WHAT IS THE ROLE OF KETAMINE IN PERIOPERATIVE MANAGEMENT?

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BY
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INTRODUCTION



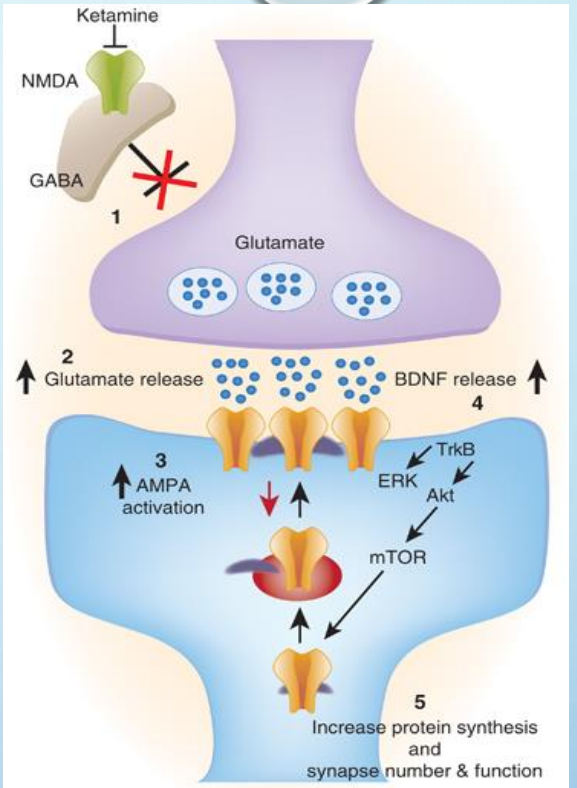
- More than 40 years ago during the Vietnam War, ketamine, a non-barbiturate phencyclidine derivative, was considered an ideal “battlefield anesthetic” because it does not alter hemodynamics and has sedative, hypnotic, analgesic, and amnestic properties.

- Its popularity warned, however, because of an undesirable side effect profile: hallucinations, delirium, lacrimation, tachycardia, and the potential for an increase in intracranial pressure (ICP) and coronary ischemia.

- Recent reports suggest that with lower doses, ketamine may not be associated with untoward effects and may reduce perioperative pain, prevent opioid-induced hyperalgesia, decrease inflammation, reduce bronchoconstriction, and improve the quality of life in a palliative care setting.



- Ketamine binds with the NMDA and sigma opioid receptors to produce intense analgesia and a state of "**dissociated anesthesia**" in which the patient appears calm, does not react to pain, and maintains airway reflexes.



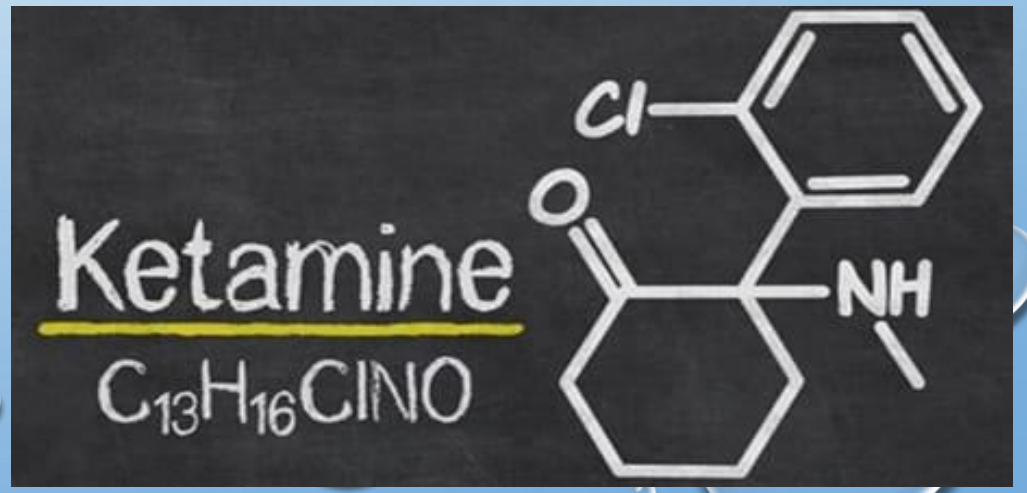
- Ketamine also interacts with nicotinic and muscarinic acetylcholine receptors, reduces neuronal sodium permeability, and blocks L-type Ca2+ channels in the muscle and myocardium.



