Neuroprotection by Ketamine: A Review of the Experimental and Clinical Evidence

Judith A. Hudetz, PhD, and Paul S. Pagel, MD, PhD

From the Department of Anesthesiology, Medical College of Wisconsin and Clement J. Zablocki Veterans Administration Medical Center, Milwaukee, WI.

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Address reprint requests to Judith A. Hudetz, PhD, Department of Anesthesiology, Clement J. Zablocki Veterans Administration Medical Center, 5000 W National Avenue, Milwaukee, WI 53295. E-mail: judith.hudetz@va.gov

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O2 DEPRIVATION AND MECHANISMS OF EXCITOTOXICITY

Cerebral neurons rapidly consume O2 and glucose and depend almost exclusively on these substrates to drive oxidative phosphorylation for energy production and are extremely sensitive to reductions in the O2 and glucose delivery.2 Restriction of O2 and glucose delivery to the brain causes a series of events that rapidly lead to cell death, including excitotoxicity, peri-infarct depolarization, inflammation, and apoptosis.3 Focal impairment of CBF restricts the delivery of O2 and glucose, thereby impairing the generation of energy required to maintain ionic gradients.4 As a result, intracellular energy supplies are rapidly exhausted, membrane potential is lost, and neurons and their supporting glial cells depolarize.5 Somatodendritic and presynaptic voltage-dependent Ca2+ channels become activated under these conditions, and excitatory amino acids (eg, glutamate) are released into the extracellular space. Energy-dependent homeostatic processes, such as presynaptic uptake of excitatory amino acids are simultaneously impeded, thereby further increasing the accumulation of glutamate in the extracellular space. The NMDA-receptor controls an ion channel that is permeable to Ca2+ and glutamate release by ischemic neurons. The activation of these receptors increases Ca2+ influx and rapidly initiates cell necrosis and apoptosis.6 Cerebral neurons that are subjected to ischemia-induced glutamate-receptor activation, Ca2+ overload, O2-derived free radicals, or mitochondrial and DNA damage may be irreversibly damaged depending on the source and intensity of the injury, the type of neural cell, and its developmental stage.7 Thus, a potential therapeutic approach to prevent this sequence of events is the blockade of NMDA receptors.8 As a result, ketamine may potentially inhibit neuronal cell death by preventing excitotoxic injury through this mechanism.9

The intracellular signaling pathways activated during excitotoxicity trigger the expression of genes that initiate inflammation, another important contributor to ischemic injury. The Ca2+-induced activation of intracellular second messengers (eg, ceramide), the release of O2-derived free radicals, and the presence of hypoxia itself stimulate transcription and translation of nuclear factor-κB and hypoxia-inducible factor 1.10,11 Ketamine suppresses nuclear factor-κB expression12 involved
in the transcription of genes encoding the proinflammatory cytokines tumor necrosis factor α (TNF-α), interleukin (IL)-6, and IL-8. Although microvascular obstruction by neutrophils may worsen the degree of ischemia, the production of toxic mediators (e.g., TNF-α) by these activated inflammatory cells and injured neurons also contributes to further exacerbation of ischemic injury during early reperfusion. For example, ischemic neurons produce the proinflammatory cytokine TNF-α that has been linked to accelerated ischemic injury through a “feed-forward” mechanism. Thus, ketamine administration may affect this process by reducing brain injury during early reperfusion.

NEUROPROTECTIVE EFFECTS OF KETAMINE: EXPERIMENTAL EVIDENCE

Several experimental studies in vitro and in vivo suggested that ketamine may be capable of producing neuroprotective effects. Glutamatergic signaling has been linked to nitric oxide metabolism. Racemic ketamine inhibited nitric oxide synthesis and nitric oxide-dependent cyclic guanosine monophosphate production stimulated by glutamate and glutamate analogs (e.g., NMDA, quisqualate, and kainate) in primary cultures of cortical neurons and glia. These findings suggested that this ketamine-induced inhibition of glutamate receptors may contribute not only to anesthesia but also cellular protection against ischemic injury.

Racemic and (S)- but not (R)-ketamine attenuated injury after glutamate exposure or axonal transection in rat hippocampal neurons in vitro. Neuroregenerative effects also were observed with (S)-ketamine but not racemic or (R)-ketamine. Synthesis of a growth-associated protein related to plasticity and repair were enhanced after glutamate injury by (S)- but not racemic ketamine in rat hippocampal neurons. To determine the relative neuroprotective activity of (S)-ketamine compared with its (R)-isomer administered after the ischemic injury in vivo, the functional and neurohistologic outcomes of rats exposed to global forebrain ischemia were examined. (S)- but not (R)-ketamine significantly reduced neuronal cell loss in the cerebral cortex. (S)- but not (R)-ketamine also restored the cortical O2 saturation to preischemic values independent of CBF. Thus, the (S)-ketamine may reduce cortical neuronal damage after cerebral ischemia by improving the ratio of O2 supply to consumption during reperfusion. (S)-ketamine also favorably influenced neuronal apoptosis by attenuating increases in expression of the proapoptotic Bax protein produced by cerebral ischemia and reperfusion in rats compared with those that did not receive the drug. These data emphasize that the salutary actions of ketamine in models of neuronal injury appear to be stereoselective.

