Ketamine Use in Acute Brain Injury: Debunking the Myth

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KEYWORDS

• Ketamine • Traumatic brain injury • Analgesia • Sedation • Intracranial pressure • Cerebral perfusion pressure

KEY POINTS

- Early evidence that demonstrated an increased intracranial pressure with ketamine administration was low quality and did not include patients with traumatic brain injury.
- Ketamine possesses several neuroprotective properties, which could reduce secondary brain injury after a traumatic brain injury.
- Contemporary evidence utilizing ketamine in patients with a traumatic brain injury demonstrates trends toward decreased intracranial pressure as well as increased cerebral perfusion pressure.

INTRODUCTION

Ketamine is a phencyclidine (PCP) derivative introduced into clinical practice in the 1970s, primarily used for its dissociative anesthetic and potent analgesic properties. It was originally developed as an alternative to PCP to provide anesthesia with a better safety profile, particularly preserving airway reflexes and cardiovascular stability.[1]

Ketamine acts as a non-competitive antagonist at the N-methyl-D-aspartate (NMDA) receptor, inhibiting excitatory glutamatergic neurotransmission. It also interacts with opioid, cholinergic, and monoaminergic systems, which likely contributes to its analgesic, antidepressant, and psychotomimetic effects.[2]

Historically, ketamine was avoided in patients with traumatic brain injury (TBI) due to fear of increased ICP, a belief rooted in early, poorly controlled studies.[3–7] However, more recent evidence demonstrates that ketamine does not increase, and may even decrease, ICP in sedated and mechanically ventilated patients with TBI or other

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Emerg Med Clin N Am 44 (2026) 523–532
https://doi.org/10.1016/j.emc.2026.03.001 **emed.theclinics.com**

Abbreviations	
CSD	cortical spreading depolarization
CSFP	Cerebrospinal Fluid Pressure
ICP	intracranial pressure
ICU	intensive care unit
IL	interleukin
MAP	mean arterial pressure
NMDA	N-methyl-D-aspartate
PCP	phencyclidine
SBI	secondary brain injury
SBP	systolic blood pressure
TBI	traumatic brain injury
TNF-α	tumor necrosis factor-alpha

neurologic conditions.[8] This evolving evidence challenges the longstanding dogma and underscores the importance of reassessing ketamine's role in neurocritical care.

Reevaluating the use of ketamine in acute brain injury is important due to its unique pharmacokinetics and pharmacodynamics. Most other sedatives lower blood pressure and risk compromising cerebral perfusion pressure (CPP) which can worsen secondary brain injury (SBI). Ketamine, in contrast, preserves or augments hemodynamics while providing effective sedation and analgesia. This profile makes it a promising agent for managing sedation and intracranial hypertension in patients with TBI and other acute brain injuries.[9,10]

This review summarizes the key pathophysiologic considerations in TBI and examines ketamine's effects on the parameters most relevant to neurologic outcomes.

EARLY RESEARCH ON KETAMINE USE IN TRAUMATIC BRAIN INJURY

Clinical observational studies and case reports originally published over 50 years ago first discussed an increase in ICP with ketamine.[3–7,11,12] The earliest report, published in 1972, described a child who received a single intravenous ketamine bolus of 2 mg/kg and subsequently developed swelling of the fontanel followed by respiratory arrest.[12] Subsequent case reports and observational studies, including investigations in healthy volunteers, reported increases in surrogate markers of ICP such as cerebrospinal fluid pressure (CSFP) and ventricular fluid pressure.[4–7] Interestingly, even in these early works one study demonstrated an increase in CPP, which could be neuroprotective.[7] Nevertheless, the prevailing interpretation emphasized the potential risk of ICP elevation.

For more than 25 years following the publication of these papers, the belief that ketamine increased ICP became deeply entrenched. Given that avoiding ICP elevation is a central principle in TBI management, ketamine was largely excluded from use in this population. This perception was further reinforced by a US Food and Drug Administration precaution advising against ketamine use in patients with elevated CSFP.[13]

Flaws in the Early Evidence

The foundational evidence supporting ketamine-induced ICP elevation consisted largely of small, uncontrolled studies and case series. These investigations were limited by small sample sizes, lack of randomization, and absence of standardized sedation protocols.

A critical limitation of these early studies is their lack of relevance to the population with TBI as most did not include patients with TBI. Intracranial dynamics in patients undergoing elective procedures or without brain injury differ substantially from those

in patients with acute TBI, where autoregulation, cerebral compliance, and metabolic demands are profoundly altered.

