Clinical Uses of Ketamine in Children: A Narrative Review

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Abstract

Ketamine is a phencyclidine derivative that acts as a noncompetitive N-methyl-D-aspartate as well as a glutamate receptor antagonist. It also has other minor mechanisms that contribute to its extensive drug profile. Ketamine is a bronchodilator and maintains normal airway reflexes and, thus, permits spontaneous respiration. This, coupled with the fact that it produces potent analgesia, makes it highly suitable for children.

Despite its many merits, the drug’s side effects, along with its cultural image of being a drug of abuse, a drug used in veterinary medicine, or a “date-rape drug” have sullied its reputation within the armamentarium of medicine. Even though it is widely used in developing countries, its use in Western nations has diminished. We have strived to explore the various clinical uses of ketamine in children through this article. In addition, the article also highlights how some of the fears associated with using the drug are unfounded and provides ways by which the drug’s side effects can be prevented and managed.

Introduction And Background

Ketamine has been used extensively as an intravenous (IV) anesthetic agent for the past 65 years [1]. When given as IV, ketamine produces dissociative anesthesia, a trance-like state characterized by catatonia, catalepsy, analgesia, and amnesia. The patient’s eyes remain open with intact corneal and light reflexes during the procedure. The drug also keeps the pharyngeal and laryngeal reflexes preserved, due to which the risk of airway obstruction is minimum. There is a feeling of being detached from the surroundings, with distortion of visual and auditory stimuli [2]. Ketamine has a unique pharmacological profile due to its action on multiple molecular targets in the central nervous system (CNS). Its antagonism at the N-methyl-D-aspartate (NMDA) receptors is largely responsible for dissociative anesthesia and its potential neuroprotective effect [3]. However, the drug’s unique and varied pharmacological profile cannot be explained with this mechanism alone. Its action on the opiate receptors produces rapid and profound analgesia, while its action on monoaminergic, cholinergic, nicotinic, and muscarinic receptors is responsible for its hypnotic and psychic effects [4]. Peripherally, ketamine has a sympathomimetic action and increases blood pressure (BP) and heart rate (HR), a quality that is extremely valuable in the emergency setting for patients who are hypotensive or in shock [4]. It can be administered via almost any route, including IV, intramuscular (IM), oral, and intranasal, although the first two are the most popular [2].

Ketamine has a distinctive role for the pediatric population and has several advantages over other anesthetics. It is the drug of choice for children with congenital heart diseases (CHD) with a right to left shunt because of its beneficial cardiovascular effects [5]. It is used extensively in head and neck surgeries, including dental procedures and cleft palate repair operations [5]. Since ketamine preserves the airway reflexes and is a bronchodilator, it is extremely useful for anesthetizing patients with reactive airway disease [6]. In addition, the drug has several non-anesthetic uses in clinical practice. Ketamine can be used as an analgesic for managing postoperative pain. It has also proven to be an excellent drug for the treatment of chronic pain. It is used as a rapid sedative-analgesic to aid in short and painful procedures in the emergency department [5]. It is also used for burns dressings and wound care [7]. Newer research has concluded that ketamine has efficacy in managing treatment-resistant depression, bipolar depression, and post-traumatic stress disorder (PTSD) [8].

Despite being a drug with excellent safety and efficacy, ketamine suffers from a deep stigma in society for being a drug used in veterinary medicine and for having abuse potential, which has limited its use in developed countries [5]. Many physicians continue to be wary of using the drug in clinical practice due to misinformation about its risks and complications. Many newer studies have suggested that most of these fears are largely unfounded [9]. On the other hand, the drug’s abuse potential and its reinforcing effects have
made it challenging to use it to treat psychiatric disorders [10].

This article aims to highlight the many uses of ketamine in the pediatric population while dispelling the false risks that are often associated with the drug. It also aims to shed light on the challenges that currently limit the usage of the drug and suggest ways in which clinicians can overcome them.

