Pediatric Anesthesia and Critical Care Journal 2023;11(2):109-115
doi:10.14587/paccj.2023.15

PACCJ

Hematuria during prolonged administration of ketamine to treat bronchospasm and respiratory failure in a toddler

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Keypoints

1. As ketamine provides both sedation and analgesia, it remains a popular agent for various clinical scenarios in infants and children including the induction of anesthesia, procedural sedation, ICU sedation, and the treatment of pain. It has also been used as a therapeutic agent in the treatment of status asthmaticus, status epilepticus, post-traumatic stress disorder, and depression.
2. In general, ketamine maintains a wide therapeutic index with a limited adverse effect profile that most commonly includes tachycardia, hypertension, sialorrhea, and emergence delirium.
3. The lower urinary tract symptoms associated with ketamine-induced cystitis closely resemble those of interstitial cystitis/bladder pain syndrome. Reports of ketamine-induced cystitis have primarily been observed in individuals who engage in chronic and repeated use or abuse of ketamine.
4. The most commonly postulated mechanism for ketamine-induced cystitis is a direct toxic effect on bladder epithelial cells from ketamine or its primary metabolite, norketamine. The definitive treatment for ketamine-induced cystitis (KIC) is the cessation and discontinuation of ketamine use.

Abstract

Given its ability to provide both sedation and analgesia, ketamine remains a popular agent for various clinical scenarios in infants and children including the induction of anesthesia, procedural sedation, ICU sedation, and the treatment of pain. Additionally, it has been used as a therapeutic agent in the treatment of status asthmaticus and status epilepticus. In general, it has a wide therapeutic index with a limited adverse effect profile that most commonly includes tachycardia, hypertension, sialorrhea, and emergence delirium. We present a 2-year-old child with a complex past medical history, including extreme prematurity and chronic lung disease including bronchopulmonary dysplasia (BPD), who developed hematuria following the prolonged administration of ketamine infusion in the ICU setting. The adverse effect profile of ketamine is reviewed, previous reports of hematuria following its use presented, and potential mechanisms of this adverse effect discussed.

Keywords

ketamine, status asthmaticus, hematuria

Introduction

Ketamine is a water-soluble phencyclidine derivative that was introduced into clinical practice in the 1960s. It largely acts as a non-competitive n-methyl-d-aspartate (NMDA) and glutamate receptor antagonist, but has several other potential mechanisms of action, which may

contribute to widespread physiologic effects and potential clinical applications.[1,2] Additional lower-affinity physiologic targets for ketamine potentially include γ-aminobutyric acid (GABA), dopamine, serotonin, opioid, and cholinergic receptors, as well as voltage-gated sodium and hyperpolarization-activated cyclic nucleotide-gated channels.[1-3] Ketamine has gained popularity in various clinical scenarios in the pediatric-aged patient due to its hypnotic, analgesic, and amnesic effects. Since first being introduced, the clinical and therapeutic uses of ketamine have grown to include anesthetic induction, procedural sedation, sedation in the ICU setting, as well as the treatment of acute and chronic pain.[4-6] It has also been used as a therapeutic agent to treat status asthmaticus and refractory status epilepticus in the ICU setting.[7,8] Catecholamine release following ketamine administration generally supports hemodynamic and respiratory function, resulting in amelioration of airway reactivity and bronchospasm.[9]

These beneficial physiologic effects are generally matched by a tolerable adverse effect profile including tachycardia, hypertension, increased salivation, and the potential for emergence delirium or agitation. We present a 2-year-old child with a complex past medical history, including extreme prematurity and chronic lung disease including bronchopulmonary dysplasia (BPD), who developed hematuria following the prolonged administration of ketamine infusion in the ICU setting during mechanical ventilation to treat severe bronchospasm related to a viral-induced BPD exacerbation. The adverse effect profile of ketamine is reviewed, previous reports of hematuria following its use presented, and potential mechanisms of this adverse effect discussed.

