



Ketamine for rapid sequence induction in patients with head injury in the emergency department

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Abstract

- Objective:** To examine the evidence regarding the use of ketamine for induction of anaesthesia in patients with head injury in the ED.
- Method:** A literature review using the key words ketamine, head injury and intracranial pressure.
- Results:** Advice from early literature guiding against the use of ketamine in head injury has been met with widespread acceptance, as reflected by current practice. That evidence is conflicting and inconclusive in regards to the safety of using ketamine in head injury. A review of the literature to date suggests that ketamine could be a safe and useful addition to our available treatment modalities. The key to this argument rests on specific pharmacological properties of ketamine, and their effects on the cerebral haemodynamics and cellular physiology of brain tissue that has been exposed to traumatic injury.
- Conclusion:** In the modern acute management of head-injured patients, ketamine might be a suitable agent for induction of anaesthesia, particularly in those patients with potential cardiovascular instability.
- Key words:** *head injury, intracranial pressure, ketamine.*

Introduction

The phencyclidine-derivative ketamine was synthesized in 1962 and first used in humans in 1965. The racemic mixture was released for clinical use in 1970.^{1,2} The S(+) isomer has about twice the anaesthetic potency of the racemic mixture^{1,3,4} and fewer side effects.¹ Green and Krauss⁵ described ketamine's clini-

cal effects as provision of 'dissociative sedation', where profound analgesia, sedation and amnesia are accompanied by retention of protective airway reflexes, spontaneous respirations and cardiopulmonary stability.

Ketamine has been widely used for many years, in settings where limited anaesthesia capacity exists. It has been shown to be safe and effective for paediatric procedural sedation in the ED.^{6–11} As an agent for

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induction of anaesthesia ketamine has many desirable attributes.^{1,2,10} Although it might have a mild direct depressant effect on the myocardium, central stimulation of the sympathetic nervous system causes induction doses of ketamine, between 0.5 and 2 mg/kg i.v., to produce an increase in heart rate, blood pressure (BP) and cardiac output. This is of value in patients with haemodynamic instability, especially as a result of hypovolaemia.^{1,12} Intravenous induction agents such as thiopentone, propofol and fentanyl are frequently used to reduce the systemic response to intubation, but tend to cause hypotension in hypovolaemic patients,¹³ which is particularly undesirable in patients with head injury.

Among a number of listed contraindications to ketamine use, a ketamine-associated rise in intracranial pressure (ICP) has led to recommendations against its use in head injury.^{1,13} The elevation in ICP, however, appears to be accompanied by an improvement in cerebral perfusion. A rise in mean arterial pressure (MAP) is accompanied by cerebral vasodilation at lower doses,¹⁴ with a further contribution from hypercarbia at higher doses.¹⁵ This most benefits areas that have reduced cerebral blood flow (CBF), close to ischaemic thresholds, as occurs in head injury. In addition, ketamine can offer protection from cellular mechanisms of neuronal death, mainly through antagonism of the N-methyl-D-aspartate (NMDA) receptor,¹⁶ to injured brain tissue that is particularly vulnerable to ischaemic insults. The other listed contraindications to ketamine use are open eye injury, ischaemic heart disease, vascular aneurysms and psychiatric disease.¹

This paper presents some important principles in the management of head injury, followed by an examination of the evidence regarding the use of ketamine as an induction agent for intubation of patients with head injury.

Method

Medline (1966 to March 2005) was searched using the strategy [exp Ketamine] AND [exp Craniocerebral Trauma] AND [exp Intracranial Pressure OR exp Cerebrovascular Circulation OR exp Intracranial Hypertension]. For each search term all subheadings were accepted. EmBase (1974 to March 2005) was searched using the strategy [exp Ketamine] AND [exp Intracranial Pressure OR exp Intracranial Hypertension]. A similar search strategy was used for Cochrane and PsycINFO. A total of 173 articles were initially

identified. One major anaesthetic textbook and Micromedex were also scanned. Bibliographies were manually searched, and selected references studied. Articles were rejected if they did not contribute to questions regarding the effects and safety of ketamine as an induction agent in the early stages of head injury management. There were no randomized controlled trials (RCT) specifically addressing this issue. The total number of articles used in this review was 66. The majority of relevant studies were prospective case series, case control studies and some case reports. Six of the articles included were in German text. Five of these full texts were translated separately by two native German speakers of which one is a doctor and co-author of this article.