- Ketamine possesses a chiral center and exists commonly as a mixture of S(+) and R(−) stereoisomers. S(+) ketamine has greater analgesic potency and a shorter duration of action compared with R(−) ketamine because it has a fourfold greater affinity for the NMDA receptor.

- The liver metabolizes ketamine via the cytochrome enzyme pathways into nor-ketamine, a weaker active metabolite that is excreted in the urine.





OPTIONS/THERAPIES

- (IV), (PCA), IM, sublingual, rectal, and epidural administration of ketamine achieves effective plasma levels.

- Ketamine is not currently approved for intrathecal administration because of the potential neural toxicity.



GENERAL ANESTHESIA



- Ketamine crosses the BBB rapidly and reaches maximal effect in 1 minute.
- A single dose of ketamine (2 mg/kg IV) lasts 10 to 15 minutes and the half-life elimination is 2.5 to 3 hours.
- Ketamine is used in clinical anesthesia as an induction agent to preserve hemodynamic stability, as an adjunctive anesthetic to spare opioid use, and as a sole anesthetic for painful procedures such as dressing changes.

INTENSIVE CARE UNIT



- Concerns about ketamine's psychotropic effects have limited its use as a sedative-analgesic in ICU.

- Ketamine's potential advantages include preserved HR and ABP for patients with poor cardiopulmonary reserve, antagonism of the NMDA receptor in patients experiencing short-term and repetitive pain (e.g., suctioning and turning), decreased opioid consumption, and bronchodilation for patients with status asthmaticus.

PALLIATIVE CARE



- Ketamine has been used as an analgesic and as an antidepressant in the palliative care setting.
- Reports of “burst doses” of ketamine to relieve symptoms have been published.
- Despite ketamine’s potential to relieve refractory cancer and neuropathic pain, a systematic review found insufficient evidence to evaluate ketamine’s effectiveness as an adjuvant to opioid treatment in cancer pain.

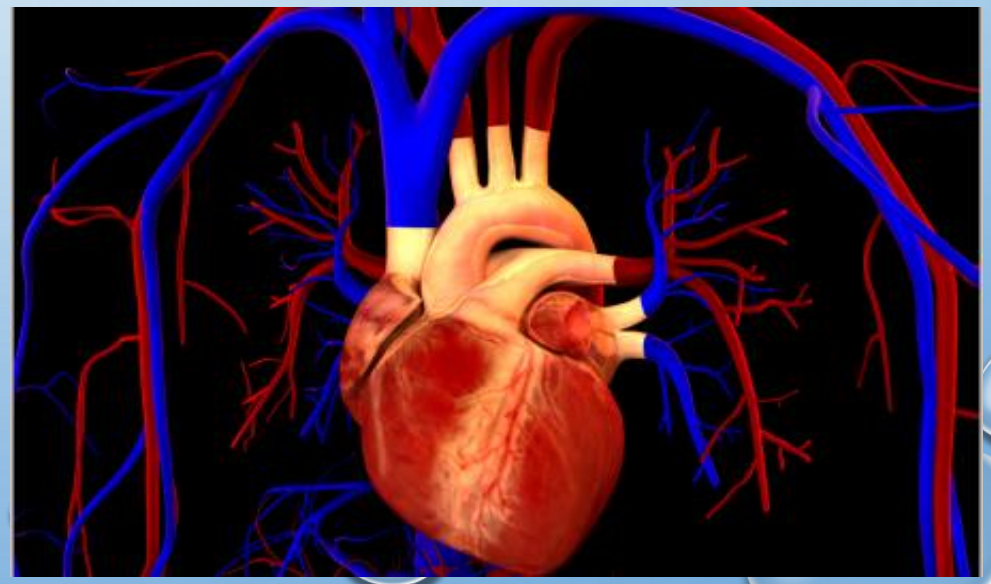
ORGAN AND PHYSIOLOGIC RESPONSES TO KETAMINE

**Cardiovascular Response:

- Ketamine acts on the heart via sympathetic-mediated stimulation and inhibition of catecholamine uptake.
- At clinical concentrations, ketamine has a positive inotropic action and induces vasoconstriction, probably by inhibiting endothelial nitric oxide production, which preserves hemodynamic stability even in septic shock.
- Ketamine may act as a myocardial depressant in patients who are catecholamine depleted.