Additionally, there was significant heterogeneity in the data with regards to patient characteristics, clinical settings, and methods used to estimate ICP. Belopavlovic and colleagues conducted possibly the best available study at the time, evaluating ketamine as an induction agent in neurosurgical patients.[14] However, there was no standardization with regards to patient characteristics, sedation level, and arterial pCO2 targets. Further these patients were already receiving one of two benzodiazepine agents. The ICP observation window was quite short, and patients received pethidine as rescue therapy which further confounds results.

KETAMINE'S IMPACT ON HEMODYNAMICS, INTRACRANIAL PRESSURE, AND CEREBRAL PERFUSION PRESSURE IN TRAUMATIC BRAIN INJURY

Hemodynamics

Hypotension is strongly associated with worse outcomes TBI including increased mortality, disability, poor neurologic function, and longer intensive care unit (ICU) stays.

A recent systematic review and meta-analysis demonstrated that hypotension (commonly defined as systolic blood pressure [SBP] <90 mm Hg) have a significant increased risk of death, with adjusted odds ratios for mortality ranging from 2.6 to 4.0 depending on the threshold and setting.[15] The risk of adverse outcomes increases with both the depth and duration of hypotension, and even "near-hypotension" (SBP up to 120 mm Hg) is associated with higher mortality.[16] The combination of hypotension and hypoxia further magnifies this risk.[15]

Ketamine produces sympathetic stimulation, typically increasing heat rate, systolic and diastolic blood pressure shortly after administration. This effect seems to peak within minutes and usually resolves within 15 minutes.[17] This is a key advantage in the patient with TBI. In contrast, propofol, a commonly used alternative to ketamine, causes direct myocardial depression and systemic vasodilation which causes dose-dependent hypotension.[18] Randomized and observational studies in TBI and trauma populations show that propofol led to more frequent and severe drops in mean arterial pressure (MAP), greater vasopressor requirements, and higher incidence of hypotension than ketamine or ketofol.[19] Similar findings have been reported in ICU sedation studies and trauma intubation cohorts.[20]

Intracranial Pressure

Elevated ICP in patients with TBI can cause direct harm by reducing cerebral perfusion, leading to brain ischemia, herniation, and increased mortality. As ICP rises, CPP drops, impairing oxygen and nutrient delivery to brain tissue. Prolonged or severe intracranial hypertension is associated with higher rates of death and poor neurologic outcomes, including persistent vegetative state and severe disability.[21] One of the earliest modern studies evaluating ketamine's effect on ICP was performed by Albanese and colleagues. They studied 8 patients with traumatic TBI in whom ICP monitoring was already instituted. Ketamine was administered to patients already sedated on propofol in bolus doses of 1.5, 3, and 5 m/kg at 6 hour intervals.[22] Cerebral hemodynamics and end-tidal carbon dioxide were continuously monitored. At all doses, ketamine was associated with a significant decrease in ICP. There was no significant difference in cerebral hemodynamics (**Table 1**).

Subsequent studies by Bourgoin and colleagues, and Schmittner and colleagues similarly demonstrated no significant differences in ICP between patients receiving ketamine and control groups.[23,24]

Table 1
Early evidence on ketamine and intracranial pressure

Author, Publication Date	Design	Data Points	Results
Tashika et al,[7] 1972	Observation of 10 healthy patients undergoing elective surgery	CPP, CVR, CBF	CPP increased on average from 88-122 mm Hg, CVR decreased from 1.91 to 1.38 mm/Hg/mL/ 100 g/min, CBF increased from 47 to 76 mL/ 100 g/min
List et al,[12] 1972	Case Series	Clinical progression	Increased cerebrospinal fluid pressure after ketamine administration
Sari et al,[6] 1972	Observation of 8 healthy volunteers	CSF pressure	Increases in CSF pressure after ketamine administration
Garner/Olson et al,[11] 1971	Observation of 11 healthy male subjects undergoing simple surgery	CSF pressure	CSF pressure increase 253.18 mm Hg ± 30.38 mm Hg after ketamine administration
Crumrine et al,[4] 1975	Observation of 26 children with hydrocephalus and shunts or external ventriculostomies	Ventricular fluid pressure	After ketamine administration, patients had a 2–5 fold increase in ventricular fluid pressure

Abbreviations: CBF, cerebral blood flow; CVR, cerebral vascular resistance.

There was some heterogeneity between these studies, most importantly with the dosage of ketamine. Studies using bolus dosage varied from 1 to 5 mg/kg.[22,24,25] Infusion rates varied from 0.3 to 200 mg/kg/h.[23,26,27] Rationale for the ketamine dosage was typically based on sedation goals.

