Although anesthetists have long assumed that ketamine’s role in neuroanesthesia is limited because of its association with increased intracranial pressure, this article presents a review of recent clinical literature suggesting otherwise. When ketamine is used as an adjuvant anesthetic agent along with mechanical ventilation to maintain normocapnia, ketamine does not have adverse cerebral hemodynamic effects. Furthermore, ketamine possesses a unique pharmacologic profile that provides analgesia, bronchodilation, and sympathetic stimulation, thereby reducing patients’ vasoactive agent requirements. Caution must be exercised because of ketamine’s action at the N-methyl-d-aspartate receptor (NMDAR), as ketamine may antagonize both neuroprotective and neurodestructive NMDAR-mediated pathways. Still, ketamine may prove to be a safe part of a neuroanesthetic regimen, and it should no longer be considered absolutely contraindicated as a result of its cerebral hemodynamic effects.

Keywords: Ketamine, neurodestruction, neuroprotection, NMDA, N-methyl-d-aspartate.

Rethinking the Paradigm: Evaluation of Ketamine as a Neurosurgical Anesthetic

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As a leading cause of worldwide disability and death, cerebral ischemia has a profoundly negative impact on patients, healthcare providers, and society. Cerebral ischemia occurs in multiple situations including cerebrovascular accident (CVA) and traumatic brain injury (TBI). In particular, CVA is the third leading cause of death and the most common reason for complex chronic disability in the international community, whereas in the United States 700,000 people suffer a CVA each year with an average rate of 1 stroke every 45 seconds.1,2 In addition, 1.4 million Americans sustain TBIs yearly, resulting in 80,000 to 90,000 people with permanent disabilities and 50,000 fatalities.3 Given the universal scale of diseases leading to cerebral ischemia and the resulting long-term sequelae, there is a clear need for treatments that lessen the severity of their impact. Since CVA and TBI often require neurosurgery, continued advances in anesthetic treatments during the perioperative period may be one way to improve these patients’ outcomes.

The ideal intravenous neuroanesthetic for cerebral ischemic injuries would possess neuroprotective properties such as maintenance of cerebral autoregulation, reduction of cerebral metabolic rate (CMRO2), reduction of cerebral blood volume (CBV), and prevention of seizure activity, and would be neither a myocardial depressant, a significant vasodilator, nor an adrenal suppressant.4 Presently, no existing anesthetic possesses all of these qualities, so clinicians routinely combine agents to achieve ideal neuroprotective effects.

• Traditional Neuroanesthetic Technique. Anesthesia clinicians combine anesthetics to create a regimen with ideal neuroprotective properties to reduce the severity of the neurologic insult.5 The intravenous anesthetic propofol is a first line anesthetic agent, which is used to reduce the patient’s CMRO2, CBV, and intracranial pressure (ICP), to prevent potential seizure activity and to facilitate quick emergence for neurologic assessment.4 Volatile anesthetics, such an isoflurane, are beneficial adjuncts because they reduce CMRO2, but they are not used as primary agents as they increase cerebral blood flow due to vasodilation in a dose-dependent manner.6 Benzodiazepines and barbiturates increase the seizure threshold and reduce ICP and CMRO2. Opioids further supplement the neuroanesthetic regimen by providing analgesia, facilitating mechanical ventilation through respiratory depression, and deepening the patient’s sedation.4

• Ketamine and Neuroanesthesia. Ketamine is an intravenously administered general anesthetic with a primary mechanism of action of noncompetitive binding to the N-methyl-d-aspartate receptor (NMDAR).7 Secondary mechanisms of action are at the μ opioid, monoaminergic and muscarinic receptors, voltage-gated sodium and L-type calcium channels, and it inhibits interleukin-6 (IL-6) and catecholamine uptake (Table 1).8-14 These mechanisms combine clinically to induce a dissociative cataleptic state, with beneficial pharmacodynamic properties including analgesia, bronchodilation, and sympathet-

Pharmacologic neuroprotection with traditional neuroanesthetics is achieved by decreasing oxygen demand, improving oxygen delivery, and reducing the pathologic...
processes that cause neuron cell death. Glutamate excitotoxicity of the NMDAR is recognized as a prominent mechanism in neuronal injury, and unlike other anesthetics, ketamine possesses a unique property that pharmacologically antagonizes the NMDAR during neuron ischemia. Conventionally, ketamine has not been used for neurological patients because it is a potent cerebral vasodilator, which may increase ICP. However, several recent studies have found that when ketamine is administered as an adjuvant to other neuroanesthetic agents and normocapnia is maintained with mechanical ventilation, ICP remains stable.