Ketamine also may decrease the severity of cerebral injury by interfering with the inflammatory response to ischemia. Ketamine suppressed lipopolysaccharide-induced TNF-α, IL-6, and IL-8 production and inhibited neutrophil adhesion to the endothelium in vitro. Racemic ketamine improved the neurologic severity score at 24 and 48 hours and reduced the volume of hemorrhagic necrosis without altering cerebral edema after head trauma in rats. Ketamine also attenuated neuronal damage in the caudoputamen of rats exposed to chronic, hypocapnia-induced cerebral hyperperfusion. The administration of racemic ketamine before the initiation of hypocapnia reduced white-matter injury, neuronal damage, and astrogliosis proliferation. These data suggested that racemic ketamine may be beneficial for preventing brain dysfunction caused by inadvertent hypocapnia during mechanical ventilation. Racemic ketamine also enhanced neurologic outcome concomitant with reductions in plasma catecholamine concentrations in a rat model of incomplete cerebral ischemia. The beneficial effects of ketamine on cerebral histopathology were dose-dependent. Ketamine (20 mg/kg) did not affect neuronal damage in the selectively vulnerable hippocampal CA1 region in a rat model of near-complete forebrain ischemia, but larger doses of ketamine administered during the reperfusion provided significant neuroprotection. These results suggested that NMDA receptor–mediated events may contribute to neuronal damage in selectively vulnerable regions of the central nervous system after the ischemia insult and further implied that ketamine may attenuate such damage. Despite the intriguing nature of these findings, it is important to emphasize that animal models of cerebral ischemia and their modulation by NMDA-receptor antagonists may not predict results in humans. In addition, the wide variation in effective doses of ketamine reported within and between animal species suggests that the dose of ketamine required for possible neuroprotection in humans is not immediately apparent.

CEREBROVASCULAR AND METABOLIC EFFECTS OF KETAMINE: EXPERIMENTAL FINDINGS

Low doses of ketamine (<2 mg/kg) have been reported to increase but also not to affect CBF and CMRO2 in experimental animals. These apparently conflicting observations may be explained at least in part because ketamine may inhibit metabolism in selected brain regions while simultaneously enhancing metabolism in others concomitant with changes in CBF. Racemic and (S)-ketamine decreased glucose cerebral metabolic rate (CMRglu) in cortical, thalamic, cerebellar, and brainstem regions but increased CMRglu in limbic areas. In contrast, (R)-ketamine caused less-pronounced reductions in CMRglu in 11 brain areas, whereas this optical isomer markedly increased CMRglu in the basal ganglia and limbic regions. This regional specificity of ketamine on CMRglu and CBF was consistent with the heterogenous effects of the drug on brain electrical activity. The actions of ketamine on regional cerebral perfusion and metabolism appear to be sensitive to preexisting cerebrovascular tone and the prevalence of other anesthetics. The balance between microregional O2 demand and supply has been shown to be heterogeneously distributed. The influence of ketamine on regional CBF and microregional arterial and venous O2 saturation were determined in the anterior cortex, posterior cortex, and pons in rats. In this setting, ketamine did not substantially affect regional CBF or O2 supply-demand relations in contrast to enhanced CBF and CMRO2 typically reported. Ketamine reduced ICP caused by space-occupying lesions to a
similar degree as methohexital and propofol, but the dissociative anesthetic also increased CPP, in contrast to the other drugs. However, ketamine, methohexital, and propofol did not affect ICP or CPP in the cytotoxic brain edema model. These data suggested that ketamine may attenuate the increase in ICP caused by space-occupying lesions but may be detrimental during generalized edema. The authors postulated that some neurons remain viable and responsive to the effects of ketamine in the presence of a space-occupying lesion. In contrast, diffuse intracellular damage occurs in the cytotoxic brain edema, CMRO₂ may be severely depressed, and autoregulation of the cerebral vasculature may be impaired. As a consequence, the cytotoxic brain becomes less responsive to the vasoactive effects of intravenous anesthetics, including ketamine.

The actions of ketamine (10⁻³ to 10⁻⁷ mol/L) on cerebral pial arterioles in a closed cranial window model were evaluated in dogs anesthetized with pentobarbital or isoflurane.⁴⁰ Neither topical nor intravenous (1 mg/kg and 5 mg/kg, respectively) ketamine caused pial arteriolar vasodilation. However, the reactivity of pial arterioles to hypercapnia was reduced after intravenous, but not topical, administration of ketamine, supporting the hypothesis that the type of baseline anesthetic affects the microvascular effects of ketamine. Ketamine was also shown to differentially modulate the cerebral circulation in the presence of volatile agents because ketamine reduced isoflurane- but not sevoflurane-induced cerebral vasodilatation.⁴¹

NEUROTOXIC EFFECTS OF NMDA-RECEPTOR ANTAGONISTS: EXPERIMENTAL EVIDENCE

In contrast to the aforementioned data, other evidence suggests that NMDA-receptor antagonists may produce neurotoxicity under certain experimental conditions. For example, complete inhibition of normal NMDA-receptor activity reduced brain cell survival and worsened physiologic outcome in rodents because NMDA-mediated signal transduction was required to express neurotrophins and survival-promoting proteins.⁴⁶ Similarly, large doses of NMDA-receptor antagonists caused apoptosis, synaptic deficits, and cognitive impairment in the developing rat brain, especially during the vulnerable phase of synaptogenesis.⁴⁷-⁵⁰ Ketamine produced acute, albeit transient, vascular changes in posterior cingulate/retrosplenial cortices in adult rats.⁵¹-⁵² The coadministration of ketamine and the NMDA antagonist nitrous oxide further enhanced vacuole formation, whereas the pretreatment with a γ-aminobutyric acid agonist prevented these adverse effects.⁵¹,⁵⁴ Low doses of NMDA antagonists, including ketamine and phencyclidine, produced reversible pathomorphologic changes in cerebral cortical neurons of the adult rat brain,⁵⁵ and higher doses of these drugs caused irreversible neuronal degeneration in several cortical-limbic brain regions.⁵⁴-⁵⁸ In vitro studies showed cell death in neurons cultured from the rat forebrain after prolonged exposure to ketamine at concentrations of 10 or 20 μmol/L, but apoptosis did not occur in the presence of 0.1 or 1.0 μmol/L of ketamine.⁵⁹ Studies conducted with cultured monkey frontal cortical neurons produced similar results.⁶⁰ These results strongly suggested that neurotoxicity produced by NMDA antagonists in vitro may be dose-related.

