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The Emerging Use of Ketamine for Anesthesia and Sedation in Traumatic Brain Injuries

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SUMMARY

Background—Traditionally, the use of ketamine for patients with traumatic brain injuries is contraindicated due to the concern of increasing intracranial pressure (ICP). These concerns, however, originated from early studies and case reports that were inadequately controlled and designed. Recently, the concern of using ketamine in these patients has been challenged by a number of published studies demonstrating that the use of ketamine was safe in these patients.

Aims—The purpose of this article was to review the current literature in regards to using ketamine in patients with traumatic brain injuries in different clinical settings associated with anesthesia, as well as review the potential mechanisms underlying the neuroprotective effects of ketamine.

Results—Studies examining the use of ketamine for induction, maintenance, and sedation in patients with TBI have had promising results. The use of ketamine in a controlled ventilation setting and in combination with other sedative agents has demonstrated no increase in ICP.

Conclusions—The role of ketamine as a neuroprotective agent in humans remains inconclusive and adequately powered; randomized controlled trials performed in patients undergoing surgery for traumatic brain injury are necessary.

Keywords

Behavioural neurology; Neuromuscular disease; Neuropsychopharmacology; Stroke

Introduction

The use of ketamine for patients with traumatic brain injuries (TBIs) and known or suspected intracranial pathology has traditionally been contraindicated due to the possibility of increasing intracranial pressure (ICP). The FDA package insert cautions that “An increase

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Disclosure

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in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure." Soon after the drug was developed, a limited number of articles were published that reportedly demonstrated that the use of ketamine resulted in increased cerebral blood flow (CBF) and cerebral metabolic rate for O_2 ($CMRO_2$), which caused a rise in ICP. Gardner et al. presented data from a series of 11 healthy patients with no pre-existing medical conditions undergoing simple surgical procedures under spinal anesthesia and found that cerebrospinal fluid pressure became markedly elevated after the administration of a standard dose of 2 mg/kg ketamine [1]. In a subsequent case series, the same authors reported that ketamine caused dramatic increases in intracranial pressure in two patients with intracranial masses [2]. Both of these patients were allowed to breathe spontaneously during their brief operative decompressions, and the ketamine anesthesia described consisted of a 2 mg/kg bolus of i.v. ketamine, with no other sedatives or anesthetic agents. Early publications consisted of case reports and small case–control studies that were inadequately controlled and designed.

Recently, this view has been challenged by a number of published studies demonstrating that the use of ketamine was safe in patients with elevated ICP in mechanically ventilated patients or in the presence of background anesthetic agents, resulting in either no significant increases in ICP or even a decrease in ICP and EEG activity. Additional studies have suggested that the use of ketamine may confer neuroprotective effects for patients at risk of ischemic brain injury, reducing cell death and neuronal degeneration. The purpose of this review is to update the current published literature concerning the use of ketamine for patients with brain injuries. Specifically, this review will focus on potential mechanisms underlying the neuroprotective effects of ketamine and its use in the preoperative, intraoperative, and postoperative periods.

Methods

Literature searches were conducted with Medline and Embase (1962 to October 2012) using the following search terms: ketamine, traumatic brain injury, intracranial pressure, neuroprotection, induction, and sedation. Following initial review of the abstracts, articles were obtained based on their relevance. References from the identified papers were also examined for further relevant studies. Case reports and letters were not evaluated.

Mechanisms of Neuroprotection

TBI continues to be a leading source of significant neurologic disability, affecting nearly 1.4 million patients each year in the United States. TBI is typically classified into primary and secondary brain injury, with primary injury occurring during the initial insult and believed to be irreversible. Secondary brain injury occurs gradually and is often a result from processes initiated by the trauma. The etiology of secondary brain injury is multifactorial and includes hypoxemia, hypotension, increased ICP, and decreased CBF [3–5].

