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Ketamine in Modern Neuroanesthesia Practice

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Abstract

Purpose of Review Ketamine has a number of clinical uses and properties that suggest a role for the drug in neuroanestheisa practice. "Dogma" and "myths" persist with regard to its effects on cerebral hemodynamics and intracranial pressure which have limited its use in Neuroanesthesia and care of the critically ill brain-injured patient. This review aims to educate the clinician on the possible role of ketamine in modern neuroanesthesia practice.

Recent Findings A number of systemic reviews support the use of ketamine in patients with acute brain injury and raised intracranial pressure (ICP). Pre-clinical work suggests that ketamine may have mechanisms of action compatible with neuroprotection including modifying glutamate excitatory-driven mechanisms of brain injury. There is emerging clinical evidence to suggest that ketamine may inhibit spreading depolarizations (SDs), a cortical electrical phenomenon associated with brain injury.

Summary Ketamine is no longer contraindicated in the care of the brain-injured patient, and its properties of potent analgesia, dissociative anesthesia, and minimal effects on both the hemodynamic and respiratory system are being utilized in the pre-hospital and emergency room setting. Good grade data on meaningful clinical outcomes is presently lacking to support the use of ketamine as a drug with neuroprotection properties but is an area of ongoing interest.

Keywords Ketamine; Cerebral blood flow · Intracranial pressure · Acute brain injury · Traumatic brain injury · Subarachnoid hemorrhage · Neuroprotection · Spreading depolarization · Epilepsy · Electoconvulsive therapy · Analgesia · Depression · Pre-hospital care

Introduction

Ketamine has been used in clinical practice for more than 50 years now. It is well known as a "dissociative anesthetic" [1] with sympathomimetic actions, making it a useful induction drug for the hemodynamically unstable agent [2]. It has also been used extensively in the pre-hospital and emergency room setting for procedural sedation due to its profound analgesic properties combined with minimal effects on respiratory drive and airway tone [3•, 4]. However, the general usefulness of ketamine as an anesthetic agent has been limited by the widely reported emergence phenomenon ranging from minor psychic reactions to vivid visual and auditory hallucinations [1, 2]. Its usefulness as a neuroanesthetic agent was pretty much abandoned for at least 20 years due to a number of case series reports of large increases in intracranial pressure after the administration of ketamine to patients [2, 3•]. With the discovery that one of the mechanisms of action of ketamine was to inhibit the action of glutamate at the N-methyl-D-aspartate (NMDA) receptor [5] and subsequent pre-clinical data suggesting a role for ketamine as a neuroprotection agent [6–8•], there has been mounting interest in the clinical use of ketamine in the brain-injured patient [9••, 10•]. This article will review the evidence for the safe use of ketamine in the brain-injured patient and when to consider the use of ketamine in modern neuroanesthetic practice.

This article is part of the Topical Collection on *Neuroanesthesia*

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The Effects of Ketamine on the Cerebral Circulation, Intracranial Pressure and Metabolism, and "Myth Debunking…"

The effect of ketamine to increase cerebral blood flow (CBF) has been known since the early 1970s. Takeshita et al. studied

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the effect of a total 3mg/kg bolus dose of ketamine on CBF using the Kety Schmidt method [11]. Cerebral perfusion pressure (CPP) increased from 88 to 102 mmHg, and CBF was calculated to increase from 47 to 76 ml/100 g/min with a corresponding decrease in cerebral vascular resistance (CVR) from 1.91 to 1.38 mm Hg/ml/100 g/min. Indices of cerebral metabolism did not significantly change after ketamine, and it was concluded that a decrease in CVR was the main determinant of the increase in CBF. More recently, Långsjö et al. largely confirmed the earlier findings of Takeshita et al. using positron emission tomography with some small regional variations of increased cerebral metabolic rate (CMR) in the thalamus and the anterior cingulate gyrus but globally no net change [12]. They also measured that cerebral blood volume (CBV) was increased by 51.9% at an anesthetic dose of ketamine. A recent systemic review of the animal and human literature investigating the cerebrovascular response to ketamine concluded that human studies display an Oxford 2b, grade C level of evidence to support a trend to increased global CBF with ketamine administration in both healthy volunteers and elective surgical patients [13].