The mechanism responsible for NMDA-antagonist neurotoxicity is unclear, but the disinhibition of excitatory neural pathways that extensively innervate the cerebral cortex may play an important role in this phenomenon. Whether the NMDA antagonist-induced neurodegeneration observed in rats also occurs in humans is presently unknown. Notably, the doses and durations of administration of ketamine-implicated neurotoxicity in experimental animals often do not correlate with and frequently greatly exceed those used to produce sedation or anesthesia in patients. Thus, the potential clinical relevance of the data obtained in rats remains to be clarified. Nevertheless, the results of a study suggested that the psychotomimetic effects of NMDA antagonists in humans may correlate with the cerebral pathologic changes observed in rats.⁶¹ Another crucial factor that must be considered when extrapolating results from experimental animals to humans is the presence or absence of ischemia. Clearly, the pathologic conditions during or after cerebral ischemic injury are profoundly different from those present in intact, uninjured tissue. Neural ischemia causes profound increases in extracellular excitatory transmitter concentration.⁶² This observation indirectly suggests that ketamine may be capable of causing additional neural excitation and further damage during ischemia-reperfusion injury, but this hypothesis has not been examined.

CEREBROVASCULAR AND METABOLIC EFFECTS OF KETAMINE IN HUMAN VOLUNTEERS

Incremental intravenous doses of ketamine (cumulative total of 3 mg/kg) increased CBF, CPP, and arterial CO₂ tension and reduced cerebral vascular resistance but did not affect the CMRO₂, CMRglu, and CMRlactate in healthy patients before elective surgery.² The actions of racemic ketamine (0.25 or 0.5 mg/kg intravenously) on spontaneous brain electrical activity and intracranial blood flow velocity were assessed in conscious volunteers.⁶³ Ketamine modestly increased heart rate and mean arterial pressure but did not affect end-tidal CO₂ tension or arterial O₂ saturation. Ketamine also caused a dose-dependent, transient shift in the electroencephalogram (EEG) to synchronous, high-voltage slow waves with an increase in total power concomitant with increases in middle cerebral artery blood flow velocity. These data suggested that enhanced intracranial blood flow velocity occurs primarily as a result of increases in neuronal activity and not because of changes in hemodynamics, ventilation, or oxygenation. Subanesthetic doses of ketamine also increased EEG theta activity, regional CBF, and metabolism in spontaneously breathing volunteers.⁶³,⁶⁶ As described earlier, these metabolic effects were dependent on the optical isomer examined. Vollenweider et al⁶⁵ investigated the effects of (S)- and (R)-ketamine enantiomers on brain energy metabolism in healthy volunteers using positron emission tomography. Psychotomimetic doses of (S)-ketamine substantially increased regional CMRglu in the frontal cortex and thalamus. These metabolic changes were associated with egodisintegration and hallucinations. In contrast, equimolar doses of (R)-ketamine suppressed regional CMRglu in the temporomedial cortex and left insula concomitant with a state of relaxation. Subanesthetic doses of (S) - and (R)-ketamine were shown to interact differently with the NMDA-and sigma-receptor sites in the human brain. The sigma receptor was first described as a novel opioid receptor but later was established as a distinct pharmacologic receptor distinguished by its unusual ability to
Table 1. Physiologic and Neurocognitive Effects of Ketamine in Humans