This article describes the physiologic responses resulting from ketamine administration. A key feature to note is the occurrence of both neuroprotective properties of physiologic synaptic NMDAR activation (Figure 1a) and neurodestruction caused by excitotoxic extrasynaptic NMDAR activation (Figure 1b). Ketamine may over-suppress the physiologic synaptic NMDAR activation preventing the neuroprotective cascade. Administration of ketamine during cerebral ischemia antagonizes excitotoxic glutamate activation of the extrasynaptic NMDAR, thereby preventing the neurodestructive cascade and decreasing neuronal cell death. A review of the recent experimental evidence evaluates ketamine’s clinical effect on cerebral hemodynamic and neurologic outcome.

### Neuroprotective Properties of Physiologic Synaptic NMDAR Activation

Physiologic levels of synaptic NMDAR activity initiate neuroprotective pathways (Figure 1a). Several of these beneficial effects are mediated by the phosphoinositide-3-kinase (PI3K)-Akt pathway, which inactivates pro-apoptotic glycogen synthase kinase-3 beta (GSK3β), forkhead box O (FOXO), and p53 transcription factor genes. Synaptic stimulation of NMDARs promotes striatal-enriched tyrosine phosphatase (STEP) degradation and concomitant extracellular signal-regulated kinase ½ (ERK½) activation, promoting cell survival. In addition, synaptic NMDAR dependent Ca²⁺ influx activates cAMP response element-binding (CREB) protein, which establishes neuronal tolerance to ischemic events, thereby preventing delayed programmed cell death, known as apoptosis. Since these prosurvival pathways are triggered by baseline synaptic NMDAR activity, oversuppression of physiologic neuronal processes by ketamine may lead to neurodestruction.

### Neurodestruction Caused by Excitotoxic Extrasynaptic NMDAR Activation

Use of ketamine after ischemic brain injury may be advantageous because it antagonizes glutamate-induced excitotoxicity at the NMDAR, thus preventing cell damage after neurological injury. Ischemia induces an excitotoxic process involving increased presynaptic release of glutamate, which activates extrasynaptic NMDARs (see Figure 1b). Higher levels of glutamate then over-activate postsynaptic NMDAR protein kinase C and tyrosine kinase signaling cascades. These cascades phosphorylate the NMDARs and up-regulate signaling currents, thus potentiating the activation of NMDARs.

When an episode of excitotoxic glutamate release occurs, it is the extrasynaptic NMDARs that are responsible for causing neurodestruction and for overriding synaptic NMDAR neuroprotective pathways. Extrasynaptic NMDAR induces cell injury by causing excessive influx of calcium (Ca²⁺), which triggers intracellular activity leading to neuron death. The disproportionate influx of Ca²⁺ activates calpain, which disables the Na⁺/Ca²⁺ exchanger and decreases the cell’s ability to transport high Ca²⁺ levels out of the neuron membrane, further augmenting cell death. Mitochondria are damaged by overactivation of Ca²⁺-dependent neuronal nitric oxide synthase, which leads to an overproduction of the compound nitric oxide and results in mitochondrial toxicity. Mitochondrial dysfunction involves both apoptotic factor release and cell death.