Two studies reported increased ICP. Kolenda and colleagues observed modest elevations of 5 and 8 mm Hg in day 8 and 10 post head injury.[28] Carciato and colleagues also noted elevated ICP but only during tracheal suctioning.[26] No study reported any adverse events or significant increase in ICP stemming from ketamine administration. Of note, in the Caricato study, ICP also increased during suctioning in the control group. Further, ketamine seemed to blunt cough reflexes that could have further increased ICP.

Among the studies that evaluated CPP, only Bar-Joesph et al., who were studying a pediatric cohort, found a small increase in CPP (+3.9 mm Hg at 2 min) after ketamine administration.[25] The remainder of studies did not show any significant change. There were no significant differences in MAP and heart rate as well.

Only 4 studies evaluated spreading depolarizations and burst suppressions.[22,27,29,30] Two studies found ketamine to significantly decrease spreading depolarizations following acute brain injury.

Regarding clinical outcomes, ketamine does not appear to effect length of intensive care unit stay, or mortality.[8,31,32] Due to limited sample sizes and heterogeneity, most reviews assign the evidence an Oxford level 2b, Grace C recommendation.[8,32,33]

Ketamine seems to have favorable effects on ICP in the pediatric population as well. Laws and colleagues recently conducted a retrospective observation study evaluating the effect of ketamine on ICP in severe TBI. They found no significant increase in ICP

with ketamine bolus dosing and actually noted a trend toward decreased ICP and improved CPP (Table 2).[34]

Ketamine's Neuroprotective Properties

Ketamine exhibits several neuroprotective properties that are relevant in the management of TBI, elevated ICP, and prevention of SBI. SBI following TBI is driven in part by a phenomenon known as a cortical spreading depolarizations (CSDs) (Fig. 1). Focal injury triggers depolarization of the neurons and glial cells, resulting in potassium and glutamate release and intracellular influx of sodium and calcium. Excess glutamate overstimulates neighboring neurons, increasing cerebral metabolic demand and contributing to excitotoxicity.[35]

CSDs promote secondary injury through excitotoxicity, increased cerebral oxygen consumption, neuroinflammation, oxidative stress, and impaired cerebral perfusion. Ketamine blocks NMDA receptors thereby reducing the glutamate-mediated excitotoxicity mitigating some of the SBI caused by overstimulation of neurons. Clinical evidence suggests that ketamine inhibits CSDs potentially reducing infarct size and improving recovery.[29] This effect appears dose dependent, with higher doses producing more consistent inhibition of the CSDs appears to be dose dependent with higher doses having more favorable results.[36]

Following TBI, SBI is also mediated by rapid upregulation of proinflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α) in both the brain and peripheral circulation. These cytokines promote blood–brain barrier disruption, leukocyte infiltration, microglial activation, and neuronal death, thereby exacerbating secondary injury and worsening outcomes. Experimental TBI models demonstrate that posttraumatic administration of subanesthetic doses of ketamine significantly reduction TNF-α and IL-6 production and is associated with improved memory and behavioral outcomes.[37]

Autophagy is another pathway implicated in SBI. After TBI, autophagy is rapidly activated in neurons and glial cells in a dysregulated manner, contributing to neuronal death, neuroinflammation, and poorer neurologic outcomes.[38,39] Experimental studies show that posttraumatic administration of subanesthetic doses of ketamine (eg, 10 mg/kg daily for 7 days) downregulates autophagy markers in the injured brain and better memory and behavioral outcomes after TBI. By limiting excessive autophagy, ketamine may further support recovery after TBI.[31,40]

Limitations

The challenges of studying ketamine's overall effect on ICP stem from the dichotomy of needing to study patients in whom ICP monitoring is required in the first place. As such, most studies reporting on the effect of ketamine on ICP are set in patients with neurologic illness whether traumatic or atraumatic. This also causes significant heterogeneity of data within the different articles. Sample sizes are generally small, and there is considerable variability in injury severity, sedation depth, mechanical ventilation strategies, and ICP measurement techniques.

An ideal study would be a randomized controlled double-blind trial with standardized ketamine dosing, uniform sedation depth, preset pCO_2 targets, and consistent ICP monitoring methods. The BIKe trial, a randomized controlled double-blind trial evaluating the effect of ketamine on ICP in severe TBI, is currently in process but has not yet reported results.[41]

Despite these limitations, ketamine is a unique drug due its pharmacokinetic and pharmacodynamic characteristics as compared to opioids and benzodiazepines. It has distinct advantages in preserving hemodynamics, bronchodilation, and neuroprotective

Table 2
Modern evidence on ketamine and intracranial pressure/cerebral perfusion pressure

