



Ketamine Infusions for Pediatric Sedation and Analgesia

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Although not approved by the Food and Drug Administration for use in children younger than 16 years of age, ketamine is among the most widely used agents for procedural sedation and analgesia in pediatrics.¹⁻³ Over the past decade, ketamine infusions have also become more widely used as an adjunct to traditional opioid and benzodiazepine regimens for long-term sedation and analgesia in children. With clinical studies in children dating from 1990, there is an extensive amount of literature describing its safety and efficacy in this population.^{4,5}

Mechanism of Action

Ketamine is a rapid-acting general anesthetic with analgesic properties. It has multiple binding sites, including N-methyl-D-aspartate (NMDA), opioid, nicotinic, and muscarinic cholinergic receptors. Its primary mechanism of action is thought to be noncompetitive NMDA antagonism, blocking the effects of glutamine. While depression of the thalamocortical system at lower ketamine concentrations produces a dissociative state, administration of larger doses or continuous administration to achieve higher drug levels results in a much deeper level of sedation due to suppression of the reticular-activating and limbic systems.¹⁻³

Ketamine offers several advantages over other sedative/analgesics. In most patients, administration of ketamine results in only minimal respiratory depression with preserved or exaggerated pharyngeal and laryngeal reflexes, normal or slightly increased muscle tone, and relatively minor elevations in blood pressure, heart rate, and cardiac output. The cardiac effects associated with ketamine result from blockade of catecholamine reuptake, producing a sympathomimetic effect. Changes typically occur shortly after injection and reach a maximum within minutes. In most patients, systolic and diastolic blood pressures peak at 10% to 50% above pre-anesthetic levels and

return to baseline within 15 minutes after drug administration is completed.¹⁻³

Pharmacokinetics and Pharmacodynamics

Ketamine is available as an injection for IV or IM use, but may also be administered intraosseously, intranasally, or orally. It is widely distributed into body tissues, with higher levels in the brain, lung, liver, and body fat. It is not bound to serum proteins. Ketamine undergoes a biphasic clearance. The initial (alpha) phase includes distribution into the central nervous system (CNS) and results in the drug's anesthetic effects. The average peak concentrations of ketamine after a single dose in adults are 0.75 mcg/mL in plasma and 0.2 mcg/mL in cerebrospinal fluid (CSF). The duration of the alpha phase is approximately 45 minutes, with a half-life of 10 to 20 minutes. The anesthetic action of ketamine ends during the beta phase, as it is redistributed out of the CNS and more extensively into the peripheral tissues.^{2,3}

During redistribution, ketamine undergoes N-dealkylation to form norketamine, an active metabolite with one-third the potency of the parent compound. The usual half-life of the beta phase is 2 to 2.5 hours in adults. In addition to N-dealkylation, ketamine is metabolized via hydroxylation of the cyclohexone ring, conjugation with glucuronic acid, and dehydration. The resulting active and inactive metabolites are excreted in the urine.^{2,3} The pharmacokinetic profile of ketamine in children has been evaluated in several studies. Hartvig and colleagues evaluated 10 children receiving ketamine infusions of 1-2 mg/kg/hr for sedation and analgesia during mechanical ventilation after cardiac surgery.⁶ The authors found clearance of 0.96 L/hr/kg, similar to studies in adults, with a beta elimination half-life of 3.1 ± 1.6 hours and a norketamine half-life of 6.0 ± 1.8 hours.

Clinical Experience

Postoperative Analgesia

The effectiveness of ketamine in children has been evaluated in a number of studies. Several recent papers have examined ketamine in unique patient populations. Asadi and colleagues compared the combination of ketamine and acetaminophen versus acetaminophen alone for post-operative pain control after pediatric adenotonsillectomy.⁷ A total of 98 children between 3 and 12 years of age were enrolled in this randomized, triple-blind trial. Induction and maintenance anesthesia were the same in all patients, and each received intravenous acetaminophen at a dose of 15 mg/kg starting 15 minutes prior to the end of the case and every 6 hours afterwards for 24 hours. Patients received either ketamine 0.25 mg/kg or placebo 15 minutes before the end of the case. All patients received opioids as needed based on Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) scores. Patients in the ketamine/acetaminophen group had significantly lower pain scores at 30 minutes and 6 hours (3.4 ± 1.2 versus 4.04 ± 0.7 in the controls at 30 minutes, $p = 0.003$ and 2.98 ± 0.9 versus 3.37 ± 0.73 , $p = 0.02$ at 6 hours). The difference in pain scores at 12 hours, as well as the incidence of nausea, vomiting, and opioid use were no different. The authors concluded that low-dose ketamine was beneficial in reducing post-operative pain without adverse effects.

Use in the Intensive Care Setting

Ketamine can be a useful addition to multimodal sedative/analgesic regimens in children requiring mechanical ventilation.^{5,6,8,9} The increase in catecholamine concentrations resulting from its use produces bronchodilation at β_2 -adrenergic receptors which may be of benefit to children with bronchospasm or status asthmaticus. Although not yet studied in children, ketamine may also reduce the development of opioid tolerance or mitigate the symptoms of opioid withdrawal in infants and children given multimodal sedation and analgesia while intubated.