<table>
<thead>
<tr>
<th>Reference</th>
<th>Size/Study Group</th>
<th>Age</th>
<th>Dose, Ketamine</th>
<th>Study Setting</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Heart surgery</td>
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<tr>
<td>Tuman et al, 1989</td>
<td>240/345/212/250/47</td>
<td>62/63/63/63/63</td>
<td>3-6 mg/kg</td>
<td>Cardiac surgery patients, no cerebral compromise</td>
<td>NC: neurologic morbidity</td>
</tr>
<tr>
<td></td>
<td>FenH/FenM/Sufen/Dia&amp;Ket/Hal</td>
<td></td>
<td></td>
<td></td>
<td>Ket&amp;Dia&amp;Ket: D: vasopressors and ECG evidence of ischemia</td>
</tr>
<tr>
<td>Roytbiat et al, 1998</td>
<td>14/17 Ket/C</td>
<td>68/65</td>
<td>0.25-mg/kg bolus</td>
<td>Cardiac surgery patients, no cerebral compromise</td>
<td>Ket: D: IL-6 during and post surgery</td>
</tr>
<tr>
<td>Zilberstein et al, 2002</td>
<td>15/15 Ket/C</td>
<td>64/58</td>
<td>0.25-mg/kg bolus</td>
<td>Cardiac surgery patients, no cerebral compromise</td>
<td>Ket: A: superoxide anion, percentage of neutrophils, C: I: superoxide anion</td>
</tr>
<tr>
<td>Nagels et al, 2004</td>
<td>50/56 Ket/Remifen</td>
<td>61/60</td>
<td>2.5-mg/kg bolus and 125 μg/kg/min</td>
<td>Cardiac surgery patients, no cerebral compromise</td>
<td>Ket: less D: Trailmaking B test</td>
</tr>
<tr>
<td>Smith et al, 2006</td>
<td>21/21 Suf/Ket&amp;Mid</td>
<td>47/47</td>
<td>0.7 mg/kg/min for induction and 2 mg/kg/h</td>
<td>Cardiac surgery patients, no cerebral compromise</td>
<td>NC: neurologic morbidity</td>
</tr>
<tr>
<td>Bartoc et al, 2006</td>
<td>15/18/17 Ket/Ket/C</td>
<td>73/73/69</td>
<td>0.25-, 0.5-mg/kg bolus</td>
<td>Cardiac surgery patients, no cerebral compromise</td>
<td>Ket&amp;D: IL-6 postsurgery in both ketamine groups Ket&amp;D: CRP postsurgery in 0.5 mg/kg ketamine group Ket&amp;D: IL-10 postsurgery in both ketamine groups Ket&amp;D: delayed figure reproduction and delayed word list recall tests Ket&amp;D: less delirium</td>
</tr>
<tr>
<td>Hudetz et al, 2008</td>
<td>24/24 Ket/C</td>
<td>68/67</td>
<td>0.25-mg/kg bolus</td>
<td>Cardiac surgery patients, no cerebral compromise</td>
<td>Ket: less D: delayed figure reproduction and delayed word list recall tests Ket: less delirium</td>
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<td>Hudetz et al, 2009</td>
<td>29/29 Ket/C</td>
<td>68/66</td>
<td>0.25-mg/kg bolus</td>
<td>Cardiac surgery patients, no cerebral compromise</td>
<td>Ket: less delirium</td>
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<tr>
<td>Neurology</td>
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<td>Mayberg et al, 1995</td>
<td>20 Ket</td>
<td>49</td>
<td>1-mg/kg bolus</td>
<td>Neurosurgical patients, mildly raised ICP</td>
<td>NC: MAP, CPP, PaCO2, AVDO2</td>
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<td>Strebel et al, 1995</td>
<td>6/6/6/6 C/Ket/Ket/Mid/Ket&amp;Esm</td>
<td></td>
<td>2-mg/kg bolus</td>
<td>Neurosurgical patients, no cerebral compromise</td>
<td>D: VMCA, ICP</td>
</tr>
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<td>Kolenda et al, 1996</td>
<td>16/17 Ket/Mid/Fen&amp;Mid</td>
<td>38/29</td>
<td>65 mg/kg/d</td>
<td>Head-injured patients, increased ICP</td>
<td>NC: MAP, VMCA, MAP</td>
</tr>
<tr>
<td>Albanese et al, 1997</td>
<td>8 Ket</td>
<td>28</td>
<td>1.5, 5, 5 mg/kg</td>
<td>Head-injured patients, increased ICP</td>
<td>Ket&amp;D: vasopressors</td>
</tr>
<tr>
<td>Bourgoin et al, 2003</td>
<td>12/13 Ket/Mid/Suf&amp;Mid</td>
<td>30/27</td>
<td>4.92 ± 1.5 mg</td>
<td>Head-injured patients, increased ICP</td>
<td>NC: CPP, HR VMCA, MAP</td>
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<td>Ket&amp;D: ICP</td>
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<td>NC: ICP, CPP</td>
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<td>Ket&amp;D: I: HR</td>
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<td>Suf&amp;Mid: I: fluid, vasopressors</td>
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<td>Study</td>
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<td>Drug(s)</td>
<td>Dosage</td>
<td>Notes</td>
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<td>Grathwohl et al, 2008</td>
<td>46/47</td>
<td>Fen/Sufen&amp;Sevo/Iso Pro&amp;Ket</td>
<td>27/27</td>
<td>5-20 μg/kg/min</td>
<td>Head-injured patients, increased ICP</td>
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<td>General surgery</td>
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<td>Roytblat et al, 1996</td>
<td>11/11</td>
<td>Ket/C</td>
<td>51/52</td>
<td>0.15 mg/kg</td>
<td>Surgical patients Ket: D: HR, MAP, IL-6</td>
</tr>
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<td>Sakai et al, 2000</td>
<td>7/7/8</td>
<td>Awake/Pro/Pro&amp;Ket</td>
<td>29/33/32</td>
<td>2 mg/kg/h</td>
<td>Surgical patients ProKet: NC: VMCA, MAP, HR</td>
</tr>
<tr>
<td>Nagase et al, 2001</td>
<td>15/15</td>
<td>Ket/Pro</td>
<td>40/40</td>
<td>1 mg/kg</td>
<td>Surgical patients, no cerebral compromise Ket: NC: VMCA Pro: D: VMCA ProKet: NC: Autoregulatory index</td>
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<tr>
<td>Engelhard et al, 2001</td>
<td>12/12</td>
<td>ProKet/Sevo</td>
<td>52/52</td>
<td>2.5 mg/kg/h</td>
<td>Surgical patients, no cerebral compromise</td>
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<tr>
<td>Beilin et al, 2007</td>
<td>9/10</td>
<td>Ket/C</td>
<td>39/44</td>
<td>0.15 mg/kg</td>
<td>Surgical patients, no cerebral compromise</td>
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<tr>
<td>Volunteers</td>
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<td>Takeshida et al, 1972</td>
<td>10</td>
<td>Ket</td>
<td>43</td>
<td>2 mg/kg and 1 mg/kg</td>
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<td>10/10</td>
<td>Ket/Ket</td>
<td>27</td>
<td>0.25 mg/kg/0.5 mg/kg</td>
<td>Volunteers, no cerebral compromise</td>
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<td>Vollenweider et al, 1997</td>
<td>10</td>
<td>S-Ket/R-Ket</td>
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<td>15-mg bolus and 0.84-1.2 mg/kg/h</td>
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<td>Holcomb et al, 2001</td>
<td>13/10</td>
<td>Ket/C</td>
<td>31/30</td>
<td>0.3-mg/kg bolus</td>
<td>Volunteers, no cerebral compromise Ket: I: rCBF in anterior cingulate, medial frontal, inferior frontal cortices Ket: D: rCBF in cerebellum</td>
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<tr>
<td>Langsjo et al, 2003</td>
<td>9</td>
<td>Ket</td>
<td>26</td>
<td>30/100/300 ng/mL</td>
<td>Volunteers, no cerebral compromise</td>
</tr>
</tbody>
</table>