In addition, the activated extrasynaptic NMDARs potentiate pro-death intracellular signaling cascades. Calpain breaks down STEP, activating p38 and promoting cell death. Meanwhile, Ca²⁺ entry through extrasynaptic NMDAR causes CREB shutoff, a pathway that is essential

#### Table 1. Ketamine’s Mechanism of Action

<table>
<thead>
<tr>
<th>Action site</th>
<th>Mechanism</th>
<th>Clinical effect</th>
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</thead>
<tbody>
<tr>
<td>NMDA receptors</td>
<td>Antagonist</td>
<td>General anesthesia</td>
</tr>
<tr>
<td>Muscarinic receptors</td>
<td>Antagonist</td>
<td>Bronchodilation and sympathomimetic</td>
</tr>
<tr>
<td>μ Opioid receptors</td>
<td>Agonist</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Monoaminergic</td>
<td>Inhibitor</td>
<td>Antinociception</td>
</tr>
<tr>
<td>Voltage-gated Na⁺ channels</td>
<td>Inhibitor</td>
<td>Local anesthesia</td>
</tr>
<tr>
<td>L-type Ca²⁺ channels</td>
<td>Inhibitor</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Catecholamine uptake</td>
<td>Inhibitor</td>
<td>Bronchodilation and sympathomimetic</td>
</tr>
<tr>
<td>IL-6 and O₂⁻</td>
<td>Inhibitor</td>
<td>Anti-inflammatory</td>
</tr>
</tbody>
</table>

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for neuron survival. Extra-synaptic NMDAR evoked signals promote nuclear import of FOXOs, which contribute to neuronal death. All of these parallel pathways culminate in immediate neuron cell necrosis or apoptosis.

Review of the Clinical Evidence

The articles reviewed in this section were limited to clinical research trials published between 2000 and 2010 that evaluated ketamine’s effect on humans (Table 2). The clinical research indicates ketamine has been safely administered as an adjuvant anesthetic to neurosurgical patients without deleterious cerebral hemodynamic or neurologic consequences.

• Ketamine Used in Neurosurgery Patients. Clinical studies have established that intravenous ketamine administration can be administered safely in patients with neurosurgical pathologies. Bourgoin et al designed a double-blind, randomized controlled trial comparing patients with TBI in the intensive care unit receiving sedation with either ketamine/midazolam or sufentanil/midazolam and found no statistical difference in ICP between the 2 groups (P = .28). The Glasgow Outcome Score of each group was measured 6 months postinjury to determine each patient’s neurologic function, and no statistical difference could be discerned (P = .99).

A retrospective study by Grathwohl et al compared the neurologic outcome of 252 patients with TBI who received total intravenous anesthesia (TIVA) with propofol and ketamine to TIVA without ketamine and to volatile anesthesia without ketamine. Upon comparison of the results, there was no statistically significant difference in the number of patient deaths between the groups (P = .36), and once again, no statistical difference in the Glasgow Outcome Score of each group (P = .47). The studies by Bourgoin et al and Grathwohl et al illustrate that patient outcomes with ketamine as an adjuvant are statistically indistinguishable from the outcomes of patients receiving anesthesia with volatile anesthetics, propofol, opioid, or benzodiazepines.