**Review**

**Brief history of ketamine**

Ketamine was synthesized from phencyclidine to overcome the parent drug’s hallucinogenic side effects and abuse potential. Its first use in humans was on August 3, 1964, when it was administered to volunteer prisoners at the Jackson Prison in Michigan, United States, by Domino et al. [11]. Initially, it only produced an out-of-body experience in the subject, but on increasing the dose, a state of general anesthesia was produced [1]. The volunteers described the experience as “floating in outer space with no sensations in their arms and legs.” This was termed “dissociative anesthesia,” a term that is still used to describe the effects of ketamine. Dissociative anesthesia was later described as an electrophysiological and functional disconnect (or “dissociation”) between the thalamocortical and limbic areas of the brain [12]. Parke-Davies patented ketamine for human and animal use in 1966. In 1969, it became available on prescription as ketamine hydrochloride, with the United States Food and Drug Administration (FDA) officially approving it for human use in 1970 [1].

When it was first introduced, ketamine was deemed an ideal and complete anesthetic since it fulfilled all the requirements for surgical anesthesia, i.e., blocked sensory, motor, autonomic, and cognitive functions [13]. However, just like its parent molecule, ketamine too produced an emergence phenomenon in the postoperative period, a state in which the patient experiences vivid dreams and could become extremely irritable and agitated. This was found to be more common in adults than children. This side effect led to a decline in the drug’s popularity among anesthesiologists [9].

However, a study of prospective data collection records conducted by Treston et al. suggested that this emergence delirium occurs in only 2.1% of children, with 39% experiencing pleasant altered perceptions. Also, none of the children in the study required any active treatment for it, and none experienced any long-term effects of this experience in the form of nightmares [14].

**Pharmacokinetics**

**Administration**

Ketamine is soluble in water as well as lipids. Thus, it can be given via almost any route, including IV, IM, subcutaneous, inhaled, oral, intrarectal, or epidural, with the first two being the most popular [1]. Recently, intranasal and sublingual formulations of ketamine have been developed, with the former providing rapid absorption and high bioavailability. Rectal administration of ketamine is a good alternative to the IV route for obtaining analgesia in children in cases where an IV route cannot be established [3,15].

**Absorption**

The drug has a transfer half-life of less than a minute with the IV route. The bioavailability is 90% by IM route, 77% by epidural, 50% by intranasal, 25% by intrarectal, and 20% by oral route (due to first-pass metabolism in the liver). IM absorption is faster in children due to lower muscle mass and higher perfusion at the site [3,16].

**Distribution**

Ketamine is highly lipid-soluble and has only 20-50% protein binding, showing more affinity for $\alpha_1$-acid glycoprotein than albumin. As a result, it has a very large volume of distribution (3–5 L/kg). It crosses the blood-brain barrier rapidly to induce anesthesia. Redistribution of the drug from the brain to the other tissues and plasma is responsible for the termination of anesthesia [1].

**Metabolism**

Ketamine undergoes extensive metabolism by the hepatic microsomal enzymes. It is demethylated to form norketamine by CYP3A4. Norketamine is the major metabolite and has some anesthetic effect, along with the psychoactive properties of ketamine. Animal studies have suggested that it crosses the blood-brain barrier and has one-fifth to one-third the potency of ketamine [17]. Studies suggest that the activity of CYP3A4 is greater in infants and children than in adults, the most dramatic differences being during the first six months of life. This difference can be a major influence on the rates of metabolism seen in children versus the ones seen in adults [18]. Ketamine also exhibits self-induction by inducing the enzymes responsible for its metabolism. This can lead to the development of drug tolerance with chronic
administration. Ketamine and norketamine are hydroxylated to form glucuronide derivatives that are highly water-soluble and easily excreted [3].

