Medical Mythology

Myth: Ketamine should not be used as an induction agent for intubation in patients with head injury

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BACKGROUND

Ketamine has many unique attributes making it well suited to certain applications in the emergency department (ED), including pediatric procedural sedation, and as an induction agent in patients with asthma and exacerbation of chronic obstructive pulmonary disease. However, ketamine has been historically contraindicated for induction use in patients with head injury because of a concern that it may increase intracranial pressure (ICP). The most recent edition of Tintinalli and colleague's *Emergency Medicine*[1] states that ketamine "should be avoided in patients with closed head injuries." There have been 2 more recent review articles on this topic challenging this myth.[2,3]

METHODOLOGY

We used the following indexed search terms in EMBASE and MEDLINE: "ketamine," "brain injuries" or "craniocerebral trauma," "intracranial pressure" or "intracranial hypertension" or "cerebrovascular circulation" or "brain circulation," and "sedation." We used the keywords/phrases "rapid sequence intubation," "rapid sequence induction," "inductive agent" and "neuroprotection." We then reviewed the abstracts and references from all initially identified papers for further relevant studies.

PHARMACOLOGY

Ketamine is a dissociative anesthetic, analgesic, amnestic and anxiolytic.[4] It can be given intravenously (IV), intramuscularly or by mouth. The typical dose of ketamine given for general anesthesia is 2–2.5 mg/kg IV, whereas the commonly used dose for rapid sequence induction (RSI) in the ED is 1–2 mg/kg IV.[5] Ketamine is known to have a stimulatory effect on the sympathetic nervous system with corresponding increases in heart rate, blood pressure and cardiac output, although the exact mechanism has not been fully determined.[4] In addition, ketamine has minimal effects on central respiratory drive, and also acts as a bronchial smooth muscle relaxant.

ORIGINS OF THE MYTH

Six studies from the 1970s are listed in Table 1.[6–11] The data on ketamine from early studies are quite variable in their methods and quality. They are a combination of case reports and small case–control studies. They identified an association between ketamine and increased ICP in patients with abnormal cerebrospinal fluid pathways (such as those caused by aqueductal stenosis, obstructive hydrocephalus and other mass effects). However, in healthy volunteers, ICP stayed within normal range (i.e., < 10 mm Hg) with a corresponding increase in mean arterial pressure (MAP) and calculated cerebral perfusion pressure (CPP).

RECENT STUDIES OF KETAMINE'S EFFECT ON ICP

Several recent studies have examined the use of ketamine as a sedative in the setting of the neurosurgical intensive care unit. Pertinent randomized prospective studies are outlined in Table 2.[12–16] These studies have some methodological limitations including small sample

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sizes and the presence of other sedative agents as potential confounders. Each of these studies examined continuous infusions of ketamine in patients treated with mechanical ventilation, so the generalizability of data from continuous infusion to induction use for RSI has not been determined. No statistically significant increase in ICP was observed following the administration of ketamine in patients with head injury. Some of the studies showed a net *increase* in CPP following ketamine administration.

KETAMINE AND CEREBRAL PHYSIOLOGY IN TRAUMATIC BRAIN INJURY

In cerebral contusions, a central core of contused tissue is surrounded by a penumbra at risk for further ischemic injury.[17–22] Some studies have looked at whether increasing CPP increases the cerebral blood flow and cerebral blood volume in ischemic brain tissue (by a norepinephrine infusion), with conflicting results.[23–25] Although the historical contraindication for ketamine in head injury was based on elevation of ICP, few studies have focused on its effect on *regional* blood flow and perfusion pressures. Ketamine, with its effect on increasing MAP (and thus CPP), may increase the blood flow to ischemic areas where autoregulation is absent, but the effect of increasing CPP in ischemic brain penumbra remains controversial.

POSTULATED NEUROPROTECTIVE CHARACTERISTICS OF KETAMINE

Some studies have supported the idea that ketamine is "neuroprotective."[3] Ketamine, an *N*-methyl-D-aspartate antagonist, decreases the release of glutamate, which is neurotoxic. This evidence is based on in vitro and animal studies.[26–28] However, very few studies have examined long-term outcomes in humans.

Two small randomized controlled trials looked at 6-month outcomes after ketamine, fentanyl or sufentanil for sedation in neurosurgical intensive care units.[13,29] They both report no differences in neurologic outcomes (Glasgow Outcome Scale in one study, and death, vegetative survival, or severe or moderate disability in the other) at 6 months. However, both studies were underpowered to detect such differences for or against ketamine.