Case report

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). A 2-year-old child presented for laryngotracheal reconstruction. The patient had a complex past medical history that included prematurity complicated by intraventricular hemorrhage, retinopathy of prematurity and bronchopulmonary dysplasia, spastic quadriplegic cerebral palsy, tracheomalacia, tracheostomy and gastrostomy tube dependence, and multiple congenital anomalies including butterfly vertebra and duplicated kidney. Past surgical history included tracheostomy and gastrostomy tube insertion. He presented at this time for decannulation and laryngotracheal reconstruction. Medications included albuterol twice daily, fluticasone/salmeterol inhaled two puffs twice daily, sodium chloride 3% aerosol 4 mL twice daily, tobramycin aerosol 160 mg once daily, gabapentin 105 mg by mouth three times daily, diazepam 0.75 mg by mouth twice daily, and ipratropium aerosol 0.5 mg every six hours as needed. The patient was admitted the day prior to procedure for preoperative hydration and transition from oral to intravenous medications. On admission he was noted to have an elevated temperature, but was otherwise in his usual state of health without constitutional symptoms. As the temperature was brief and self-resolved, it was attributed to environmental factors (overbundling) and the decision was made to proceed with surgery as scheduled. Intraoperatively, the existing tracheostomy was removed and 1.5 cm of the trachea was resected followed by an end-to-end anastomosis. As the intraoperative course was unremarkable, his trachea was extubated in the operating room and he was admitted to the Pediatric ICU. Postoperatively, progressive respiratory failure necessitated reintubation of the trachea and mechanical ventilation. Following this, he had severe hypercarbic and hypoxemic respiratory failure with status asthmaticus. A nasopharyngeal swab was positive for human metapneumovirus and coronavirus. A preoperative tracheal aspirate culture grew *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, and methicillin-susceptible *Staphylococcus aureus*, which were treated postoperatively with trimethoprim/sulfamethoxazole and ultimately broadened to cefepime and vancomycin. Treatment for the bronchospasm and hypoxemia included continuous inhaled albuterol, inhaled ipratropium, inhaled

corticosteroids, and inhaled nitric oxide. Additionally, intravenous therapies included aminophylline, magnesium, and terbutaline. Given his recent postoperative status and the surgical anastomosis site, systemic corticosteroids were initially deferred. To maintain adequate oxygenation and ventilation, sedation (dexmedetomidine, fentanyl, and midazolam) and the administration of a neuromuscular blocking agent (cis-atracurium) were required. Given the progressive nature of the bronchospasm, ketamine was added to the bronchodilator regimen with an initial bolus dose of 1 mg/kg followed by a continuous infusion of 1 mg/kg/hr. The ketamine infusion was titrated to effect with a maximum rate of 1.5 mg/kg/hr. Despite multiple bronchodilators, including the addition of intravenous corticosteroids, severe bronchospasm persisted with the requirement for significant mechanical ventilatory support. Throughout this postoperative period, intermittent vasoactive support was provided by a continuous epinephrine infusion and fluid therapy was managed with intravenous furosemide. Nine days after the start of the continuous ketamine infusion, visible hematuria was noted. The ketamine infusion had been decreased the day prior and was subsequently titrated off when the hematuria was noted. Work-up for the hematuria included urinalysis, urine culture, urinary neutrophil gelatinase-associated lipocalin (NGAL), coagulation panel, renal ultrasound, urine chemistry, and renal function tests. Initial urinalysis was positive for large occult blood and 3,185 RBCs/mm^3. A urinalysis the day before had only 1 RBC/mm^3. Urinalysis improved to moderate occult blood and 42 RBCs/mm^3 two days later, and was normal 13 days later. NGAL was within normal limits and was unchanged on repeat evaluation 20 days later. Renal function tests including blood urea nitrogen (BUN) and creatinine remained stable. Coagulation panel was unremarkable, showing normal coagulation function. The hemoglobin remained stable, and a renal ultrasound was unremarkable. The urine culture was negative. Although the hematuria was initially attributed to inadvertent trauma due to the Foley catheter, after review of his clinical course and a literature search, it was determined that the most like etiology was the prolonged ketamine infusion. Following the episode of hematuria, his urine cleared without recurrence and ketamine was not restarted. Respiratory status significantly improved following initiation of systemic corticosteroids. The high ventilator settings and bronchodilators were weaned, allowing for discontinuation of neuromuscular blockade. Given his improvement, his trachea was extubated in the OR to high-flow nasal cannula on post-operative day (POD) 20. Unfortunately, respiratory failure ensued with upper airway obstruction and stridor, requiring emergent reintubation of the trachea and mechanical ventilation. A magnesium infusion, continuous albuterol, intermittent aerosolized ipratropium, and systemic corticosteroids were restarted to treat worsening bronchospasm. There were two subsequent failed attempts at tracheal extubation. Airway clearance was optimized and his trachea was successfully extubated to bilevel positive airway pressure (BiPAP) on POD 35. He was then weaned to room air and remained stable on room air for the remainder of the admission. Due to his protracted course necessitating sedation during tracheal intubation and mechanical ventilation, he was transitioned to oral lorazepam, methadone, and clonidine for long term weaning to prevent withdrawal. A protracted taper of systemic corticosteroids was instituted. During this time, secondary hypertension developed, which was treated with isradipine as needed. The remainder of his hospital course was unremarkable.