- Its sympathetic activity can be attenuated by concomitant administration of benzodiazepines or alpha-2 agonists.

- Ketamine has been proposed as an antiarrhythmic agent and an anti-inflammatory agent because it inactivates neutrophils and suppresses cytokines.



**RESPIRATORY RESPONSE



- Ketamine causes clinically significant bronchodilation.
- Potential mechanisms include preventing reuptake of circulating catecholamines to stimulate the beta-2-adrenergic receptor, relaxation of bronchial smooth muscle via vagolysis and reduction of calcium influx, and direct antagonism of histamine.
- In contrast to other general anesthetics, ketamine preserves FRC, MV, TV and enhances thoracic compliance.

**NEUROLOGIC RESPONSE



- Ketamine increases cerebral metabolic rate and blood flow in patients breathing spontaneously.
- In patients whose lungs are mechanically ventilated, it preserves CPP without increasing ICP.
- Ketamine enhances cortical somatosensory evoked potentials and maintains or increases bi-spectral index values.
- The potential for neuroprotection against ischemic damage with ketamine is intriguing.

- During neuronal injury, the NMDA receptor is activated to release Ca^{2+} and glutamate by ischemic neurons, which initiate cell necrosis and apoptosis.
- Blockade of NMDA receptors may be therapeutic.
- Abolition of dysarthria and tremor in patients with Parkinson disease has been observed.
- Animal studies suggest that ketamine may cause neuronal cell death in newborns.

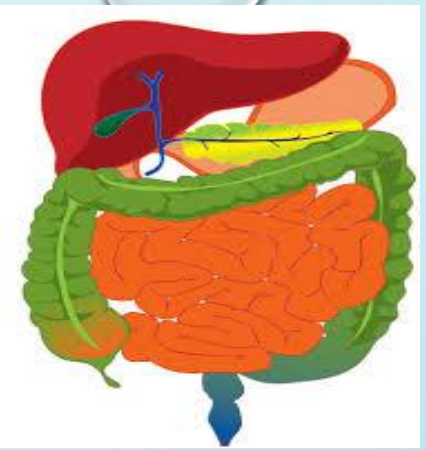
**Pain Response



- Ketamine decreases acute and chronic pain via the NMDA and opioid receptors.
- Major surgery, burns, trauma, and painful procedures in the ICU can induce prolonged noxious stimuli.
- Noxious stimuli cause central sensitization and lead to allodynia (a painful response to an innocuous stimulus), hyperalgesia (an exaggerated response to a painful stimulus), and eventually chronic pain syndromes.

- Administering short-acting opioids can result in early opioid tolerance and hyperalgesia.
- Ketamine antagonizes the NMDA receptor to block these responses, reducing windup pain and central hyper excitability.
- In both animal and human models, sub anesthetic ketamine doses prevented these effects from alfentanil, remifentanil, and fentanyl.
- Ketamine has the potential to decrease opioid requirements and tolerance and to prevent chronic pain.

**Gastrointestinal Response



- Ketamine inhibits reuptake of serotonin and may activate the chemoreceptor trigger zone to cause nausea and vomiting.

- Prolonged infusions of opioids such as fentanyl and morphine inhibit bowel function and promote constipation or even prolonged ileus.

- Ketamine does not inhibit bowel mobility and may reduce the feeding complications associated with opioids.

Evidence





Opioid Sparing



- Table 33-1 summarizes RCTs of adults receiving IV perioperative ketamine.
- Table 33-2 summarizes meta-analyses of perioperative ketamine use.
- Recent reviews suggest that ketamine spares opioid use in the perioperative period at sub anesthetic doses.
- In a meta-analysis of studies of more than 2000 patients randomly assigned to perioperative ketamine, sub anesthetic ketamine administration reduced rescue analgesic requirements, pain intensity, and 24-hour PCA morphine consumption.

- Similar findings were reported in a review of randomized trials of ketamine in surgical patients.

- In a meta-analysis of studies of IV ketamine, opioid-sparing effects were greater in procedures associated with high postoperative pain scores (e.g., upper abdominal, orthopedic, and thoracic surgery).

- Ketamine's opioid-sparing effect may not be uniform because different operations produce different stimuli for sensitization.

- The opioid-sparing effect of ketamine may be diminished in children when added to opioid-based PCA.

- In contrast to studies of adult patients, a recent meta-analysis of pediatric patients suggested that systemic ketamine reduced initial pain scores in the recovery room but did not decrease postoperative opioid requirements.