Coinciding with the introduction of ketamine into clinical practice in the late 1960s to early 1970s, there were a number of case report series published associating the use of ketamine with elevated ICP, and these have been summarized succinctly in an editorial by Green et al. [3•]. In one of those case report series, ketamine anesthesia was associated with an abrupt increase in ICP ranging from 25 to 82 mm Hg on nine occasions in five patients who either had abnormal cerebrospinal fluid flow or some other intracranial pathology [14]. It was noted by Green et al. that anesthesiologists quickly abandoned using ketamine in patients with neurological disorders, and many textbooks and review articles considered the use of ketamine in the setting of possibly increased ICP to be contraindicated [3•]. What was possibly overlooked at this time (1972) was the lessor cited study by Takeshita's group [15]. Eight healthy patients were anesthetized with a total of 3 mg/kg of ketamine, and cerebrospinal fluid pressure (CSFP) was measured from a lumbar catheter placed prior to elective surgeries. In four patients, normocarbia was maintained with assisted ventilation, and in the other 4 patients, ventilation was controlled, and mild hypocarbia to a $PaCO_2$ of 30 mm Hg was induced. In the normocarbic group, ketamine produced a 150% increase in both CBF and CSFP which returned to 110% of normal over 15 min. In the mildly hypocarbic group, the maximal increase in CBF and CSFP returned to normal 2 min following the initiation of hyperventilation and reduction of $PaCO_2$ to 30 mm Hg. The authors concluded that the cerebral vasculature remained responsive to $PaCO_2$ during ketamine anesthesia, and the undesirable effects of ketamine on CSFP could be minimized by the induction of modest levels of hypocarbia [15].

The aforementioned editorial by Green et al. [3•] was written in response to two systemic reviews of a total of 15 controlled trials, ten with the use of controlled ventilation and five regardless of ventilation in adults sedated with ketamine without adverse measures of cerebral perfusion or increased ICP nor adverse clinical outcomes attributable to the use of ketamine published in the emergency medicine literature [16, 17]. They were critical of the 1970s anesthesiologists who overlooked that the largest increases in ICP occurred in those with hydrocephalus (and often without controlled ventilation, my edit), and although ICP increased, CPP was maintained. They lament how ketamine anesthesia has revolutionized emergency department pediatric procedural sedation and how the adoption of "dogma" despite incomplete evidence may have deprived patients' effective treatment options [3•].

Ketamine for Neuroprotection in Acute Neurological Injury

There is emerging pre-clinical data suggesting a role for ketamine providing neuroprotection in acute neurological injury [6–8•]. This has spurred interest in "an old drug for new uses" [10], and a number of systemic reviews in the neurocritical care and anesthesia literature have also reported on the effects of ketamine on cerebral hemodynamics and ICP in adult and pediatric patients with acute brain injury [7, 9••, 18, 19]. The general conclusions are that ketamine can be used in this setting in combination with controlled ventilation and often with other sedative agents without increases in ICP and with a favorable effect on systemic hemodynamics and maintained CPP.

As early as 2005, it was suggested that we shift our thinking about neuroprotection by anesthetic agents from suppression of metabolism to inhibition of excitoxicity, a profound state of deregulation of neuronal calcium homeostasis that occurs as a result of excessive glutamate binding to postsynaptic NMDA receptors [6]. Glutamate spillage occurs in brain injury due to ischemia, and ketamine is a glutamate modulator exerting its effect through competitive blockade of both pre- and post-synaptic NMDA receptors [8•]. Other mechanisms that have been proposed for ketamine affording neuroprotection include inhibition of apoptosis and cell death and anti-inflammatory effects through predominately inhibition of pro-inflammatory mediators secreted by CNS glial cells and microglial [8•]. Microthombosis due to platelet aggregates is another deleterious process that occurs in both traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) disrupting oxygen and glucose delivery to neurons via the microvasculature. This may be another glutamate-driven process that is mitigated by ketamine [8•].