Elimination

The plasma clearance in children is around 16.8 ml/kg/min. The elimination half-life is shorter (100 minutes) than that of adults. In the first three months of life, however, the plasma clearance is shorter due to decreased metabolic capacity of the liver. The median value for the elimination half-life of per-rectal ketamine (5.15 h) is considerably longer than that reported after IV and IM administration of the drug (0.8-1 h) to pediatric patients. In urine, 80% of ketamine is excreted as glucuronic acid conjugates, 16% as dehydronorketamine, and 2% in the unchanged form [1].

Malinovsky et al. conducted a study to understand the pharmacokinetics of ketamine in children. Thirty-two children aged 2-9 years and falling in the weight range of 10-30 kg who were undergoing a minor urological surgery were selected [16]. They were divided into groups and administered ketamine via three different routes: IV, intranasal, and intrarectal. The first group received 3 mg/kg ketamine IV, the second received 3 mg/kg ketamine intranasally, and the third received 9 mg/kg ketamine intrarectally through a short rectal cannula. The plasma values of ketamine and norketamine were measured using gas-liquid chromatography. The peak plasma concentration with intranasal administration appeared after 20 minutes, while it appeared after 42 minutes with intrarectal administration. It was found that the calculated bioavailability was 0.50 with intranasal administration and 0.25 with intrarectal administration [16].

Clinical applications in the pediatric population

Ketamine holds a unique and invaluable position in pediatric anesthetics, having regained its popularity in the prehospital, emergency department, and operation room setting in the last decade. Its advantages as an anesthetic lie in the fact that it preserves respiratory drive and does not lead to hypotension.

Anesthetic Uses

Ketamine is used for the induction and maintenance of anesthesia for various operations. It remains a mainstay of anesthesia in several developing countries due to its rapid induction and safety profile. Even though some newer anesthetics have replaced its use nowadays, it remains the drug of choice in pediatric anesthesia for children with a difficult airway, reactive airway disease, and uncooperative children who require IV access [6].

Ketamine is an ideal prehospital anesthetic agent since it produces rapid and predictable anesthesia while maintaining hemodynamic stability and respiratory reflexes. Additionally, the drug has a versatile therapeutic profile, produces potent analgesia and sedation, and has a good safety profile. It has the distinct advantage of providing cardiovascular stability due to its sympathomimetic effect, which compensates for its direct negative inotropic action on an isolated heart. It increases the HR, BP, and cardiac output but relaxes bronchial smooth muscles [4]. This makes the drug effective for patients in shock, hypotensive patients, and ones with respiratory or cardiac problems. A randomized control trial by Jabre et al. claimed that it can be used as an effective and safe alternative to etomidate for rapid endotracheal intubation in acutely ill patients and should be considered for sepsis [19]. Ketamine is the only intravenous anesthetic that increases the mean arterial pressure without compromising the cardiac output. In addition, experimental and clinical studies have shown that it has anti-inflammatory properties and inhibits the release of proinflammatory cytokines like interleukin-6 and tumor necrosis factor-alpha [20].

There is also evidence that ketamine can be used for head trauma because of its neuroprotective effects against cerebral ischemia [21]. Prospective studies pertaining to 55 pediatric patients concluded that contrary to popular belief that ketamine increases the intracranial pressure (ICP), a bolus dose of the drug actually significantly decreased the ICP while increasing the cerebral perfusion and mean arterial pressure [22]. However, Hill et al. deduced that there was no difference in mortality between pediatric patients who were administered ketamine for head trauma in the prehospital setting from those who were not administered the drug [23]. Ketamine is considered useful for patients with cardiac tamponade due to trauma since the drug does not have a deleterious effect on afterload and maintains perfusion to the vital organs [24,25]. In addition, the drug shows its effect within minutes and can be used to restrain and anesthetize uncooperative patients, including children with intellectual deficits [5,26].