- Potential explanations for these findings include lower doses of ketamine, less painful surgeries, and lack of continuous infusions in children during the perioperative period.

- The addition of a single dose of ketamine during induction did not decrease postoperative morphine requirements in children.

- A review of studies analyzing the addition of ketamine to opioid-based PCA showed no reduction in pain scores or morphine consumption.

- Heterogeneous timing of ketamine administration and evaluation of pains scores and investigations of small patient populations limited the analysis.

TABLE 33-1 RCTs of Perioperative IV Ketamine in Adults

Author	Procedure	Size	Design	Intervention	Outcome
Lebrun et al (2006) Gillies et al (2007) McKay, Donais (2007)	Oral Mixed abdominal	*N* = 84 41 42	RPCT RDBPCT RDBPCT	Preincision versus postoperative ketamine versus placebo	No difference in total opioid consumption or pain scores
Yamauchi, Engelhardt et al (2008) Aveline et al (2009), Loftus et al (2010) Lak et al (2010)	Spine, Spine (pediatric) Orthopedic, Spine abdominal	*N* = 202, 34 75, 102 50	RPCT RDBPCT	Preincision + intraoperative ketamine versus placebo -Postop. ketamine versus placebo	Reduction of opioid consumption and pain scores
Deng et al (2009)	Orthopedic	*N* = 200	RDBPCT	Intraoperative + postoperative ketamine versus placebo	Reduction of opioid consumption and pain scores
Dullenkopf et al (2009)	Mixed	*N* = 120	RDBPCT	Preincision ketamine versus placebo	No difference in total opioid consumption or pain scores
Reza et al (2010)	Gynecologic	*N* = 60	RDBPCT	Preincision ketamine versus placebo	Reduction of opioid consumption only 0-2 hr postoperatively; no differences thereafter

***RDBPCT*, randomized double-blind placebo-controlled trial; *RPCT*, randomized placebo-controlled trial.**

TABLE 33-2 Meta-Analyses of Perioperative Ketamine

Author/ Subjects	Intervention	Outcome
Elia and Tramer (2005)/ Ketamine versus no ketamine (n = 2721) in adult and pediatric population	Perioperative ketamine (bolus/infusion/epidural/caudal/PCA) versus conventional analgesic	Reduction of total opioid consumption and decreased pain scores
Bell et al (2006)/ Ketamine versus placebo (n = 2240) in adult population	Intraoperative ketamine (bolus or infusion or epidural) versus placebo or conventional analgesic	Reduction of total opioid consumption and decreased pain scores
Bell et al (2006)/ Ketamine + opioid versus opioid only (n = 432) in adult population	Postoperative PCA with ketamine + opioid versus PCA with opioid	Reduction in opioid consumption in first 24 hr
Carstensen,Moller (2010)/ Ketamine + opioid versus opioid only (n = 887) in adult population	Postoperative PCA with ketamine + opioid versus PCA with opioid	No clear advantage of ketamine over opioid PCA except in thoracic surgery
Laskowski et al (2011)/ Ketamine versus placebo (n = 4701) in adult population	Intraoperative ketamine (bolus or infusion) versus placebo	Reduction in total opioid consumption and increased time to first opioid
Dahmani et al (2011)/ Ketamine versus no ketamine (n = 985) in pediatric population	Ketamine (systemic, local, and caudal) versus conventional analgesic	Decreased PACU pain scores and nonopioid analgesic, no opioid-sparing effect
Schnabel et al (2011)/ Ketamine + local versus local only (n = 584) in pediatric population	Intraoperative ketamine (caudal) + local versus local (caudal)	Reduction in rescue analgesic and increased time to first analgesic

PACU, post anesthesia care unit; PCA, patient-controlled analgesia.

Preventing Chronic Postsurgical Pain

- Studies examining perioperative ketamine use after thoracotomy, hysterectomy, and mastectomy with a follow-up of patients ranging from 4 weeks to 3 months did not show a benefit.

- In contrast, sub-anesthetic doses of ketamine (0.5 mg/kg followed by 0.25 mg/kg/hr) administered to patients for rectal cancer surgery decreased postsurgical pain at 2 weeks, 1 month, and 6 months postoperatively.

- This effect was not observed at lower doses (0.25 mg/kg followed by 0.125 mg/kg/hr), which suggested a dose-dependent effect.