Abbreviations: NC, no change; D, decrease; Ket, ketamine; Remifen, remifentanil; C, control; ICP, intracranial pressure; IL-6, interleukin 6; CRP, C-reactive protein; IL-10, interleukin 10; MAP, mean arterial pressure; CPP, cerebral perfusion pressure; AVDO₂, arteriovenous difference in oxygen content; VMCA, flow velocity in middle cerebral artery; Esm, esmolol; Mid, midazolam; Fen, fentanyl; HR, heart rate; Pro, propofol; Sevo, sevoflurane; S-Ket, S-ketamine; R-Ket, R-ketamine; I, increase; rCBF, regional cerebral blood flow; rCMRO₂, regional cerebral metabolic rate of oxygen; rCBV, regional cerebral blood volume; rCMRGlucose, regional cerebral metabolic rate of glucose; EEG theta, electroencephalogram theta activity; SaO₂, arterial oxygen saturation; ET-PO₂, end-tidal carbon dioxide pressure; CBF, cerebral blood flow; PaCO₂, arterial carbon dioxide pressure; CMRO₂, cerebral metabolic rate of oxygen; CMRGlucose, cerebral metabolic rate of glucose; CMRlactate, cerebral metabolic rate of lactate; O₂, superoxide anion; TNF-α, tumor necrosis factor α; Sufen, sufentanil; Dia, diazepam; FenH, fentanyl high dose; FenM, fentanyl moderate dose; Hal, halothane; Hct, hematocrit.
bind a wide variety of drugs.\textsuperscript{57} (S)-ketamine was shown to bind to the phencyclidine binding site of the NMDA receptor with a 4- to 5-fold greater affinity than the (R) enantiomer. In contrast, (R)-ketamine also had a weak affinity, whereas (S)-ketamine binds only negligibly to the sigma receptor sites.\textsuperscript{68} This observation allowed the investigators to identify the putative sigma effects of (R)-ketamine on CMRglu and mental state. Such a distinction was important because sigma receptors may modulate glutamatergic neuronal inputs or directly regulate the firing activity of dopaminergic neurons in schizophrenia.\textsuperscript{69} Hence, by modulating the glutamatergic inputs, by directly regulating the firing activity of dopaminergic neurons, or by both mechanisms, ketamine with its putative effects on the sigma receptors could affect the treatment of schizophrenia and therefore play a role in neuroprotection.

The temporal pharmacokinetic actions of racemic ketamine (0.3 mg/kg) on regional CBF were examined using positron emission tomography in volunteers.\textsuperscript{66} As observed in experimental animals, ketamine produced distinctly different temporal alterations in regional CBF in specific areas of the human brain. Ketamine increased regional CBF in the anterior cingulate, medial frontal, and inferior frontal cortices but reduced regional CBF in the cerebellum. The peak alteration in regional CBF occurred 6 to 16 minutes after administration of the drug. The trend correlations between regional CBF in selected maxima in frontal cortex/anterior cingulate and behavior suggested that these simultaneous measurements may be beneficial to link regional blood flow to function. Thus, ketamine may provide a probe to advance an understanding of psychosis from a dynamic physiologic perspective\textsuperscript{70-72} because alterations in regional blood flow change patterns may be associated with the appearance of the clinical psychotic symptoms.

Langsjo et al\textsuperscript{73} investigated the neuroprotective effects of racemic ketamine using \textsuperscript{15}O-labeled water, O\textsubscript{2}, and carbon monoxide as positron emission tomography tracers to quantify regional CBF, regional CMRO\textsubscript{2}, and regional cerebral blood volume, respectively, on selected brain regions in healthy male volunteers. Intravenous infusions of ketamine (targeted to 30, 100, and 300 ng/mL) increased regional CBF in a dose-dependent manner. Ketamine increased either absolute or relative regional CBF in the anterior cingulate, thalamus, putamen,insula, and frontal cortex. Absolute regional CMRO\textsubscript{2} was not changed; only subtle relative increases in the frontal, parietal, and occipital cortices and decreases in the cerebellum were detected. The authors concluded that subanesthetic doses of ketamine increase regional CBF but do not alter regional CMRO\textsubscript{2}, leading to a decrease in regional O\textsubscript{2} extraction. Despite the observed dissociation of CBF and CMRO\textsubscript{2}, uncoupling of cerebral blood flow and metabolism was unlikely because ketamine previously was shown to increase CMRglu. Significantly greater increases in regional CBF compared with regional CMRO\textsubscript{2} have been reported in other studies assessing the effects of focal neuronal stimulation.\textsuperscript{73,74} Indeed, alterations in regional CBF may more closely follow changes of regional CMRglu than regional CMRO\textsubscript{2}, suggesting that CBF may be regulated for purposes other than O\textsubscript{2} delivery for oxidative metabolism.\textsuperscript{74} It may be speculated that the increases in regional CBF in excess of regional CMRO\textsubscript{2} requirements may provide a reserve in O\textsubscript{2} supply for conditions with possibly compromised local blood flow. The physiologic effects of ketamine in human volunteers are summarized in Table 1.