Ketamine is widely used as a field anesthetic, especially in under-resourced areas. The United States army used it during the Vietnam war [27]. During the 2005 earthquake in Northern Pakistan, a total of 149 patients received emergency surgery in Kashmir using ketamine anesthesia with benzodiazepine premedication [28]. Due to the absence of anesthesia machines and ventilators during the 2010 earthquake in Haiti, ketamine was utilized as a general anesthetic [29]. It was also deemed the anesthetic of choice by the 25-member Australian medical team in Banda Aceh, Indonesia, for the victims of the 2004 Boxing Day tsunami [30]. Ketamine was used on 164 awake non-trapped pediatric patients with blunt trauma by London Hospital medical service and was found to be highly efficacious and safe [31]. Since it also minimizes the
decrease in core temperature, which usually occurs with anesthesia, it could theoretically benefit hypothermic patients. But this particular use has not been extensively studied [52].

In the operating room, it is used as a premedication, regional anesthetic, general anesthetic, and adjunct to other general anesthetics. Ketamine is used for induction in children because of its rapid onset of action. Different routes can be used for this, including IV, IM, oral, and intranasal. It allows preoperative anxiety in children and improves their cooperation during procedures [33]. A study by Cossovel et al. suggested that the combination of intranasal dexmedetomidine in the dose of 2μg/kg and oral ketamine in the dose of 3mg/kg can help in satisfactory separation of the child from the caretaker, allow better success rates of venous cannulation, and smooth induction of general anesthesia [34]. According to Darlong et al., the combination of 3 mg/kg oral ketamine and 0.25 mg/kg midazolam has minimal side effects and allows rapid induction of anesthesia when compared to using either of the drugs alone [53].

Ketamine in the concentration of 0.5 and 0.3% produces adequate intravenous regional anesthesia. Caudally administered ketamine can be combined with a local anesthetic to provide prolonged postoperative analgesia and fewer side effects relative to using the local anesthetic alone [36]. In inguinal herniotomy procedures, ketamine added to bupivacaine provided longer analgesia than when the latter was used alone. Cook et al. demonstrated that the combination of ketamine in the dose of 0.5 mg/kg with bupivacaine provided longer-lasting postoperative anesthesia after orchidopexy than the combination of clonidine in the dose of 2μg/kg or epinephrine in the dose of 5μg/kg with bupivacaine [37]. Hence, caudal blocks under basal ketamine are widely used for abdominal and lower limb surgeries, especially for uncooperative children. Intravenous ketamine in the dose of 0.5 mg/kg can be given prophylactically before neuraxial block to decrease the incidence of shivering, improve analgesia, and prevent the recall of the surgical events [38]. It can also be combined with regional anesthetics for ocular surgeries in children [59].

Ketamine is the general anesthetic of choice for children with congenital heart diseases (CHD) with a right to left shunt, like the tetralogy of Fallot, because of its beneficial cardiovascular effects [40]. It increases the systemic vascular resistance, decreasing the venous return and, hence, decreases the shunting of blood in the heart [41]. It is used widely for head and neck surgeries like tonsillectomies, cleft palate repair operations, and dental procedures [42-44]. Studies suggest that it can be used in surgeries for traumatic brain injuries with increased intracranial pressure (ICP) since it decreases ICP without decreasing the systemic BP and cerebral perfusion [22]. It is also the agent of choice for induction in children with reactive airway disease and difficult airways because of its broncho-dilating effect [6]. When ketamine is used as a co-induction agent with propofol, midazolam, or dexmedetomidine, it provides the benefits of hemodynamic stability, reduced pain on injection, and less respiration depression [54,55].

Non-Anesthetic Uses

Ketamine has several uses outside of its value as an anesthetic agent. These uses are attributed to its interaction with NMDA, opioid, cholinergic, monoaminergic, purinergic, and adrenergic receptors [1].