Discussion

Ketamine, an intravenous anesthetic agent, is a phencyclidine derivative that was introduced into the clinical practice of medicine in the 1960's.[10] Ketamine contains a chiral carbon in its chemical structure and is clinically available as either the racemic mixture of the two optical isomers [S(+) and R(-)] or the isolated isomer [S(+)]. Metabolism occurs primarily by hepatic N-methylation to norketamine, which is further metabolized via hydroxylation pathways with subsequent urinary excretion. Norketamine retains

approximately one-third of the analgesic and sedative properties of the parent compound. A unique clinical feature of ketamine is that it produces dissociative anesthesia which refers to a state in which patients may keep their eyes open and yet are amnestic and unresponsive to painful stimuli. Beneficial properties of ketamine include preservation of cardiovascular function in most clinical scenarios, limited effects on respiratory mechanics, and maintenance of central control of ventilation in the majority of patients. The hemodynamic effects of ketamine are mediated indirectly through the sympathetic nervous system and the release of endogenous catecholamines.[11] This effect also accounts for the bronchodilatory properties related to ketamine. The indirect sympathomimetic effects resulting from endogenous catecholamine release generally overshadow any direct negative inotropic properties; however, hypotension and even cardiovascular collapse may occur in patients with diminished myocardial contractility when the endogenous catecholamine stores have been depleted by chronic illness or co-morbid conditions. Another adverse effect of ketamine on hemodynamic function is increased pulmonary vascular resistance (PVR). Although early studies suggested an elevation of PVR, most recently studies with control of ventilation and $PaCO_2$ have demonstrated no effect on PVR.[14-16]

An additional area of controversy surrounding ketamine is its effects on intracerebral dynamics with early studies suggesting that ketamine increased cerebral blood flow (CBF) and intracranial pressure (ICP). As with studies evaluating its effects on PVR, when ventilation and $PaCO_2$ are controlled, the effects of ketamine on CBF and ICP are minimal.[17-19] Likewise, although initially thought to be contraindicated in patients with seizures, ketamine is now a frequently used therapeutic agent for patients with refractory status epilepticus that have failed to respond to first line agents.[20,21] With everyday clinical use, the adverse effect of ketamine that raises the most concern tends to be its potential to cause emergence phenomena or hallucinations. Emergence phenomena result from the alteration of auditory and visual relays in the inferior colliculus and the medial geniculate nucleus leading to the misinterpretation of visual and auditory stimuli.[22] These are generally managed by the co-administration of ketamine with a benzodiazepine. A final concern with the clinical use of ketamine is that it is commercially available in three different concentrations (100 mg/mL, 50 mg/mL and 10 mg/mL), and therefore dosing errors (inadvertent over or underdosing) may occur due to errors in medication dilution and dose calculation. The 100 mg/mL concentration is generally used for intramuscular or oral administration to minimize the volume required while the 10 mg/mL concentration is frequently used for the small incremental intravenous doses needed for procedural sedation.

While the adverse respiratory, cardiovascular, and CNS effects of ketamine are well documented, its potential impact on the genitourinary system has more recently been noted. In 2007, Shahani et al. reported a first case series of ketamine-induced cystitis (KIC), coinciding with the growing popularity of ketamine as a street drug.[23] The lower urinary tract symptoms associated with ketamine-induced cystitis closely resemble those of interstitial cystitis/bladder pain syndrome (IC/BPS).[24] These symptoms include suprapubic pain, urgency, polyuria, dysuria, nocturia, and hematuria which is often accompanied by ulcerative cystitis.[25] Previous reports of ketamine-induced cystitis have primarily been observed in individuals who engage in chronic and repeated use or abuse of ketamine. However, there have also been case reports in which patients present with onset of lower urinary symptoms coinciding with the initiation of ketamine use as a recreational drug.[23] The severity of lower urinary tract symptoms in these individuals are positively correlated with dose, frequency, and duration of use.[24,26] However, we are not aware of previous reports of these effects in the ICU setting.