CEREBROVASCULAR AND METABOLIC EFFECTS OF KETAMINE IN SURGICAL PATIENTS

Early studies suggested that ketamine causes parallel increases in CBF, cerebral blood volume, and CMRO\textsubscript{2}; and, as a result, may produce undesirable increases in ICP in surgical patients.\textsuperscript{75-78} Recent research disputes these long-held suppositions.\textsuperscript{79,80} Ventilation was not controlled in many older studies, and ketamine, especially when combined with propofol or midazolam, was shown to reduce ICP and CMRO\textsubscript{2} in the presence of mechanical ventilation.\textsuperscript{79} When changes in anterior fontanel pressure (a noninvasive indicator of ICP) were compared during ketamine, fentanyl, isoflurane, or halothane anesthesia in preterm neonates without neurologic disease during mechanical ventilation, ketamine caused similar reductions in anterior fontanel pressure compared with the other drugs.\textsuperscript{80} Kolenda et al\textsuperscript{81} examined the effects of ketamine on ICP and CPP in patients with moderate-to-severe head trauma randomly assigned to receive ketamine or fentanyl in combination with midazolam. In the absence of controlled ventilation, patients sedated with ketamine/midazolam required lower quantities of vasoactive drugs but also had higher ICP and CPP than those receiving fentanyl/midazolam. These results suggested that ketamine may be deleterious when used for conscious sedation in patients with intracranial trauma. In contrast, Mayberg et al\textsuperscript{78} investigated the effects of ketamine on ICP and CBF velocity in isoflurane/nitrous oxide-anesthetized, mechanically-ventilated patients undergoing craniotomy for brain tumor resection or cerebral aneurysm clipping. Ketamine (intravenous bolus of 1 mg/kg) reduced ICP, middle cerebral artery blood flow velocity, and total EEG power, but CPP, O\textsubscript{2} extraction, and arterial CO\textsubscript{2} tension were unaffected.\textsuperscript{78} Racemic ketamine (1.5, 3, or 5 mg/kg) also significantly decreased ICP in neurosurgical patients with traumatic brain injury during propofol anesthesia and mechanical ventilation.\textsuperscript{79} Again, no differences in CPP, jugular vein bulb O\textsubscript{2} saturation, and middle cerebral artery blood flow velocity were observed between ketamine- and placebo-treated patients. Bourgoin et al\textsuperscript{82} examined and compared the relative safety and efficacy of racemic ketamine and midazolam in patients with severe head injury during mechanical ventilation. Neither ketamine/midazolam nor sufentanil/midazolam altered ICP or CPP, but patients randomized to receive ketamine/midazolam required less aggressive volume resuscitation early during treatment and also showed a trend toward reduced use of vasoactive drugs to maintain arterial pressure compared with those treated with sufentanil/midazolam. Notably, ketamine/midazolam did not produce adverse effects or contribute to more pronounced morbidity or mortality. The authors concluded that ketamine/midazolam sedation compares favorably with sufentanil/midazolam in maintaining ICP and CPP in this vulnerable patient population. Nagase et al\textsuperscript{83} examined the actions of ketamine and propofol on the cerebrovascular response to CO\textsubscript{2} in mechanically ventilated patients undergoing elective surgery during isoflurane anesthesia. Middle cerebral artery blood flow velocity and pulsatility index assessed using transcranial Doppler were determined under hypo-, normo-, and hypercapnic conditions in the pres-
ence or absence of ketamine (1 mg/kg) or propofol (2 mg/kg followed by an infusion of 6-10 mg/kg/h). Ketamine, but not propofol, modestly reduced the cerebrovascular response to CO$_2$ and prevented increases in middle cerebral artery blood flow velocity during hypercapnia. Such actions may be beneficial in patients with increased ICP. Taken together, these data suggest that ketamine may exert beneficial neurologic effects in anesthetized, mechanically ventilated patients with increased ICP without causing adverse changes in cerebral hemodynamics. The physiologic effects of ketamine in surgical patients are summarized in Table 1.