Its analgesic effect is due to its action on opioid receptors as well as its propensity to decrease nociceptive stimuli [5]. Ketamine is an ideal drug for prehospital analgesia since it provides potent pain relief without jeopardizing the speaking capacity of the patient. It can be used as an analgesic for amputations, burns, and fracture reduction in the field. A combination of 40 mg of IV ketamine with 5 mg of IV morphine has proven to be more beneficial than using the latter alone. It can also be used as an analgesic while extracting a trapped patient in the case of disasters [45].

The sedative-hypnotic effect of ketamine is due to the antagonism of NMDA receptors and hyperpolarization-activated cation channels. Thus, the combination of ketamine and propofol mixed in the same syringe (called "ketofol") is used widely for procedural sedation in infants and children [46]. This combination is advantageous because ketamine prevents hypotension associated with propofol, while propofol mitigates agitation and nausea associated with ketamine. It can be used for short and painful procedures like cardiac catheterization, radio studies, dressing changes, foreign body removal, laceration repair, fracture reduction, abscess drainage, emergency cardioversion, amputations, and chest tube insertion, especially in children who are uncooperative or have intellectual deficits [47-50]. It can also be used for long-term sedation in children with retinoblastoma [51]. Ketamine is used as a sedative-analgesic for attacks of severe acute respiratory distress syndrome (ARDS). It can also be used for sedation during hyper-cyanotic spells in children with tetralogy of Fallot [52].

Neaver case reports and systemic reviews have illustrated that ketamine is a wonder drug for acute and chronic pain. Its action on NMDA receptors and its anti-inflammatory effect make it an excellent drug for postoperative pain relief. When combined with other drugs like propofol, it prolongs the postoperative analgesia. Intranasal ketamine can be used to provide postoperative analgesia after endoscopic nasal surgery [53]. Ketamine spray can be used in the tonsillar fossa to numb the area after a tonsillectomy [54]. Clinical trials have suggested that ketamine can be combined with opioids to reduce pain sores. This ketamine-opioid combination reduces the amount of morphine required to maintain the same level of analgesia [55]. It is also efficacious for postoperative pain relief after surgery for scoliosis in adolescents, as shown by a
Ketamine can also be utilized for chronic pain disorders, especially ones with a neuropathic component, like ischemic limb pain, phantom limb, neuropathic pain, fibromyalgia, complex regional pain syndrome (CRPS) type I, irritable bowel syndrome, and even migraine. An IV infusion of ketamine in the dose of 0.1 to 0.3 mg/kg/hour given over four to eight hours per day for 16 hours for three consecutive days has shown to significantly decrease the intensity of pain in adolescents and children with chronic pain, with the most benefit being seen in CRPS [58]. However, its use as an IV infusion or topical cream is mostly restricted to treatment-resistant neuropathic pain due to the lack of research. The drug has also shown efficacy in cancer pain, especially when used as an adjunct to opioids. Several randomized control trials have suggested the benefit of ketamine in opioid refractory cancer pain [59]. The drug is now on the World Health Organization (WHO) list of essential drugs for patients resistant to opioids or who have predictable breakthrough pains. Additionally, its NMDA blocking mechanism is theorized to have an anti-tumor effect [60].

Ketamine provides pain relief during dressing, excision, and grafting for burns and is safe and well-tolerated in children. It can be given by IM route in patients with severe burns in whom establishing a venous line is difficult [61,62].

New studies have shown that ketamine, particularly its esketamine (S-ketamine) enantiomer, is efficacious in major depressive disorder, post-traumatic stress disorder (PTSD), anxiety disorders, and bipolar depression [8]. A trial concluded that IV infusion of ketamine had higher remission rates and clinical response compared to a placebo [63]. It significantly improved the depression score in 127 cases of major depression in another trial [64]. A double-blinded clinical trial was conducted by Dwyer et al. to check the efficacy of ketamine on adolescents in the age group of 13 to 17 years who were diagnosed with major depressive disorder. The participants had previously tried at least one antidepressant drug and had a score of >40 on the Children’s Depression Rating Scale-Revised. The trial found that ketamine was well tolerated by the patients and showed significant short-term efficacy lasting for two weeks in comparison to a placebo [65].