CONTROVERSIES



**Ketamine and Premedication with Benzodiazepines

- Benzodiazepines are often co-administered with ketamine to prevent emergence agitation.

- A large meta-analysis and two RCTs studying children received ketamine in ER; found no reduction in emergence delirium with benzodiazepine administration.

- Compared with adults, children may tolerate ketamine better with low incidence of recovery reactions.

- In one small study, the addition of ketamine prevented emergence delirium in children who received sevoflurane anesthesia.

**Ketamine and Intracranial Pressure

- Clinicians have avoided ketamine in patients at risk of elevated ICP.

- Some studies have shown, however, that ketamine does not increase cerebral blood flow or ICP if CO^2 levels are controlled.

- In children with intracranial hypertension whose lungs are mechanically ventilated, ketamine decreased ICP and increased cerebral perfusion pressure.

- In combination with benzodiazepines, ketamine prevented fluctuations in ICP.

- Hemodynamic variables appear to be preserved in patients with brain or spinal cord injuries.

- These results suggest that the adequacy of sedation is more important than the choice of sedative in the management of ICP.

**Ketamine and Hemodynamic Changes

- In normotensive patients, ketamine infusions do not significantly alter hemodynamic profiles.

- Given the potential for direct negative inotropy with hemodynamic instability in a catecholamine-depleted state, avoiding ketamine as an induction agent in patients with decompensated ventricular failure or catecholamine depletion has been advised.

- As an infusion, however, ketamine may improve hemodynamic profiles in tachycardic, hypotensive, or critically ill patients.

- Although clinicians may not give ketamine to patients with coronary artery disease and hypertension, there is little evidence that increased coronary perfusion in a hyperdynamic state accompanies an increase in myocardial oxygen demand.

**Ketamine and Psychotropic Effects

- Although ketamine use is associated with mind-altering effects such as hallucinations and delirium, psychotropic effects are unlikely with sub anesthetic doses.
- The analgesic effects of ketamine occur at plasma concentrations lower than those associated with its psychotropic activity.
- Effects are likely dose dependent and attenuated by simultaneous administration of hypnotics such as propofol or midazolam.

- In a Cochrane database review of sub-anesthetic ketamine, 21 of 37 trials found no psychotropic effects.
- Another review of perioperative ketamine found 30 trials with reports of hallucinations.
- Almost all patients who experienced hallucinations were awake or sedated and had not been pre-medicated with benzodiazepines
- Risk factors for psychotomimetic effects included male sex, old age, history of psychopathology, high ketamine dosage, and rapid IV infusion.

AREAS OF UNCERTAINTY



- The lack of correlation among ketamine dosing, efficacy, and neuropsychiatric effects is problematic.
- The clinical advantage of the more potent S(+) isomer compared with the racemic mixture is not clear.
- It would be interesting to evaluate the potential dose-sparing effect of S(+) ketamine for reduction of undesirable side effects.

- Studies with long-term follow-up are necessary, especially in groups at risk of chronic postsurgical pain.

- Although ketamine has been administered to humans for decades, it is not clear whether the neurotoxic effects of ketamine observed in animals are clinically relevant in humans.



GUIDELINES



- After reviewing meta-analyses of RCTs, the ASA suggests in their Practice Guidelines for Acute Pain Management in the Perioperative Setting that the combination of morphine and ketamine is equivalent to morphine alone in terms of pain or nausea scores and analgesia (level of evidence: C).

- The 2010 German sedation guidelines recommend ketamine in burn patients for sparing of opioids and preventing secondary hyperalgesia, especially in children.

- These guidelines suggest that racemic ketamine with a gamma-aminobutyric acid receptor agonist can be used in patients with traumatic brain injury, intracranial hypertension, or both during mech. Vent. and that cerebral perfusion pressure can be maintained.



AUTHORS' RECOMMENDATIONS



What is the role of ketamine in perioperative management?

- Based on the evidence presented, ketamine is a unique sedative analgesic that may spare opioid use and prevent postoperative pain and hyperalgesia.

- Ketamine may be used safely in brain-injured patients whose lungs are mechanically ventilated and who are receiving a gamma-aminobutyric acid (GABA) antagonist.

- Although studies of ketamine for patients in ICU are sparse, sub anesthetic ketamine should be considered for managing bronchoconstriction, ensuring hemodynamic stability in patients who are not catecholamine depleted, preventing hyperalgesia, and improving quality of life in a palliative care setting.



Thank You