**CEREBROVASCULAR AND METABOLIC EFFECTS OF KETAMINE COMBINED WITH OTHER DRUGS IN HUMANS**

The cerebral hemodynamic and metabolic effects of racemic ketamine have been shown to depend on the presence of other anesthetics. Strebel et al. investigated the actions of ketamine alone or in combination with midazolam or esmolol in mechanically ventilated patients anesthetized with isoflurane. Ketamine-induced changes in cerebral hemodynamics were measured by using transcranial Doppler ultrasound. As expected, ketamine alone increased middle cerebral artery blood flow velocity and mean arterial pressure compared with placebo. Ketamine-induced increases in middle cerebral artery blood flow velocity were unaffected when mean arterial pressure was maintained at baseline values by infusion of intravenous esmolol. In contrast, the deleterious effects of ketamine on middle cerebral artery blood flow velocity were abolished in the presence of midazolam. The results suggested that midazolam profoundly affects the cerebrovascular actions of ketamine in isoflurane-anesthetized patients. The effects of racemic ketamine/propofol anesthesia on intracerebral hemodynamics were compared with those produced by propofol alone using transcranial Doppler ultrasound. Ketamine/propofol anesthesia did not affect heart rate, mean arterial pressure, or middle cerebral artery blood flow velocity. During normocapnic conditions, middle cerebral artery blood flow velocity was lower in propofol-anesthetized patients with or without ketamine compared with the conscious state. The cerebral vascular responses to CO$_2$ in patients receiving propofol/ketamine also were similar to propofol alone. These results suggested that racemic ketamine does not adversely influence middle cerebral artery blood flow velocity or the cerebrovascular response to CO$_2$ during propofol anesthesia in patients without intracranial pathology. The effects of (S)-ketamine (2.5 mg/kg/h) and propofol (target-controlled plasma concentrations of 1.5-2.5 µg/mL) on cerebrovascular autoregulation were compared with sevoflurane (2.0 minimum alveolar concentration) in patients undergoing elective abdominal surgery. Autoregulation was maintained during (S)-ketamine/propofol anesthesia but was attenuated during the administration of sevoflurane. Thus, the addition of (S)-ketamine to propofol anesthesia does not appear to affect intracranial hemodynamics or autoregulation in surgical patients.

The effect of anesthetic techniques on neurologic outcomes in combat-related traumatic brain injury and the potential benefits of total intravenous compared with volatile anesthesia recently were described in a retrospective study. No differences in the lowest intraoperative systolic blood pressure were observed in patients receiving volatile compared with ketamine-propofol anesthesia groups. The neurologic outcome also was similar between groups. These data suggested that intravenous propofol-ketamine anesthesia was as efficacious and safe as volatile anesthesia in these severely injured patients. The results also confirmed the findings of other studies indicating that the addition of ketamine to propofol anesthesia attenuates the systemic hypotension associated with propofol alone by preserving CPP through sympathomimetic effects. The physiologic effects of ketamine in humans are summarized in Table 1.

**KETAMINE AND NEUROLOGIC IMPAIRMENT AFTER CARDIAC SURGERY**

Postoperative neurologic deterioration is common in cardiac surgical patients, especially when CPB is used. Reduced perfusion pressure during CPB places patients at risk of cerebral ischemia. Embolization of air or particulate matter during aortic cannulation or weaning from CPB may produce focal neurologic damage and neuropsychiatric complications. CPB also causes a systemic inflammatory response, which may contribute to the development of neurologic injury. This systemic inflammation may be mediated by surgical trauma, blood contact with the extracorporeal bypass circuit, and lung reperfusion injury after the discontinuation of CPB. Attenuating this inflammatory response is an important therapeutic objective and is associated with improved outcome. Pulmonary function may deteriorate significantly after CPB, and this acute lung injury also may impair cognitive performance. Acute lung injury after CPB was shown to be related to the activation of neutrophils and reductions in the body temperature during CPB. Neutrophils and the inflammatory mediators that they produce play an important role in the pathogenesis of postoperative neurologic dysfunction in cardiac surgery patients. Lung injury during and after CPB precipitates an accumulation of activated neutrophils in the pulmonary circulation with the subsequent release of toxic mediators that contribute to the injury of other vulnerable tissue, including the brain. Neutrophil elastase may be 1 such mediator of injury. Elastase is a potent protease, capable of damaging intact neurons and elevated plasma concentrations of elastase that occur in patients after CPB. Notably, the cellular response to the extracorporeal circulation was shown to be delayed after hypothermia, provoking a delayed onset of neutrophilia and elevated plasma pulmonary elastase concentrations. Thus, the adverse consequences of CPB may affect postoperative neurologic function.

Ketamine may produce neuroprotective effects in part by inhibiting this systemic inflammatory response. Zilberstein et al. showed that the administration of ketamine (0.25 mg/kg) during anesthetic induction attenuates neutrophil activation in patients after CPB as indicated by reductions in superoxide anion production and total postoperative neutrophil count. Ketamine also may favorably affect cognitive function and postsurgical inflammation after CPB. Patients undergoing CABG surgery using CPB were randomized to receive ketamine (0.25 mg/kg) or 0.9% saline solution during anesthetic induction with fentanyl. In contrast to placebo, ketamine produced a sustained suppression of increases in serum IL-6 concentrations.
through the 7th postoperative day. Notably, serum IL-6 concentrations correlated with the patient’s clinical course after surgery, implying a more beneficial outcome for patients receiving ketamine pretreatment compared with those who did not. The degree of the systemic inflammatory response has been correlated with patient outcome in cardiac surgical patients. Inflammation also occurs in the brain after off-pump coronary artery bypass graft surgery or after nonneurologic, noncardiac surgery, as indicated by increased concentrations of proinflammatory cytokines in the cerebrospinal fluid. Notably, inflammatory changes in the hippocampus may adversely affect learning, memory, and other cognitive domains. The administration of ketamine (0.25 to 0.5 mg/kg) also attenuated increases of serum C-reactive protein, IL-6, and IL-10 concentrations during and after cardiac surgery compared with placebo. The addition of a single low dose of ketamine to the other drugs used for anesthetic induction did not produce adverse hemodynamic effects during induction, intubation, incision, or sternotomy, nor did this intervention contribute to postoperative dysphoria. However, the mean arterial pressure and systemic vascular resistance remained higher at the end of surgery, upon arrival in the intensive care unit, and during the first postoperative day in patients receiving ketamine compared with those who did not receive the dissociative anesthetic. In contrast to these intriguing results with ketamine, opioids alone did not substantially affect serum C-reactive protein, IL-6, IL-8, and cortisol concentrations when used as adjuncts to an inhaled anesthetic. Quantitative EEG designed to detect postoperative neurologic injury was similar between patients receiving a ketamine-midazolam–based anesthetic compared with those receiving sufentanil anesthesia in patients undergoing cardiac surgery with CPB. These data suggested that a ketamine-midazolam anesthetic technique does not cause cerebral electrical activation or exacerbate postoperative neurologic injury. The results of this study indirectly supported earlier data by Tuman et al showing that ketamine-diazepam anesthesia was associated with decreased incidences of cerebral ischemia (assessed by EEG) and perioperative hypotension requiring vasoactive drug support compared with other anesthetic techniques.