Clinical Evidence for Neuroprotection

There is presently not clinical outcome data to support the use of ketamine for neuroprotection. However, there is emerging data that does support the hypothesis that ketamine may protect the brain. SDs are an EEG phenomenon that occur after brain injury and represent near-complete breakdown of neuronal transmembrane ion gradients and have been associated with poor neurological outcomes in patients with TBI [9••]. They occur in relation to local ischemia and also after ischemia due to a lack of energy supply to the tissues. Carlson et al. recorded electrocorticography recordings from electrode strips placed at craniotomy in eight patients with SAH and two patients with TBI [20]. All ten patients were sedated with alternating ketamine or other sedative agent for periods of 6 h. A strong dose-dependent effect (O.R. > 13) with hours off ketamine or ketamine < 1.15 mg/kg/h was associated with an increased risk of SDs. They concluded that ketamine effectively inhibits SDs over a wide range of doses commonly used for sedation in neurocritical care. A recent systemic review of twenty studies showed that ketamine effectively blocks SDs in rats, swine, and humans in the setting of a number of conditions including migraine with aura, TBI, SAH, and hemorrhagic and ischemic stroke. It was concluded that more randomized controlled trials are needed to determine whether interrupting the ketamine-blockable SDs effectively leads to an improvement in outcome [21]. Ketamine use in other hyper excitable neuronal states such as refractory status epilepsy (RSE) has also been investigated. A systemic review analyzing 23 studies and 110 patients identified a 56.5% response rate of RSE to ketamine with duration of treatment lasting from days to weeks [22]. In a single-center retrospective study of 68 consecutive patients with super-refractory status epilepticus treated with ketamine, there was class IV evidence that ketamine decreased seizures in this group [23].

Ketamine's antineuroinflammatory effects have led to one group being interested in the potential of ketamine to mitigate delirium in patients undergoing cardiopulmonary bypass. In a small study, Hudetz et al. with 29 patients in each group gave ketamine 0.5 mg/kg on induction prior to cardiac surgery with cardiopulmonary bypass [24]. The incidence of delirium was found to be 31% in the control (placebo) group and only 3% in the ketamine group (O.R. 12.6). In another small study, 32 geriatric patients received 0.3 mg/kg of ketamine prior to undergoing eye surgery under retrobulbar block [25]. Cognitive performance was measured with an abbreviated version of the Short Portable Mental Status Questionnaire (SPMSQ). Two hours after surgery, an increased number of patients in the ketamine group performed within the normal range on the SPMSQ (n = 28, 84.4%; P = 0.03), whereas the percentage of patients in the control (placebo) group with a normal cognitive performance remained almost unchanged (n = 24, 75%; P = 0.62). Ketamine produced no increase in intraocular pressure, and analgesic behavior was better in the ketamine group. Avidan et al. reported the results of the Prevention of Delirium and Complications Associated with Surgical Treatments Trial (PODCAST) [26••]. This was a prospective multi-centered randomized control trial. Prior to either cardiac or non-cardiac surgery, 222 patients received placebo, 227 received 0.5mg/kg, and 223 received 1.0 mg/kg ketamine after induction of anesthesia and before surgical incision. There was no difference in delirium found between the control and ketamine groups (19.4 vs 19.8%). More hallucinations were experienced by the patients who received ketamine. This study recruited a large number of patients and was designed to answer the question as to whether or not ketamine may have an effect on clinical outcomes, primarily delirium and it did not, but it may cause an undesirable side effect.

Clinical Utility for Ketamine in Neuroanesthetic Practice

The pre-hospital setting is perhaps the most obvious clinical utility for the use of ketamine. It can be given via either the intravenous or intramuscular route, has profound analgesic and sedative properties, favorable hemodynamic effects in the shocked patient and minimal effects on respiration and airway tone when given as a sole agent [1, 2, 27]. Indeed, the Tactical Combat Casualty Care (TCCC) guidelines recommend ketamine as the primary battlefield analgesic in the setting of moderate-to-severe pain and hemodynamic compromise [28]. Despite the evidence presented, failing to support the association between ketamine and worse outcomes in head trauma TCCC guidelines continues to state that ketamine may worsen severe traumatic brain injury [28]. Torres et al. report that in a retrospective analysis of more than 4000 combat casualties with serious head injuries, 209 were given ketamine [28]. On univariate analysis, the ketamine group was more likely to die (OR 0.2; 95% CI: 0.45–0.86); however, when controlling for the presence of an airway intervention and the mechanism for injury, the result was non-significant. The American College of Surgeons Committee on Trauma and the American College of Emergency Physicians have just published a joint statement endorsing that ketamine can be safely administered to the trauma patient with a head injury as it has minimal effects on ICP and has no adverse effect on CPP or neurologic outcomes [29].