A retrospective review has shown that the use of long-term oral ketamine in patients with PTSD reduced hospital admissions by 65% and in-patient hospital stays by 70% [8,66]. A double-blinded trial with 12 patients having treatment-resistant generalized anxiety disorder and social anxiety disorder elucidated that the administration of ketamine improved the anxiety rating of the participants within an hour, with the effects lasting for up to one week [67,68]. A study also showed that using S-ketamine during electroconvulsive therapy reduced the number of sessions needed, produced lower depression scores, and improved cognitive ratings [69]. It has also been claimed that ketamine could be used for autism spectrum disorders. A 2006 case report concluded that ketamine produced a substantial but short-lived remission of the core symptoms of autism in a patient with severe intellectual disability [70].

Ketamine has a promising role in refractory status epilepticus, which occurs in 30% of cases of status epilepticus. Ketamine is used in the mean dose of 40 μg/kg/min for children and has proved to be quite effective in terminating the seizure [71].

Some lesser-known uses of ketamine include its use for treating postoperative sore throat when administered in the form of a gargle and its use in acute porphyria [72,73]. Although, the latter is considered controversial.

**Procedure for anesthesia with ketamine**

*Preoperative Preparation*

The details of the surgical procedure and its complications must be explained to the parent or caretaker, and informed consent must be obtained from them. The child’s baseline vitals, including HR, BP, respiratory rate (RR), temperature, and oxygen saturation must be recorded. The risk of unpleasant postoperative complications can be minimized by building a good rapport with the child. Some distraction techniques like toys or music can be used to take the child’s mind off the procedure [74]. If ketamine is supposed to be applied topically, it should be done at least 45 minutes prior to the operation since the drug takes time to get absorbed through the skin [75].

*Administration*

The drug route is selected based on the procedure and on whether IV access is available or not. IV route is the most widely used since it allows for the quickest recovery. An initial dose of 1 to 1.5 mg/kg is administered over one to two minutes before the procedure. Subsequent doses of 0.25–0.5 mg/kg can be given every 10 minutes (maximum 4.5 mg/kg) if they are required. However, doses more than 2.5 mg/kg are associated with adverse events like hemodynamic instability. Hence, if higher doses are required, the anesthesiologist must consider alternatives to ketamine like midazolam and propofol [76].
The IM route may be used if IV access cannot be obtained, for example in a severely dehydrated child. An initial dose of 4 mg/kg (maximum being 6 mg/kg) is given, followed by doses of 2 mg/kg repeated every 10 minutes (if required). The IM route is handy in remote areas or emergencies where sophisticated equipment is not available [77].

Oral ketamine can be used as a pre-anesthetic medication. The taste of the oral solution of ketamine in children can be masked by using sour cherry juice or cola-flavored drinks. A study by Gutstein et al. has suggested that administering oral ketamine with flavored fluids before induction of general anesthesia does not increase the risk of aspiration, and is thus safe for children who refuse to accept oral ketamine because of its unpalatable taste [33]. Orally, ketamine is generally given in the dose of 6 mg/kg. This dose provides adequate and predictable sedation. It allows calm separation of the child from the parent or caretaker and is associated with minimal side effects. Table 1 discusses the routes of administration of ketamine.

| Study                      | Route of administration | Time taken for onset of anesthesia | Time taken for termination of anesthesia | Dose                                      |
|----------------------------|-------------------------|-----------------------------------|------------------------------------------|------------------------------------------|
| Dallimore et al., 2008 [76]| Intravenous             | 1-2 minutes                       | 20-60 minutes                            | 1 to 1.5 mg/kg is administered over 1-2 minutes followed by 0.25-0.5 mg/kg every 10 minutes |
| Green et al., 1998 [77]    | Intramuscular           | 10-15 minutes                     | 30-120 minutes                           | 4 mg/kg, followed by doses of 2 mg/kg repeated every 10 minutes (if required). |
| Gutstein et al., 1992 [33] | Oral                    | 20-30 minutes                     | 60-90 minutes                            | 6 mg/kg                                  |

**TABLE 1: Routes of administration of ketamine**

**Postoperative Care**

The child should be monitored at the hospital till they return to their usual state of health. They should be kept in a quiet and dimly lit environment to avoid agitation. The parents or caretaker should be alerted that the child may feel nauseated or vomit on their way home.