Principles of head injury management

Principles of head injury management include optimization of haemodynamic and other parameters that impact on the brain's recovery,¹⁷ provision of appropriate analgesia and sedation,^{13,18} strategies to protect against secondary ischaemic injury, an understanding of cerebral circulatory pathophysiology, and surgical management of significant mass lesions.

Secondary ischaemic insults in head injury

Primary brain injury is the cerebral injury caused directly by the traumatic insult. Secondary brain injury is further injury resulting from additional brain insults that occur following primary injury. This can add to primary damage, impair neuronal healing,¹⁹ markedly influence outcome, and can be minimized by optimal therapy.²⁰ Major causes of secondary brain injury can be divided into two categories: poor cerebral perfusion and hypoxaemia. Cerebral perfusion pressure (CPP) represents the BP gradient across the brain's vascular bed, and can influence CBF. CPP is defined as MAP – ICP. Reduction in CPP can be caused by reduced systemic BP, raised ICP, or a combination of both.²¹ Hypoxaemia and ischaemia promote the formation of lactate which is a potent vasodilator and which acts to increase cerebral blood volume (CBV). This might raise ICP further.²² Intracranial hypertension occurs commonly in severe head injury, even after evacuation of an intracranial mass. A significant rise in ICP can cause distortion and compression of the brainstem²¹ and is associated with increased morbidity and mortality. This association supports the use of ICP monitoring in management protocols.²³

Studies of patients with head injury have identified the link between outcomes and the occurrence of hypotension and hypoxia. The confounding variables of age and severity of multiple trauma were controlled for in a study of 717 patients with severe head injury (GCS \leq 8).²⁴ In this study the major determinant of overall increased morbidity and mortality was systemic hypotension whereas hypoxia was the next most significant factor.

In a large retrospective review of deaths in major trauma victims in the USA there were no patients dying of operable mass lesions.²⁵ However, 48.1% of all deaths were caused by central nervous system (CNS) injury, and 66% of those patients who died of a CNS injury had autopsy evidence of secondary brain injury, because of either cerebral ischaemia or hypoxia.

In patients with severe head injury undergoing surgery, the occurrence of an episode of intraoperative hypotension was found to be associated with a significantly increased mortality.²⁶ Increasing duration of intraoperative hypotension was significantly associated with worse outcome.

Pathophysiology of the cerebral circulation²⁷

The main purpose of cerebral circulation is to provide sufficient oxygen and glucose to the brain. Early endotracheal intubation and support of ventilation helps to reduce the risk of hypoxaemia. Oxygen transport is then often the limiting factor determining oxygen supply. In moderate to severe head injury an inadequate CBF can contribute to irreversible ischaemic cell damage.²⁰ Patient outcome after severe head injury can be improved by a systematic approach to the control of raised ICP and the maintenance of adequate CPP.²⁸ Ideally, CPP should be titrated to adequacy of CBF in each individual patient. An increase in cerebral vessel diameter will increase the CBV (normally 3.5 mL/100 g of brain tissue in healthy people). However, CBF and CBV are not directly coupled.²⁷ A rise in CBF can potentially cause reflex arteriolar vasoconstriction, so reducing CBV and ICP.²⁰

Cerebral autoregulation refers to blood flow regulation through alterations in arteriolar muscle tone under a wide variety of situations to maintain a balance between CBF and cerebral metabolism.²⁰ This is believed to occur via metabolic mediators, intrinsic myogenic reactivity to pressure changes, and less importantly, regional neuronal reflexes.²⁷ Cerebral metabolism is often represented as the cerebral metabolic rate (CMR) for a particular metabolite. The CMR

for oxygen (CMRO₂), for example, is a function of both the arterio-venous difference in concentration of O₂, and of the CBF. A tight coupling between CBF and cerebral metabolism is necessary for normal neuronal function. A 50% reduction of CBF (to approximately 23 mL/100 g/min) can be compensated by the brain increasing O₂ extraction from the blood. Neuronal dysfunction occurs below this level. The infarction threshold of CBF is defined as 18 mL/100 g/min. This can be lowered by iatrogenic suppression of synaptic function (e.g. using barbiturates). In normal humans CBF remains constant at approximately 55 mL/100 g/min within an MAP range of 60–150 mmHg.