These secondary injury mechanisms are comprised of several different processes that include an increased inflammatory response, elevated glutamate concentrations, ion imbalances, free radical release, and apoptosis. Elevated levels of glutamate and other excitatory neurotransmitters are associated with certain pathological states, including TBI [6]. The increase in glutamate is thought to be a result of decreased ATP production associated with TBI and ischemia. Glutamate uptake and transporters are dependent on electrochemical ion gradients, which in turn are dependent on ATP. The primary action of ketamine, the noncompetitive inhibition of N-methyl-D-aspartate (NMDA) receptors, is believed to provide neuroprotection through the prevention of stimulation of the excitatory amino acid receptor and a reduction in glutamate excitotoxicity [7]. Excitotoxicity is the

process by which neurons are injured through excessive stimulation and has been established as an important process in secondary injury. In addition, excitotoxicity is believed to be involved in a number of other central nervous system pathologies, such as stroke and spinal cord injury. Following increased levels of glutamate and other excitatory neurotransmitters, a high influx of Ca^{2+} occurs, activating a number of calcium-dependent enzymes that lead to neuronal injury [8]. With increasing levels of calcium within the neuronal cell, proteolytic enzymes are activated leading to apoptosis [9]. In addition to calcium influx, it has been noted that NMDA receptor activation also activates a cAMP response element binding protein shutoff, resulting in the loss of mitochondrial membrane potential and apoptosis [10]. The administration of ketamine resulting in the reduction in glutamate concentrations in the brain has recently been confirmed with the use of magnetic resonance imaging [11].

Another potential mechanism of action of ketamine's neuroprotective properties is its effects on the inflammatory response. Ketamine's antiinflammatory properties are believed to act through its suppression of lipopolysaccharide-induced microglial activation and reducing inflammatory cytokines such as tumor necrosis factor and IL-6 [12]. Elevated plasma concentrations of IL-6 have been investigated as markers of prognosis and infectious complications in patients with brain injuries [13]. Although there have been no human studies that have examined plasma concentrations of inflammatory markers in TBI patients following the administration of ketamine, Bhutta et al. examined the effects of ketamine and its noninflammatory properties in association with patients undergoing cardiopulmonary bypass [11]. The study randomized 24 infants to receive ketamine or placebo before cardiopulmonary bypass. Based on plasma inflammatory markers collected at different time intervals, no significant differences were observed.

The use of ketamine for unstable patients has long been advocated due to its enhancement of a centrally mediated sympathetic response and maintenance of hemodynamic stability. This is of particular importance in the setting of TBI, where hemodynamic instability should be avoided. Hypotension can be the result of blood loss in the field or sedating medications and can be caused by an isolated head injury [14]. Numerous studies have demonstrated that hypotension is a major predictor of outcomes in patients with TBI [15–18]. Compared with patients without hypotension, even a single episode of hypotension has been associated with worsening secondary brain injury and increased morbidity and mortality [15,19]. Manley et al. found that 2 or more hypotensive episodes in patients presenting with a Glasgow Coma Score (GCS) <13 increased the relative risk of mortality to 8.1 (95% CI 1.63–39.9) [20]. Activation of the sympathetic nervous system with the administration of ketamine can result in maintaining cerebral perfusion pressure (CPP) for patients with TBI. Certainly, either an isolated decrease in MAP or an isolated increase in ICP or a combination of the two can negatively affect CPP and potentially cause brain ischemia. Struchen et al. followed a cohort of 184 brain injured patients in the neurosurgical ICU and found that a CPP <60 mm Hg was associated with worse outcomes [21]. Schmittner et al. demonstrated that the need for vasopressors when using ketamine for sedation in comparison with fentanyl is decreased [22].

Recent studies have examined the effects that ketamine has on spreading depolarizations [23,24]. Spreading depolarizations are described as propagating waves of neuronal and glial depolarizations. Under normal conditions in an intact central nervous system, these depolarizations result in depression of neuronal activity. However, in patients with TBI who already have a depressed neuronal activity, these depolarizations cannot cause further depression. Under these circumstances, they result in further neuronal injury and are associated with poorer neurological outcome. When measuring electrocorticographic recordings with the administration of ketamine, a sustained inhibition of spreading

depolarizations was observed. This finding suggests another potential mechanism underlying ketamine's use as a neuroprotective agent.