A neuropsychologic test battery was used to examine and compare the potential neuroprotective effects of ketamine and remifentanil in patients after cardiac surgery. Ketamine improved cognitive performance in only 1 test (the Trailmaking B test, a measure of executive functions) compared with remifentanil. However, interpretation of these results was complicated because propofol, a drug with well-known potent anti-inflammatory properties, was used as a baseline anesthetic, and many young patients who are not at risk for long-term postoperative cognitive dysfunction were enrolled in the study. In contrast to the findings of Nagel et al, the authors recently showed that the administration of ketamine (0.5 mg/kg) during anesthetic induction attenuated short-term postoperative cognitive dysfunction as indicated by several neuropsychologic tests in patients anesthetized with isoflurane and fentanyl undergoing cardiac surgery. These findings were accompanied by reductions in serum C-reactive protein concentrations on the first and third postoperative days in ketamine- compared with placebo-treated patients. In this investigation, the preservation of cognitive functions concomitant with reduced C-reactive protein concentrations suggested that the neuroprotective effect of ketamine may be caused, in part, by an anti-inflammatory action of the drug. Hudetz et al also showed that the administration of ketamine (0.5 mg/kg) during anesthetic induction attenuates postoperative delirium in a similar patient population. The incidence of postoperative delirium was significantly lower in patients receiving ketamine (3%) compared with those treated with placebo (31%). Postoperative C-reactive protein concentration also was significantly lower in the ketamine-compared with placebo-treated patients, again suggesting that improvement in short-term neurocognition was related to an anti-inflammatory effect. Whether these ketamine-induced neuroprotective effects will translate into long-term benefits remains to be established, but it is clear that perioperative cognitive dysfunction is an important risk factor for long-term disability. The physiologic and neurocognitive effects of ketamine in cardiac surgical patients are summarized in Table 1.

Preoperative depression is a risk factor for postoperative delirium. Depression may be precipitated by fear of surgery and its outcome concomitant with unfamiliar environmental surroundings. Limited concentration and attention are among the most commonly reported symptoms, but impairment in recent verbal and nonverbal memory and impaired executive functions also have been found in patients with depression. NMDA-receptor antagonists may be effective for treating depression. Ketamine (0.5 mg/kg) significantly improved the symptoms of patients with depression within 72 hours after administration. Ketamine (1 mg/kg) also improved postoperative depression in patients 1 day after orthopedic surgery. Thus, alleviating depression symptoms may reduce cognitive impairment after surgery.

Postoperative delirium and postoperative cognitive dysfunction occur frequently in elderly patients undergoing cardiac surgery using CPB. Postoperative delirium often precedes and may predict the subsequent development of postoperative cognitive dysfunction. To date, few therapeutic options for the prevention of postoperative cognitive dysfunction have been shown to be effective. Postoperative cognitive dysfunction may be observed in as many as three-quarters of cardiac surgical patients at the time of hospital discharge, and these deficits may persist in one-third of patients after 6 months. Postoperative cognitive dysfunction is characterized by impaired recent memory, concentration, language comprehension, and social integration. Patients with postoperative cognitive dysfunction may experience delayed transfer from the intensive care unit after surgery, prolonged hospitalization, and a longer recovery before returning to work. These patients also may experience impaired self-care, increased dependency, increased attrition from rehabilitation, and higher rates of hospital readmission. Thus, identifying treatment interventions that reduce or eliminate postoperative cognitive dysfunction in cardiac surgical patients is an essential goal with direct clinical implications.

**CONCLUSION**

Ketamine has long been considered contraindicated in patients with brain injury, but paradoxically this dissociative anesthetic may provide beneficial effects in neurologically
impaired patients during controlled ventilation. Ketamine may exert neuroprotection because the drug inhibits the NMDA-receptor activation, mediates beneficial changes in apoptosis-regulating proteins, and interferes with the inflammatory response to injury when used in typical sedative or anesthetic doses. Cardiovascular stimulation by ketamine may also improve cerebral perfusion, and this action may be advantageous in patients after brain injury. Conversely, other laboratory investigations have suggested that ketamine may cause neurotoxicity when administered in larger doses. Intriguing recent clinical evidence has emerged, suggesting that ketamine exerts beneficial short-term actions on postoperative delirium and cognitive dysfunction in patients after cardiac surgery. Whether favorable effects also protect against long-term cognitive dysfunction is currently unknown. It is also unclear whether ketamine is capable of exerting neuroprotective effects in other groups of surgical patients who are not subjected to the stress of CPB. Thus, a clear recommendation for the clinical use of ketamine as a neuroprotective drug cannot be definitely established at present. Based on the evidence accumulated to date, an American Heart Association “class intermediate” recommendation for the use of ketamine in cardiac surgery patients is warranted. Thus, further research will be required to examine the safety, efficacy, and potential limitations of ketamine as a neuroprotective agent before the drug can be formally recommended for routine clinical use in the cardiac or noncardiac surgical setting.

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