Studies of paediatric head injury populations have reported the ability to maintain CPP at a minimum of 50 mmHg to be an important predictor of survival,²⁹ and a low mean CPP (<40 mmHg) to be lethal.³⁰ CBF-targeted therapy, developed by Rosner *et al.*,³¹ recommends maintenance of high CPPs. This approach is widely adopted, including in Australasian practice, and has continued to be recommended in the American Brain Trauma Foundation's Guidelines of 2000.²³

Following head injury there is an early (initial 12–24 h), global reduction in CBF.³² CBF in an area of contusion is lower than that of adjacent (pericontusional) parenchyma, which in turn is lower than that of the surrounding (normal) brain parenchyma.³³ Pericontusional CBF tends to be above the infarction threshold. An increase in regional CBF, such as arising from an increase in CPP, can protect pericontusional tissue against ischaemic damage.³⁴ Increasing CPP in this situation appears to produce no change in relative response of pericontusional oedema compared with non-oedematous tissue.³⁴

Autoregulation is frequently preserved to some extent in head-injured patients, though pressure regulation is lost at lower levels of CPP,²⁰ making the brain even more susceptible to injury from systemic hypotension. Reactivity of CBF to variations in CO₂ occurs passively, independent of other variables. Following head injury, pericontusional CO₂ vasoresponsivity might be significantly enhanced, producing a high ischaemic risk for this tissue from excessive hyperventilation.³⁵

The case against ketamine usage in head injury

Recommendations against the use of ketamine in patients with head injury appear to have been derived mainly from the following three studies in this literature

review, dating back to 1972. In these early human studies the changes in ICP were measured as changes in cerebrospinal fluid (CSF) pressure at the lumbar spine^{36,37} and intracranial lateral ventricle^{38–40} levels, and deduced from changes in CBF.¹⁴

Gardner *et al.*³⁸ studied two patients requiring diagnostic pneumoventriculograms. Both patients received a single ketamine dose of 2 mg/kg i.v. and were allowed to breathe spontaneously. The patient with obstructed CSF pathways from a thalamic glioma exhibited rapid rise in CSF pressure from a baseline of 31.5 mmHg (quoted as 42 cm water) to a peak of 84.4 mmHg. The other patient, with normal CSF pathways, showed a CSF pressure rise from 3.2 to 13.7 mmHg. Both patients showed a concomitant rise in BP, pulse and respiratory rate. CPP dropped in the patient with glioma by 32.6 mmHg (to 12.6 mmHg), 2 min following ketamine, and increased by 3.6 mmHg (to 93.7 mmHg) in the patient with normal CSF pathways.

Shapiro *et al.*³⁹ studied seven patients with CSF shunts, given 2 mg/kg i.v. ketamine, or 4 mg/kg i.m. The two patients with normal CSF pathways, and no clinical evidence of raised ICP initially, demonstrated only a small rise in ICP, which remained below its normal limit of 10 mmHg. The CPP showed a rise of 14 to 121 mmHg in one of these patients, and a fall of 5 mmHg, to 83 mmHg, in the other. The remaining five patients with abnormal CSF flow dynamics all exhibited augmented ICP responses to ketamine, and a significant drop in CPP. Other studies^{37,40} have reported a similar, clear difference in response to ketamine between patients with normal and abnormal CSF pathways. This effect is also seen using certain volatile anaesthetic agents.⁴¹

Takeshita *et al.*¹⁴ administered a total ketamine dose of 3 mg/kg i.v. to healthy patients breathing spontaneously. This led to increased CBF and a reduction in cerebral vascular resistance, suggesting a mechanism of cerebral vasodilatation. The rise in CBF was described by the article as being potentially harmful by possibly causing raised ICP. CPP, calculated here as MAP – JVP, rose by 14 mmHg from a baseline of 88 mmHg. Indices of cerebral metabolism did not change significantly. PaCO₂ increased only slightly, indicating a direct cerebral vasodilating potency of ketamine.⁴²

Based on detailed analysis of these studies, including the calculation of CPP from the published data, it can be demonstrated that ketamine generally improves cerebral perfusion. Ketamine was shown to raise ICP deleteriously, and without an accompanying

maintenance of CPP, only in those patients with obstructed CSF pathways.