In the March 2016 issue of the *Annals of Pharmacotherapy*, Golding and colleagues published a review of the reports of ketamine continuous infusions for sedation or bronchospasm in children.⁸ The authors identified three studies, three case series, and five case reports in both intubated and spontaneously breathing children. A total of 74 patients were included, with 72 receiving a loading dose between 0.2 and 2 mg/kg and an infusion ranging from 0.2 to 3.6 mg/kg/hr. The higher doses were typically used in patients treated for bronchospasm. Overall, the authors of these papers reported satisfactory sedation and analgesia, improved pulmonary compliance and oxygenation, and minimal adverse effects. There

were two reports of nystagmus, one case of flushing, and one report of hypertension.

Of the papers included in this review, only two reports described the use of a ketamine infusion for sedation and analgesia during mechanical ventilation. In 1990, Tobias and colleagues described five children (7 months to 14 years of age) who received ketamine after developing adverse effects with opioids or benzodiazepines.⁵ Four of the children were receiving mechanical ventilation. The patients each received a loading dose of 0.5 to 1 mg/kg over 2-3 minutes followed by an infusion of 0.6-0.9 mg/kg/hr. The duration of infusion ranged from 48 to 96 hours. No adverse effects were attributed to ketamine use; however, one patient developed elevated liver transaminases felt by the authors to be the result of postoperative hypoperfusion. An additional case report described an 11-year-old patient with meningococcal septic shock who developed hypotension and bradycardia with midazolam at a dose of 0.18 mg/kg/hr.⁹ Ketamine was initiated at 0.24 mg/kg/hr and the midazolam infusion was decreased to 0.05 mg/kg/hr, resulting in stabilization of blood pressure. He remained on ketamine for 26 hours without adverse effects.

Use in Chronic Pain

In 2015, Sheehy and colleagues at the Children's National Health System published an intriguing longitudinal study of 63 children (median age 15 years) who received ketamine infusions for treatment of chronic pain.¹⁰ The majority of the patients (37%) were being treated for complex regional pain syndromes, with the remaining patients treated for chronic headache or fibromyalgia. The most frequent location was the lower extremities, in 35% of patients. Treatment consisted of an infusion of 0.1-0.3 mg/kg/hr administered by a nurse and anesthesiologist in a clinic setting for 4 to 8 hours per day. Treatments could be provided for a maximum of 16 hours over a 3-day period. The primary objective of the study was the change in pain scores before and after treatment. The use of oral opioids was evaluated as a secondary outcome.

A total of 277 ketamine administrations were documented over 15-month period. Ketamine produced a significant reduction in pain scores compared to baseline (mean reduction -1.6 ± 0.24 , $p < 0.001$). The reduction was most pronounced in patients with complex regional pain syndromes, compared to other diagnoses, and in patients with a history of trauma, chemotherapy-induced neuropathy, or postural orthostatic tachycardia syndrome (POTS). In 37% of the treatments, ketamine produced a 20% or greater reduction in pain scores compared to baseline. There was no significant difference in overall opioid use (mean change -0.1 ± 0.05

mg/kg/day in morphine-equivalent intake, $p = 0.3$). Ketamine was well tolerated, with no significant psychotropic or hemodynamic adverse effects. The authors concluded that ketamine infusions in the outpatient setting may be a beneficial option for patients who do not respond to or require high-dose opioid therapy.

An additional case report described a 5-year-old with acute myeloid leukemia and graft versus host disease (GVHD) who was managed with hydromorphone and a ketamine infusion for over 5 months.¹¹ The dose was gradually increased to a maximum dose of 0.54 mg/kg/hr. An attempt to reduce the dose resulted in an increase in pain scores and a return to the previous dose. Following clinical improvement, both the opioid and ketamine were gradually weaned. Mild irritability and restlessness were noted after discontinuation of both drugs, but resolved within 3 days without intervention.

Warnings and Precautions

As a result of its sympathomimetic effects, ketamine is contraindicated in patients with clinically significant underlying hypertension. Cardiovascular function should be continually measured during administration in patients with any degree of cardiac disease. Ketamine may produce respiratory depression or apnea at higher doses or with rapid administration. Due to the potential for laryngospasm, ketamine should not be used alone in cases involving the pharynx, larynx, or bronchial tree.³

Ketamine is a class III controlled substance. Prolonged use may result the development of tolerance and dependence.³ Withdrawal symptoms may occur after long-term use, but have not been well described in children.

Adverse Effects

Emergence reactions occur in approximately 5-12% of patients receiving ketamine.^{2,3} These reactions: dysphoria, agitation, anxiety, and other behavior changes, as well as hallucinations or nightmares are not correlated to patient age or dose. Most symptoms resolve quickly, but can continue for up to a week. Clinicians have traditionally administered a benzodiazepine with ketamine in an effort to reduce emergence reactions, based on an early study showing benefit. Newer research, including two controlled trials in children and a meta-analysis, have not found this to be effective and may place the patient at risk for adverse effects.¹¹ Benzodiazepines may be of benefit in children with a high level of anxiety at the time of the procedure. Emergence reactions may also be reduced if verbal and tactile stimulation is minimized; however, the effectiveness of this approach has not been well studied.