Another randomized controlled trial (120 patients) looked at ketamine for bypass surgery and possible neuroprotective effects. There was no difference in neuropsychological testing between groups at 10 weeks, except in 1 test, which was ascribed to chance.[30]

COMPARISON TO OTHER INDUCTIVE AGENTS

Ketamine may be of value as an inductive and sedative agent in patients with hemodynamic instability, since

Table 1. Summary of 1970s studies on ketamine and intracranial pressure

Study	Study type	Ketamine dosage	Study population	ICP	MAP	Calculated CPP
Garner et al.[6]	Case–control	2 mg/kg IV	11 healthy males for simple surgery	CSFP ↑ by mean 18 mm Hg	↑ by mean 28 mm Hg	↑
Wyte et al.[7]	Case report	2 mg/kg (route unknown)	2 patients (aged 8 and 17 yr) with VP shunts, obstructive hydrocephalus (secondary to aqueductal stenosis and astrocytoma)	ICP ↑ to 75 mm Hg in only 1 patient; no change in other patient	—	—
Gibbs[8]	Case–control	1–1.3 mg/kg IV	11 healthy patients for lumbar discectomy; second group of 9 patients with intracranial space occupying lesions	No change in CSFP in healthy patients; in group 2, CSFP ↑ by ~ 12 mm Hg in 6/9	↑ by 24 mm Hg	↑
Gardner et al.[9]	Case report	2 mg/kg IV	13-year-old boy with glioma, midline shift	CSFP ↑ by ~ 8 mm Hg	↑ by ~ 16 mm Hg	↑
Shapiro et al.[10]	Case–control	2 mg/kg IV or 4 mg/kg IM	7 patients (5 with external shunts and ↑ ICP)	No change in patients without shunts; ICP ↑ up to 60 mm Hg in certain patients	↑ up to 22 mm Hg	Variable
List et al.[11]	Case–control	2 mg/kg IV	7 patients with hydrocephalus	1 patient had ↑ CSFP to ~ 25 mm Hg; others had mild ↑ CSFP within normal range	—	—

CPP = cerebral perfusion pressure; CSFP = cerebrospinal fluid pathways; ICP = intracranial pressure; IM = intramuscularly; IV = intravenously; MAP = mean arterial pressure; VP = ventriculoperitoneal.

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other inductive agents such as propofol can cause hypotension.[31] Hypotension has been shown to predict increased mortality and worsen secondary brain injury.[32] Etomidate is a common induction agent in patients with hemodynamic instability. However, etomidate is often not available in smaller EDs across the country. In addition, recent concerns have been expressed about etomidate and adrenal suppression, particularly in septic patients.[33–36]

CONCLUSION

Based on its pharmacological properties, ketamine appears to be the perfect agent for the induction of head-injured patients for intubation. The evidence for neuroprotection in humans remains inconclusive at this time. However, more recent prospective data examining ketamine usage as a sedative agent in patients treated with mechanical ventilation suggests that there is no association with increased ICP in head injury.

Despite limited evidence specific to its use as an induction agent, we feel that additional consideration must be paid to the possible usage of ketamine for RSI in patients with head injury, especially when alternative agents that do not cause hypotension are unavailable.

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Table 2. Key studies of prospective trials of ketamine and intracranial pressure

Study	Study type	Study population	ICP	CPP
Mayberg et al.[12]	Prospective trial	• 20 neurosurgical patients (10 with supratentorial tumours, the rest with intracranial aneurysms) • ICP measured before and after administration of ketamine 1 mg/kg IV	Small but statistically significant decrease in ICP after ketamine administration	No significant change over 10 min
Kolenda et al.[13]	Prospective RCT	• 35 patients with moderate or severe head injury • Ketamine + midazolam sedation v. fentanyl + midazolam sedation	Slightly higher ICP values in the ketamine group (~ 2 mm Hg difference)	Higher in the ketamine group than the control group by average of 8 mm Hg
Bourgoin et al.[14]	Prospective double-blind RCT	• 25 patients with severe head injury • Continuous infusion ketamine-midazolam v. sufentanil-midazolam infusion	No significant difference between groups	No significant difference between groups
Bourgoin et al.[15]	Prospective double-blind RCT	• 30 patients with TBI receiving sufentanil-midazolam or ketamine-midazolam using target controlled infusion	No significant difference between groups	No significant difference between groups
Schmittner et al.[16]	Randomized prospective trial	• 24 patients with TBI • Group 1: methohexitone + ketamine sedation • Group 2: methohexitone + fentanyl sedation	No significant difference between groups	No significant difference between groups

CPP = cerebral perfusion pressure; ICP = intracranial pressure; IV = intravenously; RCT = randomized controlled trial; TBI = traumatic brain injury.

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