Ketamine for Induction in the Head Injured Patient

When the decision has been made to intubate the patient with a suspected or known head injury, the chosen induction agent should provide optimum intubating conditions and minimize secondary brain injury. Ketamine in combination with a neuromuscular blocking agent like succinylcholine provides amnesia and analgesia during intubation and has been shown to yield similar success rates when used by emergency personnel for prehospital and presurgical intubation [25,26]. The wide availability of ketamine, its affordability, and provision of advantageous intubating conditions make it a suitable choice for induction when aspiration is a risk.

Early studies on ketamine as an induction agent for neurosurgical procedures concluded that it was an inappropriate agent for any patient with increased ICP. Wyte et al. described two cases in which ketamine was used as the induction agent [27]. The first patient had a known, pre-existing elevated ICP and had a significant increase in ICP following ketamine administration. The second patient did not have intracranial hypertension and had only mild fluctuations in ICP following ketamine. Of note, both patients were allowed to spontaneously breathe after induction with ketamine. When controlled ventilation was initiated in the first patient, ICP decreased precipitously. Belopavlovic et al. studied the effect of two induction drug combinations on the ICP of patients undergoing neurosurgical procedures [28]. One group received midazolam (0.15 mg/kg) followed by ketamine 1 mg/kg, and the other group received diazepam (0.2 mg/kg) followed by ketamine (1 mg/kg). They concluded that the combination of midazolam and ketamine cannot be recommended for induction in neurosurgical patients due to a critically reduced CPP. Although not extensively discussed in the article, the calculated CPP following the initial midazolam dose decreased in 8 of 10 patients. After the subsequent ketamine dose, the calculated CPP improved in 5 of 10 patients, declined an average of 15.65% (range 5–18%) in 4 patients, and was unchanged from baseline in one patient. In the setting of head injury, an induction including a large dose of midazolam is difficult to justify, making the results of this study not applicable to the question of whether ketamine can be safely used for induction in head injury patients.

More recent studies call into question the assertion that ketamine is an inappropriate induction drug for brain injury patients. Jabre et al. conducted a randomized controlled single-blind trial on 655 patients who required sedation for emergency intubation [29]. Patients were randomly assigned to receive either etomidate (0.3 mg/kg) or ketamine (2 mg/kg) for intubation. Sixty-nine percent of the patients in each group were intubated due to coma. The final diagnosis was trauma in 24% of the etomidate group and 20% of the ketamine group. The study does not present the number of patients with a diagnosis of head injury. They found no difference between the groups in terms of sequential organ failure assessment (SOFA), difficulty of intubation, early complications after intubation, 28-day mortality, catecholamine-free days, duration of weaning from the ventilator, and length of stay in the ICU. There were no serious adverse events with either study drug. Smischney et al. conducted a randomized, double-blind, placebo-controlled trial comparing induction and intubation with propofol to induction and intubation with a mixture of propofol and ketamine (ketofol) as an induction "cocktail" in ASA I and II patients [30]. They concluded that ketofol provided better hemodynamic stability than propofol in the 10 min following induction. Recent drug shortages in the United States have affected the availability of a variety of medications including thiopental, propofol, etomidate, and succinylcholine. Although many anesthesiologists would choose etomidate as a first-line induction medication for traumatically injured patients because of its association with hemodynamic

stability, drug shortages have often forced them to choose an alternative medication. Given the previously established goal of maintaining both SBP and CPP, ketamine may very well have a role as an induction agent for brain injury patients. In catecholamine-depleted patients or in patients who lack autonomic control, ketamine's myocardial depressant effects may predominate [31,32]. However, acutely injured patients are not catecholamine depleted and ketamine is likely to result in a rise in heart rate (HR), SBP, and cardiac index (CI) [33]. In hypotensive or hypovolemic patients who have a head injury, induction of ketamine may improve hemodynamics, including SBP and CPP.