Nausea and vomiting are reported to occur in 8-25% of children given ketamine.^{3,12} Higher rates have been associated with larger doses (an initial dose ≥ 2.5 mg/kg or total dose ≥ 5 mg/kg), IM administration, use with opioids, and increasing patient age. In a study of 8,282 pediatric patients, the peak age for emesis was 12 years. Ondansetron is often effective in reducing emesis. Other commonly reported adverse effects reported with ketamine include erythema or rash, injection site pain, transient diplopia or nystagmus, and tonic clonic movements that may resemble seizures.³

Several rare but potentially life-threatening adverse effects have been associated with ketamine use, including laryngospasm, apnea, impaired cardiac function, increased intracranial pressure, and diabetes insipidus. Recent analysis of more than 8,282 children given ketamine for procedural sedation identified a 0.3% incidence of laryngospasm.¹³ There was no association with age or dose. Analysis of a case-control subset found no difference in the incidence of laryngospasm in patients given an anticholinergic (OR 0.22, 95% CI 0.02-3.2, $p = 0.269$). In contrast, concomitant benzodiazepine use resulted in a lower incidence (55% versus 38% in patients not given a benzodiazepine, OR 13.7, 95% 1.51-125, $p = 0.02$).

While most patients experience no change in cardiac function or increased function while receiving ketamine, the negative inotropic effect of ketamine on the myocardium outweighs its sympathomimetic effect in some patients. In a recent paper from Eken and colleagues, the effects of ketamine on cardiac function were measured in 22 children (mean age 3.5 ± 2.2 years) receiving procedural sedation during suturing of incisions on the face, scalp, or hand.¹⁴ Cardiac contractility was measured prior to and 10 minutes after a 1.5 mg/kg IV ketamine dose. Ejection fraction was reduced in 14 patients (63.6%), with a mean reduction of $5.6 \pm 3.1\%$. Systolic blood pressure was reduced in 10 of the 14 patients with a reduced ejection fraction. The mean decrease from baseline was -7.6 ± 10.9 mmHg. In contrast, 80% of the patients without a reduction in ejection fraction had an elevated systolic blood pressure. While the small sample size limits the conclusions which can be drawn, this paper may stimulate future research to aid in determining which children are more likely to experience adverse cardiac effects.

Ketamine has the potential to increase intracranial pressure (ICP), and it is recommended that ketamine not be used in the initial management of patients with an elevated ICP. Once stabilized, ketamine has been shown to reduce ICP and improve cerebral perfusion in both traumatic and non-traumatic brain injury.

Alternative sedatives should be used in patients with cerebrospinal shunt malfunction, meningitis, intraventricular hemorrhage, or other causes of impaired CSF circulation.^{2,3}

There are rare reports of diabetes insipidus (DI) occurring after ketamine use, including a recent case in a 2-year-old child with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and hypertrophic cardiomyopathy.¹⁵ The patient was admitted for pneumonia and subsequent respiratory failure requiring intubation. A ketamine infusion was initiated for sedation and facilitation of mechanical ventilation. The patient developed symptoms of DI shortly after ketamine was started and was successfully managed with vasopressin. The authors suggested that inhibition of glutamate produced by ketamine may prevent arginine vasopressin release from the neurohypophysis and that patients receiving ketamine infusions should have close monitoring of serum sodium and urine output prior to, during, and after infusion.

Ketamine has been shown to produce neuronal apoptosis in immature animal models and in isolated human neuronal cells. While current research with ketamine for procedural sedation has not revealed a significant risk for adverse neurologic effects, there is limited information available on the potential cognitive effects of long-term use.^{16,17} A recent study of 11 children receiving oral ketamine for chronic pain found no decline in neurocognitive testing over a 14-week period.¹⁸

Drug Interactions

Concomitant administration of CNS or respiratory depressants with ketamine may produce additive effects or a longer duration of effect. Administration of ketamine in the same IV catheter or syringe as barbiturates or diazepam may result in a precipitate.³

Availability and Dosing Recommendations

Ketamine is available in 100 mg/mL 5 mL vials and 50 mg/mL 10 mL vials. It may be diluted to a concentration of 1 or 2 mg/mL with 5% dextrose or normal saline. For perioperative use or for sedation and analgesia during mechanical ventilation, an initial loading dose of 0.5-2 mg/kg may be followed by an infusion starting at 0.5 mg/kg/min.^{3,6-10} Lower doses (0.1-0.3 mg/kg/hr) were used by Sheehy and colleagues for the treatment of chronic pain.⁹

Summary

The use of ketamine for sedation in children has grown considerably over the past decade. It is now a frequent choice for procedural sedation, and more recently has become a component of multimodal sedation/analgesic regimens in the perioperative setting and in critically ill children.

Low-dose infusions have also been studied for children with bronchospasm or chronic pain. While there are currently only a small number of papers in the medical literature, the utility of ketamine infusions and the relatively low frequency of adverse effects reported with their use may lead to more definitive treatment recommendations in the future.

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