Bar-Joseph et al prospectively evaluated ketamine’s neurologic effect in mechanically ventilated children with increased ICP that were well sedated with midazolam, 2-5 μg/kg/min, and morphine, 20-50 μg/kg/min. These children were given ketamine boluses (1-1.5 mg/kg) before stimulating events or during episodes of ICP elevation. Ketamine boluses were found to decrease ICP by an average of 30% (P < .001) and achieve modest increases in cerebral perfusion pressure (P < .005). In only one out of the 82 administrations of ketamine did ICP increase. This pretest-posttest research design suggests that, during neurosurgical sedation, adjuvant administration of ketamine with other anesthetic agents results in favorable cerebral hemodynamic responses.
<table>
<thead>
<tr>
<th>Article</th>
<th>Adjuvant ketamine dose</th>
<th>Primary anesthetic</th>
<th>Control group</th>
<th>Study size/setting</th>
<th>Ventilation method</th>
<th>Cerebral hemodynamic effect</th>
<th>Neurologic effect</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurosurgical patient population</strong></td>
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<tr>
<td>Bar-Joseph et al, 19 2009</td>
<td>1-1.5 mg/kg bolus, racemic</td>
<td>Midazolam 2.5 μg/kg/min gtt and morphine</td>
<td>Baseline</td>
<td>30 pediatric patients with intracranial hypertension, 82 ketamine doses</td>
<td>Mechanical</td>
<td>↓ ICP 30% 25.8 ± 8.4 mm Hg to 18.0 ± 8.5 mm Hg within 2 min of bolus (P &lt; .001); ↑ CPP from 54 ± 12 mm Hg to 58 ± 14 mm Hg (P &lt; .005)</td>
<td>↔</td>
<td>Prospective pretest, posttest</td>
</tr>
<tr>
<td>Bourgoin et al, 20 2003</td>
<td>82 ± 25 μg/kg/min gtt, racemic</td>
<td>Midazolam 1.64 μg/kg/min gtt</td>
<td>Sufentanil 0.008 ± 0.002 μg/kg/min gtt, midazolam 1.63 ± 0.37 μg/kg/min gtt</td>
<td>25 Traumatic brain injury patients</td>
<td>Mechanical</td>
<td>↔ ICP (P = .28)</td>
<td>↔ Glasgow outcome score (P = .99)</td>
<td>Double-blinded, RCT</td>
</tr>
<tr>
<td>Grathwohl et al, 40 2008</td>
<td>5-20 μg/kg/min gtt, racemic</td>
<td>Propofol 75-150 μg/kg/min with opioid infusion</td>
<td>Propofol gtt/opioid gtt or volatile gas/opioid gtt</td>
<td>252 Traumatic brain injury patients</td>
<td>Mechanical</td>
<td>↔</td>
<td>Glasgow outcome score (P = .47)</td>
<td>Retrospective</td>
</tr>
<tr>
<td><strong>Volunteer patient population</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Holcomb et al, 41 2001</td>
<td>0.3 mg/kg bolus, racemic</td>
<td>None</td>
<td>Placeo</td>
<td>23 Volunteers</td>
<td>Spontaneous</td>
<td>↑ rCBF (anterior cingulate, medial frontal, inferior frontal cortex), ↓ rCBF in cerebellum</td>
<td></td>
<td>Prospective pretest, posttest</td>
</tr>
<tr>
<td>Långsjö et al, 42 2003</td>
<td>Serum level of 30, 100, 300 ng/mL, racemic</td>
<td>None</td>
<td>Baseline</td>
<td>10 Volunteers—ASA class 1</td>
<td>Spontaneous</td>
<td>↑ rCBF in concentration dependent manner (highest in anterior cingulate, thalamus, putamen, frontal cortex), ↔ CMRO₂</td>
<td></td>
<td>Prospective pretest, posttest</td>