Study Title	Year	Design/N	Population/Setting	Key Findings	Limitations
The ketamine effect on intracranial pressure in traumatic brain injury: systematic review	2014	Systematic review; 7 studies (∼156 patients)	Adults and pediatric severe TBI, sedated/ventilated	No study showed increase in ICP; several showed reductions in ICP; CPP generally preserved	Small studies; heterogeneous settings; mostly non-RCT; variable protocols
Ketamine as an anesthetic for patients with acute brain injury: a systematic review	2020	Systematic review; 11 studies (334 patients)	TBI and other acute brain injuries under anesthesia/sedation	No evidence ketamine worsens ICP/CPP in ventilated brain-injured patients; mild ICP changes clinically insignificant	Low evidence quality; variable ventilation and CO_2 control; small sample sizes
Ketamine boluses are associated with reduction in intracranial pressure and increase in cerebral perfusion pressure	2022	Retrospective observational; 44 patients	Severe TBI with refractory ICP >20 mm Hg	Median ICP decreased 3.5 mm Hg post-bolus; CPP increased by ∼2 mm Hg	Single center; retrospective; potential confounders; non-randomized
Acute effects of ketamine on intracranial pressure in children with severe traumatic brain injury	2023	Retrospective observational; 33 children, 127 doses	Pediatric severe TBI with ICP/CPP monitoring	In sedation doses, ICP/CPP stable; during ICP crisis boluses, ICP decreased and CPP improved	Retrospective; small pediatric cohort; non-standardized dosing
Clinical outcomes of ketamine in patients with traumatic brain injury: a systematic review	2024	Systematic review; 21 studies (∼886 patients)	Adult and pediatric TBI under anesthesia/sedation	Four studies reported ICP reduction; two showed increases; majority showed no significant change	Mixed populations and study designs; not all studies monitored ICP directly

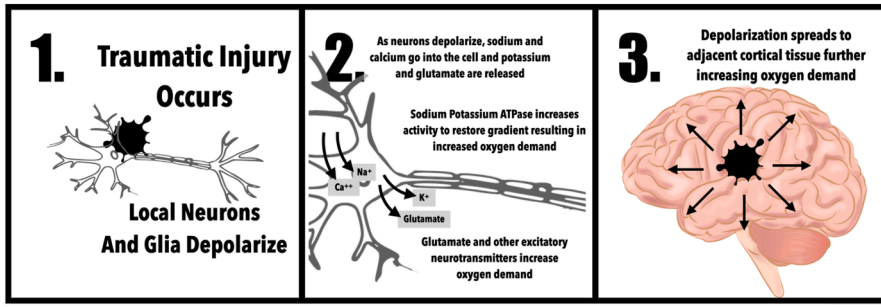

Fig. 1. Cortical spreading depolarization. (*Image Courtesy* This image is the courtesy of Dr Steven T. Haywood; and Brain neuron. Credit: OpenClipart-Vectors via Pixabay, CC0 Public Domain; and Neuron illustration in Figure 1: Sketch of a brain neuron by OpenClipart-Vectors (2018), sourced from Wikimedia Commons [https://commons.wikimedia.org/wiki/File:Sketch_of_a_brain_neuron.png]. It is licensed under the Creative Commons CC0 1.0 Universal Public Domain Dedication, permitting unrestricted use without attribution.)

effects. While the evidence available is limited and does not allow for a higher grade of recommendation, modern studies consistently fail to demonstrate clinically significant increases in ICP associated with ketamine.

SUMMARY

TBI can result in death or severe, permanent neurologic impairment. During acute resuscitation, any intervention or medication with the potential to adversely affect hemodynamics or cerebral perfusion should be used cautiously. Historically, this concern led to the exclusion of ketamine in patients with TBI, as the limited data available at the time suggested that avoidance was safest. However, no high-quality evidence demonstrates that ketamine raises ICP or worsens outcomes in this patient population. In addition, our understanding of TBI, SBI, and ketamine's pharmacologic profile has evolved. The best available evidence indicates that ketamine may preserve or even improve CPP and could offer neuroprotective benefits against SBI. Dispelling the myth that ketamine increases ICP is critical given its favorable hemodynamic profile and potential neuroprotective effects. It is time to abandon outdated assumptions and aversions and interpret the available evidence within its proper clinical context.

CLINICS CARE POINTS

- Ketamine does not seem to cause a clinically significant increase in ICP.
- No major adverse outcomes have been reported in modern literature with Ketamine use in TBI.
- Ketamine's hemodynamic profile and neuroprotective effects make it a very appealing choice for analgosedation in patients with TBI.
- Ketamine can be combined with other sedatives, but large boluses of multiple sedatives should be avoided due to risk of decreased CPP.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors used Generative AI. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

DISCLOSURES

The authors have nothing to disclose.

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