The initial investigative approach when evaluating hematuria focuses on the exclusion of alternative causes, such as inadvertent trauma from the Foley catheter, infection, glomerular disease, or renal bleeding. Preliminary work-up should include a comprehensive urinalysis and urine culture. Typically, these will demonstrate sterile pyuria, but in

patients with associated ulcerative cystitis, urinalysis may also show gross hematuria.[23,27] Additional diagnostic modalities include evaluation of coagulation function, cystoscopy, renal ultrasound, and retrograde pyelography. With KIC, cystoscopy reveals varying degrees of bladder epithelial inflammation and neovascularization, with severe cases exhibiting petechial hemorrhages and mucosal ulcers.[27] Biopsies of the bladder demonstrate pathological alterations characterized by epithelial denudation, ulceration, and inflammation, accompanied by infiltrates comprising eosinophils, lymphocytes, and plasma cells.[28] Renal ultrasound typically reveals unilateral or bilateral hydronephrosis upon initial assessment, while signs of papillary necrosis have also been reported.[27] Retrograde pyelogram, which is less commonly performed, can also demonstrate hydronephrosis. Urodynamic studies reveal a notable reduction in urinary bladder capacity and hyperactivity of detrusor muscles, which in some patients can result in urge incontinence.[28]

Since the initial report, there has been further documentation of significant upper and lower urinary tract complications associated with ketamine use including epithelial bladder damage, diminished bladder storage capacity with increased pressure, ureteral stenosis, impairment of kidney function, and even kidney failure.[25] Despite the growing prevalence of ketamine-induced cystitis and its associated complications, the precise pathophysiological mechanism remains incompletely understood, although several potential theories have been proposed. Most theories highlight a direct toxic effect of ketamine and its active metabolite, norketamine on urothelial cells.[29] Additionally, alternative pathophysiological mechanisms have been proposed, including the activation of inflammatory cells, disruption of the bladder-urothelial barrier, dysregulation of neurotransmission, cell apoptosis, and induction of oxidative stress.[28] However, further research is needed to establish a comprehensive understanding of the underlying processes contributing to ketamine-induced cystitis and its associated urinary tract complications.

The definitive treatment for ketamine-induced cystitis (KIC) is the cessation and discontinuation of ketamine use. This remains the primary and most effective approach in managing KIC, with the degree of success contingent upon the severity and duration of ketamine use.[29] Due to its varying effect, several additional treatment regimens have been developed to help alleviate symptoms and enhance the quality of life for affected individuals.[28] Following ketamine cessation, the next step in the treatment plan involves oral pharmacologic interventions. These may include nonsteroidal anti-inflammatory agents (NSAIDs), selective cyclooxygenase-2 (COX-II) inhibitors, corticosteroids, anticholinergic agents, as well as other analgesics such as paracetamol and phenazopyridine, aimed at relieving bladder pain and discomfort.[29] In cases where pharmacologic interventions fail to yield satisfactory results, intravesical treatments are often recommended. These treatments may involve the administration of substances such as hyaluronic acid, botulinum toxin, chondroitin sulfate, and platelet-rich plasma directly into the bladder.[25,29] Surgical interventions are considered as a last resort and are reserved for patients who do not respond to other treatment options.[29]

In our patient's case, hematuria was observed on the ninth day of a continuous ketamine infusion, administered for the treatment of bronchospasm. Ketamine was promptly discontinued and hematuria resolved. A comprehensive hematuria work-up was conducted, which involved urinalysis, urine culture, NGAL assessment, coagulation panel, renal ultrasound, urine chemistry, and renal function tests. No other underlying causes of hematuria were identified during this investigation. Given the rapid improvement of symptoms following ketamine discontinuation and the absence of adverse effects on follow-up renal function tests and renal ultrasound, further evaluation such as cystoscopy and biopsy were deemed unnecessary.

The increasing popularity of ketamine in various clinical contexts, including its therapeutic use in treating severe bronchospasm, as observed in our patient's case, highlights the importance of vigilant monitoring during prolonged or repeated exposure. It is essential to consider the

potential for ketamine-induced urinary complications, particularly ketamine cystitis, especially if hematuria develops. Health care providers should remain mindful of the possible dose-dependent relationship between ketamine use and urinary tract symptoms and should exercise caution when combining ketamine with other medications, particularly opioids, as this may exacerbate lower urinary tract symptoms.[24] Routine and systematic assessment of renal function and urinalysis during ketamine therapy is suggested to allow for early identification of this adverse effect. In the presence of hematuria or clinical symptoms (pain, dysuria, urgency), there should be consideration of discontinuing ketamine therapy.

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