Intraoperative Use of Ketamine in the Patient with TBI

Growing evidence demonstrates that the intraoperative use of ketamine appears to be a promising addition in the anesthesiologist's formulary. Ketamine has shown neuroprotective effects against ischemic brain injury and glutamate-induced brain injury in rodent models, and its intraoperative administration might also allow the use of lower concentrations of potent volatile anesthetics, thereby minimizing cerebral vasodilation [34]. Because other intravenous anesthetics (such as propofol, thiopental, and etomidate) reduce cerebral blood flow, intracranial pressure, and $CMRO_2$, administration of these agents might more rationally be expected to provide optimal operating conditions and a metabolically quiescent, slack brain, these agents would seem to be more rational choices for intraoperative administration in cases of neurotrauma.

Unfortunately, no high-quality trials have been performed to date on the intraoperative use of ketamine for neurotrauma. The limited human data that exist are either retrospective multicenter reports or reports on the use of intraoperative ketamine during craniotomies for indications other than TBI. No randomized, controlled trials have been performed directly addressing this area of substantial clinical uncertainty.

Mayberg et al. studied the cerebral hemodynamic effects of ketamine on 20 patients undergoing craniotomy for intracranial tumor or aneurysm [35]. After thiopental induction, endotracheal intubation, and institution of positive pressure ventilation, anesthesia was maintained with isoflurane and nitrous oxide in oxygen. Subsequent intraoperative administration of intravenous ketamine 1 mg/kg reduced intracranial pressure from 16 ± 1 mmHg to 14 ± 1 mmHg ($P < 0.001$) and likewise reduced middle cerebral artery blood velocity from 44 ± 4 cm/s to 39 ± 4 cm/s ($P < 0.001$).

Grathwohl et al. performed a retrospective review of all patients admitted to a US military Combat Support Hospital for operative treatment of TBI [36]. Of 214 patients meeting inclusion criteria over a 15-month period, 94 received total intravenous anesthesia, of whom 47 received ketamine and 47 did not. Modified propensity score analysis and matching on injury severity and other variables were performed to eliminate possible sources of bias. No difference in mortality was found, nor was there any difference in neurosurgical outcome: Glasgow Outcome Score (GOS) was 4 (4–5) in the ketamine group, versus 4 (3–5) in the no-ketamine group ($P = 1.0$), with no difference in the proportion of patients achieving a good outcome (GOS 4 or 5).

Hertle et al. conducted an exploratory retrospective multicenter study of 115 patients undergoing craniotomy for neurotrauma, subarachnoid hemorrhage, or malignant stroke during the course of which electrode strips were placed on the surface of the affected cortex [23]. These patients received a variety of anesthetic regimens, as no standard regimen had been prescribed prospectively. Spreading waves of cerebral depolarization, thought to be indicative of neuronal swelling due to the breakdown of ion transport across cell membranes, were observed in 76 patients. 26 of these 76 patients received ketamine (median total dose 200 mg) at some point during their stay in the intensive care unit, with

administration of ketamine peaking on the seventh day after injury. Of the variety of sedative agents administered while electroencephalograms were being recorded, ketamine was linked with a reduction in the frequency of spreading depolarizations and in the frequency of temporally associated spreading depolarization clusters. The clinical significance of this observation is unclear, as no other outcomes such as GOS or death were recorded. As a cautionary note, in contrast to this latter finding, of 7 anesthetic/sedative agents given after controlled cortical impact in rats, ketamine 10 mg/kg i.v produced the greatest degree of hippocampal neuronal death, whereas isoflurane produced the greatest degree of hippocampal neuronal survival [37].

The Use of Ketamine for Sedation in the Patient with TBI

The goal of sedation in critically ill patients with TBI is to produce anxiolysis, prevent agitation, and facilitate manipulation of mechanical ventilation [38]. The gold standard for monitoring sedation in these patients is the neurologic examination. The choice of sedative agent can often obscure pertinent clinical findings. The confusion and agitation that accompany brain injury increase brain metabolism and precipitate struggling and resistance to nursing care and mechanical ventilation [39]. An important objective in this group of patients is to maintain adequate cerebral perfusion pressure. This can be accomplished by maintaining adequate mean arterial pressure, blood gases, body temperature, serum glucose concentration, electrolytes, and osmolarity.