</tr>
<tr>
<td><strong>General surgery patient population</strong></td>
<td></td>
<td></td>
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<tr>
<td>Engelhard et al, 43 2001</td>
<td>42 μg/kg/min gtt, S(+)</td>
<td>Propofol 1.5-2.5 μg/mL target plasma concentration</td>
<td>4% Sevoflurane</td>
<td>24 general surgery patients—ASA class 1 and 2</td>
<td>Mechanical</td>
<td>↔ Autoregulatory index from baseline</td>
<td></td>
<td>RCT</td>
</tr>
<tr>
<td>Nagase et al, 21 2001</td>
<td>1 mg/kg bolus, racemic</td>
<td>0.98 ± 0.13% Isoflurane</td>
<td>Propofol 2 mg/kg bolus, 6-10 mg/kg/h gtt</td>
<td>30 General surgery patients—ASA class 1 and 2</td>
<td>Mechanical</td>
<td>↔ CBF to baseline, ↓ cerebrovascular CO₂ response (P &lt; .05)</td>
<td></td>
<td>Prospective pretest, posttest RCT</td>
</tr>
<tr>
<td>Sakai et al, 22 2000</td>
<td>2 mg/kg bolus, 33 μg/kg/min gtt, racemic</td>
<td>Propofol 2.5 mg/kg bolus, 100 μg/kg/min gtt</td>
<td>Placebo with propofol or awake</td>
<td>38 general surgery patients—ASA class 1</td>
<td>Spontaneous and mechanical</td>
<td>↔ CBF, ↔ cerebrovascular CO₂ response</td>
<td></td>
<td>Double-blinded, RCT</td>
</tr>
<tr>
<td>Article</td>
<td>Adjuvant ketamine dose</td>
<td>Primary anesthetic</td>
<td>Control group</td>
<td>Study size/setting</td>
<td>Ventilation method</td>
<td>Cerebral hemodynamic effect(^\text{a})</td>
<td>Neurologic effect(^\text{a})</td>
<td>Study design</td>
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<td>Bartoc et al,(^\text{14}) 2006</td>
<td>0.25, 0.5 mg/kg bolus, racemic</td>
<td>Midazolam, fentanyl, etomidate, isoflurane</td>
<td>Placebo, midazolam, fentanyl, etomidate, isoflurane</td>
<td>50 cardiac surgery patients</td>
<td>Mechanical</td>
<td>↓ IL-6 in both ketamine groups, ↓ CRP in 0.5 mg/kg bolus group ((P &lt; .05))</td>
<td>Double-blinded, RCT</td>
<td></td>
</tr>
<tr>
<td>Nagels et al,(^\text{44}) 2004</td>
<td>2.5 mg/kg bolus and 125 μg/kg/min gtt, S(+)</td>
<td>Propofol 1-4 μg/mL plasma concentration</td>
<td>Remifentanil 6-14 μg/mL and propofol 1-4 μg/mL plasma concentrations</td>
<td>106 cardiac surgery patients</td>
<td>Mechanical</td>
<td>↔ Cognitive deficit ((P = .54))</td>
<td>RCT</td>
<td></td>
</tr>
<tr>
<td>Smith et al,(^\text{49}) 2006</td>
<td>700 μg/kg/min bolus until loss of consciousness, 33 μg/kg/min gtt, racemic</td>
<td>Midazolam 70 μg/kg/min bolus, 0.2 mg/kg/h gtt, isoflurane</td>
<td>Sufentanil 0.7 μg/kg/min induction, 3 μg/kg/h gtt, isoflurane</td>
<td>42 cardiac surgery patients</td>
<td>Mechanical</td>
<td>↔ Neurologic morbidity - measured by QEEG ((P = .9))</td>
<td>RCT</td>
<td></td>
</tr>
<tr>
<td>Zilberstein et al,(^\text{45}) 2002</td>
<td>0.25 mg/kg bolus, racemic</td>
<td>Midazolam, fentanyl, isoflurane</td>
<td>Placebo, isoflurane, fentanyl, midazolam</td>
<td>35 cardiac surgery patients</td>
<td>Mechanical</td>
<td>↓ Superoxide production ((P &lt; .0001))</td>
<td>Double-blinded, RCT</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Table of Evidence