The case for ketamine usage in head injury

Relevant human studies

Ketamine is a frequent choice of anaesthetic agent in settings where levels of monitoring facility, and suitably trained medical staff, are relatively low, such as in developing world hospitals, military field hospitals and prehospital trauma situations. Its ease of administration, and overall protection against cardiorespiratory depression^{43,44} make it relatively safe. Complication rates are reported as low.⁴⁵ Procedures using ketamine can be performed either with or without controlled ventilation.^{44,46}

Sub-anaesthetic doses of ketamine were found to produce only a small increase in regional CBF in healthy volunteers.⁴⁷ There was no change in regional CMRO₂. However, ketamine is known to induce regional neuro-excitation, which leads to stimulation of regional glucose consumption.^{48,49} As MAP is elevated by ketamine, only a slight additional vasodilation is required for sufficient increase in CBF to support increased glucose requirements. Ketamine at sub-anaesthetic doses did not produce hypercarbia, in keeping with other studies that used low doses of 2 mg/kg i.v. or 4 mg/kg i.m.^{36,38,39}

A clinical prospective trial by Gofrit *et al.*⁵⁰ reported no early complications attributable to ketamine from its use to aid prehospital intubation in trauma patients even where head injury was the primary site of injury. Use of ketamine in titrated doses to aid extrication of entrapped prehospital road trauma victims was reported by Cottingham and Thomson.⁵¹ One of their four cases was a confused, combative patient with clinical signs of a basal skull fracture. A total of three 25 mg boluses of i.v. ketamine helped with his extrication, and he made a full recovery. Although interesting these two reports provide no substantial evidence to support ketamine's safety in terms of haemodynamic parameters and long-term outcome.

The following three studies provide stronger evidence, looking at ICP and CPP. Even though the last two of these were RCT the patients were mechanically ventilated prior to the study, and ketamine was used as an infusion. Their results are therefore only indirectly relevant to the question of ketamine's suitability as an

induction agent in head injury, and although promising their findings must be interpreted with caution.

A study in eight propofol-sedated, ventilated patients with traumatic brain injury showed ketamine to produce a significant decrease in ICP at doses of 1.5, 3 and 5 mg/kg, with no change in CPP.⁵² Patients undergoing gas anaesthesia have demonstrated a slight decrease in ICP, with no change in MAP or CPP, in response to ketamine.⁵³

Bourgoin *et al.*⁵⁴ compared ketamine/midazolam with sufentanyl/midazolam infusion for sedation in patients with severe head injury. They found no significant differences between the two groups in the mean daily ICP or CPP. There was a trend for lower use of vasopressors, in the ketamine group.

Similarly, Kolenda *et al.*⁵⁵ compared ketamine/midazolam with fentanyl/midazolam in patients with moderate to severe head injury. There was a lower requirement for catecholamines and higher CPP in the ketamine group, and only a slightly higher ICP, with no difference in outcome at 6 months between the two groups.

Relevant animal studies

Klose *et al.*⁵⁶ created a haemodynamic animal model of systemic blood loss and a traumatic intracranial space-occupying haemorrhage. They inflated a foley catheter in the extradural space of 12 normocapnic ventilated dogs, then induced hypovolaemia. This caused a marked drop in CPP. An i.v. ketamine dose of 0.5 mg/kg given prior to fluid resuscitation, and a 1 mg/kg dose given after restoration of blood volume, were demonstrated to produce an overall increase in CPP, and a smaller rise in ICP. The study results suggest that in a patient with head injury and associated hypovolaemia, administration of an i.v. ketamine dose of 0.5–1 mg/kg can produce beneficial changes in CPP without causing a disproportionate rise in ICP.

Schwedler *et al.*¹⁵ administered a 5 mg/kg dose of i.v. ketamine to goats with intact autoregulation. Spontaneously breathing goats were compared with ones that were mechanically ventilated. Their findings suggest that CBF rises with this dose, resulting from a combination of increase in MAP, and hypercarbia from a degree of respiratory depression.

Studies in rats, of incomplete cerebral ischaemia, have attempted to evaluate outcome using neurological outcome scores over 3 days, and by changes in neurohistopathology after the 3 day neurological evaluation period.^{57,58} These studies used continuous i.v. infusions

of ketamine and are therefore not directly relevant to the question of ketamine's potential as an induction agent. They nevertheless showed improved neurological outcome with ketamine, which might have been related to suppression of plasma catecholamines.