Agents used for sedation of TBI patients are similar to those used for other critically ill patients. They include benzodiazepines, opioids, clonidine, dexmedetomidine, propofol, etomidate, and ketamine. Selection of shorter-acting agents may have the advantage of allowing a brief interruption of sedation to evaluate neurologic status [40]. The agents can be used on their own or in combination in order to achieve adequate levels of sedation for mechanically ventilated patients while maintaining stable hemodynamics. A systematic review of all agents by Roberts et al. found no evidence that one agent is more effective than the others in improving neurologic outcome or mortality of critically ill adults with TBI [38]. They did find that boluses and short infusions of opioids resulted in clinically and statistically significant increases in intracranial pressure and decreases in mean arterial pressure and cerebral perfusion pressure compared with baseline in three trials [41–43].

Historically, ketamine has not been used to provide sedation in patients with TBI due to the risk of increasing intracranial pressure in this group of patients. Ketamine antagonizes excitatory amino acids at the NMDA receptor and may reduce the consequent calcium ion mobilization and neuronal damage that occurs in head injury [44]. However, it has not gained widespread use as a sedative agent in TBI patients due to reported detrimental effects on cerebral blood flow, $CMRO_2$, and intracranial pressure [45]. Another potential disadvantage is the reduction in seizure threshold [46]. There are four studies that specifically address the issue of ketamine sedation for patients after TBI. The first study conducted by Albanese et al. involved 8 patients with TBI [47]. These patients were sedated with propofol infusion at 3 mg/kg/h, had neuromuscular blockade with vecuronium bromide at 9 mg/h, and had $PaCO_2$ maintained between 35 and 38 mm Hg. Ketamine was added to the sedation regimen at doses of 1.5, 3, and 5 mg/kg given in 6-h intervals in order to gauge its effects on intracranial pressure, cerebral perfusion pressure, jugular vein bulb oxygen saturation, middle cerebral artery blood flow velocity, and electroencephalogram. The researchers found no statistically significant difference in heart rate, mean arterial pressure, and cerebral perfusion pressure at any of the ketamine doses given when compared with baseline. Of interest, intracranial pressure in this study decreased between 18 and 30% depending on the dose of ketamine given. This contradicts the common assumption that ketamine increases intracranial pressure.

A study by Kolenda et al. prospectively allocated 35 TBI patients to sedation with ketamine and midazolam or fentanyl and midazolam [48]. In the study, the average dose of ketamine required for adequate sedation was 104 mg/kg/day compared with 100 μg/kg/day of fentanyl. The average midazolam dose was comparable between the groups with an average of 11.1 mg/kg/day for the ketamine group and 10.7 mg/kg/day for the control group. Although the average intracranial pressure in the ketamine group was 2 mm Hg higher, the cerebral perfusion pressure was also improved at 8 mm Hg higher due to an increase in mean arterial pressure of 10 mm Hg. In addition, the researchers reported improved tolerance to tube feeding in the ketamine sedation group, although this was not a primary outcome.

Bourgoin et al. performed two prospective, randomized trials studying ketamine for sedation in patients with TBI. The first study compared sedation with ketamine and midazolam to sedation with sufentanil and midazolam in 25 patients with TBI under controlled mechanical ventilation [49]. Patient in the study had a starting Glasgow Coma Scale score ranging from 3 to 8. The goal of sedation in this study was to obtain a quiet patient with an intracranial pressure less than 25 mm Hg and cerebral perfusion pressure greater than 70 mm Hg. Average infusion rates used were 82 ± 25 μg/kg/min of ketamine and 1.64 ± 0.5 μg/kg/min of midazolam in the ketamine group compared with 0.008 ± 0.002 μg/kg/min of sufentanil and 1.63 ± 0.37 μg/kg/min of midazolam in the sufentanil group. Sedation efficacy was assessed during endotracheal suctioning of these patients. The researchers found no significant differences in the mean daily values of intracranial pressure and cerebral perfusion pressures. Patients in the ketamine group did have a longer recovery time after the infusion was stopped when compared with sufentanil. Both patient groups showed the same tolerance to enteral nutrition.