\(^\text{a}\) Information in these columns relate to 2 key points in the article.

Abbreviations: ↓, decrease; ↑, increase; ↔, statistically equivalent; CMRO2, cerebral metabolic rate; CPP, cerebral perfusion pressure; gtt, infusion; ICP, intracranial pressure; QEEG, quantitative electroencephalography; RCT, randomized controlled trial; rCBF, regional cerebral blood flow; IL-6, interleukin-6; CRP, C-reactive protein.
designed studies have examined ketamine’s effect on cerebral blood flow (CBF) in spontaneously ventilating volunteers by measuring baseline and postketamine administration CBF with a positron emission tomography (PET) scanner. Holcomb et al.14 and Långsjö et al.15 observed that ketamine increased regional CBF in the anterior cingulate and frontal cortices. Långsjö et al15 also found that CMRO2 was not directly correlated with CBF changes, and CMRO2 did not increase after ketamine was administered. It is important to note that both of these studies involved spontaneously ventilating patients who did not receive any anesthetic other than ketamine. However, among neurosurgery patients, ketamine would only be used as an adjuvant anesthetic during mechanical ventilation because of the potential to cause hypoventilation.

**Ketamine Used in General Surgery Patients.** Clinical research in mechanically ventilated, general surgery patients measured time-mean middle cerebral artery blood flow velocity (Vmca) to determine if adjuvant ketamine administration increased CBF. Sakai et al’s22 double-blind, randomized controlled trial used transcranial Doppler ultrasound measurements to demonstrate that ketamine administration during propofol anesthesia was not alter Vmca or cerebrovascular carbon dioxide response. Despite reductions in the proinflammatory pathway on a cellular level, studies have not been able to detect an improvement in cognitive outcomes after ketamine is administered, although they have demonstrated that outcomes are the same. In a large randomized controlled trial, 106 CPB patients underwent neurocognitive tests before surgery and at 1 and 10 weeks postoperatively. These neurocognitive tests measured no significant difference in cognitive outcomes between those patients who received no ketamine and those who received adjuvant ketamine or placebo during 1% isoflurane anesthesia and reinforced that ketamine increased regional CBF in the anterior cingulate and frontal cortices. Långsjö et al.42 also found that CMRO2 was not directly correlated with CBF changes, and CMRO2 did not increase after ketamine was administered. It is important to note that both of these studies involved spontaneously ventilating patients who did not receive any anesthetic other than ketamine. However, among neurosurgery patients, ketamine would only be used as an adjuvant anesthetic during mechanical ventilation because of the potential to cause hypoventilation.

**• Ketamine Used in Cardiopulmonary Bypass (CPB) Surgery Patients.** Ketamine’s neuroprotective properties have been tested on patients undergoing CPB, since this patient population is at risk for postoperative neurocognitive deterioration related to neuron ischemia and cellular inflammation associated with surgical trauma, the extracorporeal circuit apparatus, and reperfusion injury.14,44,45 Inflammation activated by CPB begins with an increased cytokine IL-6 cascade that delays neutrophil apoptosis resulting in larger populations of activated neutrophils for adhesion and production of free radical superoxides.46 In addition, IL-6 increases C-reactive protein (CRP) synthesis in the liver.47 Such a result is detrimental because activated neutrophils, increased free radical superoxides, and elevated CRP levels perpetuate inflammation and are associated with increased morbidity and mortality after CPB.48 Zilberstein et al49 measured the end product superoxide anion generation in a double-blind, randomized controlled trial of 35 CPB patients receiving either an adjuvant ketamine 0.25 mg/kg bolus or a placebo during the induction of anesthesia. This study revealed that patients who received the ketamine bolus had significantly lower superoxide levels 6 days after surgery (P < .0001). Bartoc et al’s14 double-blind, randomized controlled trial with 50 CPB patients tested either adjuvant ketamine (0.25 mg/kg or 0.5 mg/kg) or a placebo during the induction of general anesthesia. Both ketamine doses resulted in statistically significant and equivalent reductions in IL-6 levels compared with the control group for 7 postoperative days after CPB (P < .05).14 The 0.5 mg/kg dose also reduced CRP production compared with the control group (P < .05).14 Despite reductions in the proinflammatory pathway on a cellular level, studies have not been able to detect an improvement in cognitive outcomes after ketamine is administered, although they have demonstrated that outcomes are the same. In a large randomized controlled trial, 106 CPB patients underwent neurocognitive tests before surgery and at 1 and 10 weeks postoperatively. These neurocognitive tests measured no significant difference in cognitive outcomes between those patients who received no ketamine and those who received adjuvant ketamine 2.5 mg/kg bolus during induction followed by a ketamine 125 μg/kg/min infusion throughout surgery.44 A second randomized controlled trial with 42 CPB patients compared their neurologic outcomes after CPB using quantitative electroencephalography, which is correlated with neurocognitive deterioration.46 As with the previous study, those patients receiving 0.7 mg/kg ketamine bolus and ketamine, 33 μg/kg/min, infusion demonstrated equivalent neurologic morbidity to the control group.49 The lack of clinical improvement in neurologic outcome demonstrates the complexity of linking the positive subclinical effect of ketamine on neuronal cells to measurable differences in clinical neurologic outcomes.