Studies performed mainly in rodent animal models have demonstrated neuroprotective effects of ketamine by examining its effects on physiological parameters. Under conditions of normo-thermic cerebral ischaemia there is an increase in the extracellular concentration of excitatory amino acids, mainly glutamate.^{16,59} This promotes activation of the NMDA receptor complex, which in turn leads to accumulation of intracellular calcium, and hence a stimulation of cell-destroying enzyme systems such as phospholipases, proteases and endonucleases. Phospholipid metabolism generates destructive free radicals. In cell cultures, ketamine blocks the phenylcyclidine receptor located in the NMDA receptor channel, so halting the degradational chain reaction.¹⁶

Shapira *et al.*⁶⁰ investigated the effect of ketamine on calcium and magnesium content of brain tissue following closed head injury in rats. Administration of 180 mg/kg intraperitoneal ketamine, at 1 or 2 h after injury, was found to reduce the accumulation of brain tissue calcium at 48 h. In addition, ketamine reduced the depletion in brain tissue magnesium which also tends to follow head injury, and can be associated with a reduction in cognitive function.⁶¹ Early administration appears to be important for these protective effects.⁶²

Discussion

Ketamine is the most widely used anaesthetic in the world for its safety and low cost.¹⁰ Early studies demonstrating a significant elevation in ICP from ketamine were performed on patients with non-traumatic intracranial lesions, and often with CSF outflow obstruction. Space occupying lesions (SOLs) from acute head injury effect cerebral haemodynamics differently to those developing gradually, and the results of such earlier studies are of very limited applicability to the emergency management of head injury with its focus on reducing secondary brain injury. Compensatory mechanisms of CSF,⁶³ venous blood and even brain tissue redistribution are intact in the acute situation. Therefore, increases in CBV, such as following volatile anaesthetic agents²³ and ketamine, can occur without causing a large increase in ICP. A rise in ICP from use of ketamine is accompanied by rises in systemic BP, CPP and CBF. Vasoresponsivity to CO₂ is preserved during

ketamine anaesthesia so that, at higher doses, a dose-dependent respiratory depression in spontaneously breathing subjects can contribute to cerebral vasodilatation and increased CBF.¹⁵ Most ketamine studies have shown no increase in CMRO₂.⁶⁴

In the setting of a patient with multiple trauma and head injury an early requirement for fluid resuscitation accompanies the need for rapid control of their airway. An important role of the Emergency care provider managing such a patient is to ensure that minimal secondary brain insults arise during the resuscitation and stabilization phases of the patient's care. The patient might be irritable, combative, in pain, and consequently prone to a high level of systemic sympathetic response, and to an increase in ICP. Thiopentone, propofol or fentanyl might lead to hypotension during induction, particularly in hypovolaemic patients, which might worsen outcome. Klose's experimental animal model of hypovolaemia and raised ICP shows low-dose ketamine to produce a rise in CPP in this situation rather than a fall, in association with a small change in ICP.⁵⁶ In addition, ketamine can offer cellular neuroprotection to the injured brain. There is also evidence that continuing ketamine for sedation in the Intensive Care Unit (ICU) in these patients has other advantages that include maintenance of haemodynamic stability and CPP, absence of withdrawal, and improved tolerance of enteral nutrition.⁵⁴

Adjunctive agents are already used alongside ketamine anaesthesia and include anticholinergics to minimize airway hypersecretion in children,⁸ and benzodiazepines to minimize psychic emergence phenomena in adults.^{43,65-67} The possibility of causing an excessive rise in ICP in patients with traumatic SOLs can be minimized without detriment to CPP by judicious addition of agents such as midazolam,^{54,55} and thiopentone.^{39,40}

This review of available literature finds that the current recommendations against ketamine's use in head injury are based on a small number of studies which do not involve patients undergoing emergency management of head injury. In contrast, there is sufficient data regarding its safety in patients with head injury to support further study in this area.

An RCT of ketamine use as an induction agent in head injury and its effects on CPP, ICP and neurological outcome compared with other induction agents (e.g. thiopentone, propofol and fentanyl) is required. Such a trial needs to be multicentre and will require ED, ICU and neurosurgical staff to adopt a standard head injury management protocol. Monitoring of ICP would not be

practical in the ED environment, so suitable surrogate markers will need to be carefully evaluated and validated.

Conclusion

Our current practice of avoiding ketamine use in rapid sequence induction and intubation of head-injured patients is not evidence based. We recommend that a formal trial is conducted, and we believe that the addition of ketamine to our therapeutic armamentarium for patients with head injury might help us to improve their neurological recovery, particularly in those presenting with multiple trauma and cardiovascular instability.

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Competing interests

None declared.

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