In the absence of contemporary data supporting an association between ketamine use and increases in ICP when ventilation is controlled, there are reasonable theoretical considerations to promote the use of ketamine for craniotomy. Ketamine is a non-opioid analgesic and could improve analgesia after craniotomy if used as part of a balanced anesthetic technique. In addition, its sympathomimetic effects could limit the use of inotropes and vasopressors to support blood

pressure. It has a favorable profile if neurophysiological monitoring with either somatosensory- or motor-evoked potentials (or both) is to be used. In the setting of TBI or SAH any neuroprotective effects may improve the clinical outcome of the patient. Bhardwaj et al performed a small study with 20 patients in each group undergoing a craniotomy for clipping of an intracerebral aneurysm in the setting of a good grade SAH [30]. The patients either received "ketofol" (ketamine and propofol in a 1:5 ratio) or propofol alone. Hemodynamics were better maintained in the "ketofol" group with less hypotension (only 15% of patients having > 20% fall in mean arterial pressure from baseline intraoperatively) compared with 45% in the propofol alone group (P = 0.038). Total mean phenylnephrine dose use was less in the "ketofol" group (P = 0.015), but mean ICP values and brain relaxation scores were comparable between the two groups. Ketamine has been given previously as a bolus dose to patients at our institution with SAH also undergoing craniotomy for aneurysm clipping who were receiving an isoflurane anesthetic without any increase in ICP [31]. Presently we often administer a "ketofol" anesthetic comparable to that described by Bhardwaj et al. and with similar experiences.

The analgesic properties of ketamine have been reported since it first came into use in the 1970s and is widely utilized in the pre-hospital and emergency room setting. Following the reporting in 2010 of a reduction in opioid consumption in a group of opiate dependent patients who received ketamine prior to undergoing spine surgery both in the first few days after surgery but lasting for up to 6 weeks after surgery [32•], ketamine has gained widespread popularity in our experience as part of a multimodal enhanced recovery protocol for patients undergoing complex spine surgery [33]. However, a recent pragmatic study comparing a multimodal analgesic technique for patients undergoing complex spine surgery that included ketamine with a group who received placebo found no difference in the quality of recovery scores between the patients [34]. It is possible that the benefits of ketamine in spine surgery are perhaps limited to patients with some degree of opiate dependency. In the previously discussed PODCAST trial, the unexpected secondary finding was that there was no effect of ketamine on either pain scores or opioid consumption [26••].

An antidepressant action of ketamine has also been reported in depressed patients. This has led to investigations as to whether or not ketamine administered for electroconvulsive therapy (ECT) improves treatment outcomes. Gamble et al. reported that ketamine anesthesia provided faster response and remission after ECT compared with propofol anesthesia [35]. However, two other clinical trials suggest that ketamine anesthesia may not significantly improve depression after ECT [36, 37]. In a separate reporting of patients recruited to the PODCAST trial, Mashour et al. reported that major surgery is associated with new onset symptoms suggestive of depression (in patients > 60 years old), but the intraoperative administration of a subanesthetic dose of ketamine did not appear to prevent or treat those symptoms [38].

Conclusion

Ketamine causes an increase in CPP and CBF. The mechanism for increase in CBF is predominately cerebral vasodilation. The effects of cerebral vasodilation on CBV and ICP can be mitigated by controlling $PaCO_2$. Early reports of ketamine causing large increases in ICP were often in patients with obstructed hydrocephalus who received large doses of ketamine and ventilation was often not controlled. There are many clinical benefits to using ketamine in the brain-injured patient. Its use in the pre-hospital setting to stabilize the brain injured patient has recently been endorsed [29]. Pre-clinical work suggests that ketamine may have a role as a glutamate modulator inhibiting excitation in the setting of brain injury. This has yet to be proven with clinical evidence but is an area of ongoing clinical research particularly in the setting of SAH and TBI. Clinical trials investigating ketamine's usefulness as an adjunctive analgesic, antidepressive, or even delirium sparring agent to date have been disappointing.

Declarations

Conflicts of Interest The author does not have any potential conflicts of interest to disclose.

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- •• Of major importance

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