, H. (2019). Effect of combination of ketamine and propofol (ketofol) on cerebral oxygenation in neurosurgical patients: A randomized double-blinded controlled trial. *Anesthesia: Essays and Researches*, *13*(4), 643. https://doi.org/10.4103/aer.aer_119_19

Mayberg, T. S., Lam, A. M., Matta, B. F., Domino, K. B., & Winn, H. R. (1995). Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous

oxide anesthesia in patients undergoing craniotomy. *Anesthesia & Analgesia*, *81*(1), 84–89. https://doi.org/10.1097/00000539-199507000-00017

Mihaljevic, S., Pavlovic, M., Reine, K., & Cacic, M. (2020). Therapeutic mechanisms of ketamine. *Psychiatria Danubina*, *32*(3–4), 325–333. https://doi.org/10.24869/psyd.2020.325

Nagelhout, J. J., & Elisha, S. (2018). *Nurse anesthesia* (6th ed.). Elsevier.

Oddo, M., Crippa, I. A., Mehta, S., Menon, D., Payen, J. F., Taccone, F. S., & Citerio, G. (2016). Optimizing sedation in patients with acute brain injury. *Critical Care*, *20*(1). https://doi.org/10.1186/s13054-016-1294-5

Prabhu, A. J., & Matta, B. F. (2004). Anaesthesia for extra-cranial surgery in patients with traumatic brain injury. *Continuing Education in Anaesthesia Critical Care &Amp; Pain*, *4*(5), 156–159. https://doi.org/10.1093/bjaceaccp/mkh043

Roberts, D. J., Hall, R. I., Kramer, A. H., Robertson, H. L., Gallagher, C. N., & Zygun, D. A. (2011). Sedation for critically ill adults with severe traumatic brain injury: A systematic review of randomized controlled trials. *Critical Care Medicine*, *39*(12), 2743–2751. https://doi.org/10.1097/ccm.0b013e318228236f

Sehdev, R. S., Symmons, D. A., & Kindl, K. (2006). Ketamine for rapid sequence induction in patients with head injury in the emergency department. *Emergency Medicine Australasia*, *18*(1), 37–44. https://doi.org/10.1111/j.1742-6723.2006.00802.x

Smischney, N. J., Beach, M. L., Loftus, R. W., Dodds, T. M., & Koff, M. D. (2012). Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent. *Journal of Trauma and Acute Care Surgery*, *73*(1), 94–101. https://doi.org/10.1097/ta.0b013e318250cdb8

Takeshita, H., Okuda, Y., & Sari, A. (1972). The effects of ketamine on cerebral circulation and metabolism in man. *Anesthesiology*, *36*(1), 69–75. https://doi.org/10.1097/00000542-197201000-00013

Telles, J. P. M., Welling, L. C., Coelho, A. C. S. D. S., Rabelo, N. N., Teixeira, M. J., & Figueiredo, E. G. (2021). Cortical spreading depolarization and ketamine: A short systematic review. *Neurophysiologie Clinique*, *51*(2), 145–151. https://doi.org/10.1016/j.neucli.2021.01.004

Wang, X., Ding, X., Tong, Y., Zong, J., Zhao, X., Ren, H., & Li, Q. (2014). Ketamine does not increase intracranial pressure compared with opioids: Meta-analysis of randomized controlled trials. *Journal of Anesthesia*, *28*(6), 821–827. https://doi.org/10.1007/s00540-014-1845-3

Wright, D. R. (2021, July 19). *Ketamine in Modern Neuroanesthesia Practice*. SpringerLink. https://link.springer.com/article/10.1007/s40140-021-00465-2?error=cookies_not_supported&code=34c0d412-0b5e-475f-810b-43f9541034fe

Zanos, P., Moaddel, R., Morris, P. J., Riggs, L. M., Highland, J. N., Georgiou, P., Pereira, E. F. R., Albuquerque, E. X., Thomas, C. J., Zarate, C. A., & Gould, T. D. (2018). Ketamine and ketamine metabolite pharmacology: Insights into therapeutic mechanisms. *Pharmacological Reviews*, *70*(3), 621–660. https://doi.org/10.1124/pr.117.015198

Zanza, C., Piccolella, F., Racca, F., Romenskaya, T., Longhitano, Y., Franceschi, F., Savioli, G., Bertozzi, G., De Simone, S., Cipolloni, L., & La Russa, R. (2022). Ketamine in acute brain injury: Current opinion following cerebral circulation and electrical activity. *Healthcare*, *10*(3), 566. https://doi.org/10.3390/healthcare10030566

Zeiler, F. A., Teitelbaum, J., West, M., & Gillman, L. M. (2014). The ketamine effect on ICP in traumatic brain injury. *Neurocritical Care*, *21*(1), 163–173. https://doi.org/10.1007/s12028-013-9950-y

Zietlow, J., Berns, K., Jenkins, D., & Zietlow, S. (2019). Prehospital use of ketamine: Effectiveness in critically ill and injured patients. *Military Medicine*, *184*(Supplement_1), 542–544. https://doi.org/10.1093/milmed/usy422