The second study by Bourgoin et al. looked at the effects of a target-controlled infusion of sufentanil and ketamine on cerebral hemodynamics [50]. Thirty patients with TBI and Glasgow Coma Scale less than 9 were enrolled in the study and randomized to one of the groups. Sedation was initiated with a target plasma concentration of 0.3 ng/ml sufentanil and 100 ng/ml midazolam in the sufentanil group and 1 μg/ml ketamine and 100 ng/ml midazolam in the ketamine group. Mean arterial pressure, cerebral perfusion pressure, intracranial pressure, and mean velocity of middle cerebral artery flow were continuously measured, and $PaCO_2$ was maintained between 35 and 38 mm Hg throughout. Twenty-four hours after the initiation of sedation, target plasma concentrations of sufentanil or ketamine were doubled. Initial values for intracranial pressure and cerebral perfusion pressure, as well as the values after doubling the concentrations of both agents, were not statistically different between the groups. The twofold increase in sufentanil or ketamine concentrations did not involve significant change in mean arterial pressure, intracranial pressure, and cerebral perfusion pressure compared with the baseline values.

The studies described above report no increase in intracranial pressure of TBI patients receiving ketamine for sedation when ventilation is controlled or when midazolam was given concurrently. Potential advantages of ketamine administration compared with opioids are maintenance of hemodynamics and cerebral perfusion pressure, better tolerance of enteral nutrition, and absence of withdrawal symptoms [49]. However, the total number of patients studied to date is insufficient to make any conclusions as to whether ketamine in addition to other agents, or by itself, should be used routinely for sedation of TBI patients. These data suggest that ketamine should be considered as an adjunct for sedation, especially in patients where hypotension is a major problem. It does not appear to adversely affect intracranial pressure in the setting of controlled mechanical ventilation. Future well-controlled, randomized controlled trials are needed in order to determine whether ketamine should become a common sedation agent in TBI (Table 1).

Conclusions

In conclusion, while there are promising signs that the use of ketamine during TBI procedures may increase in the future, the data are too sparse to provide firm guidance at this time. As discussed, studies examining the use of ketamine for induction, maintenance, and sedation in patients with TBI have had promising results. The use of ketamine in a controlled ventilation setting and in combination with other sedative agents has demonstrated no increase in ICP, which is the major concern of anesthesiologists regarding ketamine for patients with TBI. However, the role of ketamine as a neuroprotective agent in humans remains inconclusive and adequately powered, randomized controlled trials performed in patients undergoing surgery for TBI are necessary.

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Table 1

Summary of studies on ketamine for induction, maintenance, and sedation

Reference	Study Size	Setting	Ketamine dose	Findings
Jabre et al. [29]	655	Etomidate or ketamine for intubation	2 mg/kg	No difference between the groups
Smischney et al. [30]	84	Propofol or mixture of propofol/ketamine for induction	0.75 mg/kg of ketamine	Propofol/ketamine resulted in better hemodynamic stability
Mayberg et al. [35]	20	Intraoperative administration of ketamine for craniotomy	1 mg/kg	Ketamine reduced intracranial pressure
Grathwohl et al. [36]	214	Total intravenous anesthesia compared with inhalational anesthesia	Varied	No difference in mortality or neurosurgical outcome between groups
Roberts et al. [38]	380	Systematic review of different agents used for sedation in ICU	Varied	No evidence that one agent is more effective in improving neurologic outcome
Albanese et al. [47]	8	Propofol sedation with the addition of ketamine	1.5 mg/kg, 3 mg/kg, and 5 mg/kg	No difference in cerebral perfusion pressure at any of the doses compared with baseline
Kolenda et al. [48]	35	Sedation with ketamine/midazolam or fentanyl/midazolam	Average of 104 mg/kg/day	Increased intracranial pressure but improved cerebral perfusion pressure with ketamine group
Bourgoin et al. [49]	25	Sedation with ketamine/midazolam or sufentanil/midazolam	Average of 82 μg/kg/min	No difference in intracranial pressures and cerebral perfusion pressures
Bourgoin et al. [50]	30	Target-controlled sedation with ketamine/midazolam or sufentanil/midazolam	Plasma concentrations of 1 and 2 μg/ml ketamine	No difference in intracranial pressures and cerebral perfusion pressures