**Discussion**

The belief that ketamine is contraindicated in neurosurgical patients because of its cerebral hemodynamic effects is supported by clinical studies like Holcomb et al.14 and Långsjö et al.50 However, these studies examined ketamine’s cerebrovascular effects in spontaneously ventilating volunteers receiving ketamine as the sole anesthetic, thereby failing to construct a setting in which ketamine’s efficacy could be properly evaluated. In the clinical setting neurosurgical patients receive a combination of anesthetics to achieve ideal neuroanesthetic effects, and they are carefully ventilated to maintain hypocapnia or normocapnia.
A body of evidence has formed suggesting adjuvant administration of ketamine in mechanically ventilated neurosurgical patients is safe and does not cause undesired cerebral-hemodynamic consequences. The most common study designs were small to moderate size randomized controlled trials with 1 study enrolling neurosurgical patients and 3 studies enrolling general surgery patients. There was also 1 pretest-posttest designed study of neurosurgical patients. Sample sizes ranged from 24 to 106 patients.

Among the clinical studies examining mechanically ventilated patients who received a primary anesthetic, such as propofol, CBF and ICP was equivalent or reduced when ketamine was administered. A comparison of Sakai et al's and Engelhard et al's findings that a propofol infusion and adjuvant ketamine maintained baseline CBF, cerebrovascular carbon dioxide response, and autoregulation with Nagase et al's findings showing that 1% isoflurane and adjuvant ketamine only maintained CBF, suggests that propofol may be the ideal primary anesthetic to administer with ketamine.

Use of adjuvant ketamine in mechanically ventilated patients resulted in neurologic outcomes equivalent to more traditional anesthetic techniques. In these studies the most common design was randomized controlled trial with 1 study enrolling neurosurgical patients and 2 studies enrolling cardiac surgery patients. Another study was retrospective and it examined neurosurgical TBI patients. The sample sizes were between 25 and 252 patients. When adjuvant ketamine administration was compared with traditional anesthetics in patients at risk for neurologic damage, the studies revealed they had equivalent neurologic outcomes. Of particular importance were studies by Bourgoin et al and Grathwohl et al who examined adjuvant ketamine administration in acutely injured TBI patients, and both concluded that the group that received ketamine had identical neurologic outcomes as the control group.

Two other randomized controlled trials involving cardiac surgery patients demonstrated a reduction in the proinflammatory pathway when ketamine was administered at the beginning of the surgical case. These cardiac surgery studies examined inflammation caused by either cellular ischemia or the extracorporeal circuit apparatus and reperfusion injuries. They provide promising evidence that inflammation caused by either cellular ischemia or CPB is reduced by adjuvant ketamine boluses.

Despite these promising results, additional research is needed to create acceptable evidence-based guidelines for adjuvant ketamine administration in neurosurgical patients. Future clinical studies should consider evaluating the proper dose and duration of ketamine, as these variables influence its effect on neurologic functional outcome. The currently available literature lacks consensus on optimal dosing for desired cerebrovascular and neuroprotective effects. A wide range of ketamine bolus doses were used, ranging from 0.25 mg/kg to 2.5 mg/kg. Among the 6 clinical studies involving continuous infusions of ketamine, doses ranged from 5 to 107 μg/kg/min, and most infusions were administered intraoperatively while others were given in the intensive care unit.

The neuroprotective effects of physiologic synaptic NMDAR should not be overlooked. Physiologic synaptic NMDAR activity may be suppressed by NMDAR antagonism, thereby potentiating neurodestruction. This physiologic process highlights the difficulty of dosing any NMDAR antagonist for patients with ischemic injuries. It has been suggested that a more efficacious approach to avoiding physiologic synaptic NMDAR oversuppression, while antagonizing glutamate excitotoxicity, may be to develop a treatment that selectively antagonizes extrasynaptic NMDAR activation or a latter component of the neurodestructive cascade. However, neither strategy has been clinically devised.

Summary
Anesthetists have long assumed ketamine has no role in neuroanesthesia because of the potential for undesirable cerebral hemodynamic effects. Recent literature has provided a solid foundation for suggesting that adjuvant ketamine administration in mechanically ventilated patients has benign cerebrovascular effects. Most importantly, clinical evidence indicates that adjuvant administration of ketamine with neuroanesthetics is not detrimental to neurosurgical patients’ outcomes. Ketamine should not be considered absolutely contraindicated in treatment of neurosurgery patients, although anesthetists should be cautious, as ketamine possesses properties that may result in antagonism of both neuroprotective and neurodestructive NMDAR-mediated pathways.

REFERENCES