**Side Effects and Their Management**

Despite its excellent safety profile, the drug has some well-known side effects and limitations. It is known to produce tachycardia and hypotension. These are linked to the sympathomimetic action of ketamine and are usually transient [78]. The drug is contraindicated in infants younger than three months due to its propensity to produce laryngospasm [79]. Another reason why the drug is considered unsafe for neonates is because of the risk of it decreasing the respiratory drive and causing apnea. Its use in infants up to 12 months old is also considered controversial. Some physicians prefer to not use ketamine in children suffering from upper respiratory tract infections because of the risk of laryngospasm. However, there is data that proves that these concerns are somewhat unfounded. Green et al. analyzed a sample of 8,282 emergency department admissions who were administered ketamine and found no correlation between the incidence of laryngospasm with the patient’s age, dose, underlying physical illness, route, or simultaneous administration of anticholinergics and, hence, concluded that the incidents of laryngospasm were idiosyncratic and not related to the dose of ketamine used [80]. An emergency series reported that the incidence of laryngospasm was only 0.4%. Out of the 11,589 patients studied, only two required an intervention [9,81].

Other side effects of ketamine include jerky non-purposeful movements, muscle twitching, and nystagmus. However, these are transient and do not require treatment [9]. The drug’s effect on increasing intracranial pressure is still debated, with some studies showing that it actually decreased intracranial pressure in the subjects [22]. Nausea and vomiting are some of the most typical side effects of the drug seen in the pediatric age group, especially in children older than eight years [82].

Emergence phenomenon is very uncommon in children. However, it may occur in adolescents. It is defined as an abnormal mental state developing when the subject transitions from unconsciousness induced by the general anesthetic to a complete awakening. It can present with hypoactivity or hyperactivity. A study of 745 prospective records found that only 12.5% of the children cried on awakening, 39% experienced pleasant altered sensations, and 2.1% experienced emergence delirium. Therefore, the belief that emergence delirium is a frequent side effect of ketamine is incorrect, and even a pleasant emergence phenomenon is possible [14]. These episodes can lead to anxiety on rare occasions, but it tends to resolve on their own. Premedication with midazolam has been shown to reduce the incidence of emergence reactions with ketamine sedation [85].
Emergence delirium, although common with inhalational anesthetics like sevoflurane and desflurane, is rare with ketamine. Rather, the administration of ketamine in the form of an intraoperative sedative can help prevent it [84]. Other side effects include dizziness, drowsiness, and insomnia. Psychomimetic side effects of ketamine range from unpleasant dreams to hallucinations. The incidence of these is minimized by pretreatment with propofol or by administering lamotrigine [46,65]. Urinary and liver toxicity is only seen when high doses of ketamine are given regularly. As such, the margin of safety of ketamine is high, and a single accidental overdose does not cause organ toxicity [86]. The risk of ketamine dependence is present with long-term ketamine infusions, for example, when used for chronic pain. Clinicians should be wary of this and should taper the dose of ketamine infusion when given for more than 72 hours by 5 μg/kg/min every 8-12 hours. The incidence of acute ketamine withdrawal can be treated by administering benzodiazepines to calm the patient [87].

Long-Term Complications

Ketamine is thought to be a drug of abuse, but many case reports have reported no significant tolerance or psychomimetic effects with long-term use of ketamine infusion [88]. But some research suggests that it can lead to behavioral changes like apathy/withdrawal, separation anxiety, general anxiety, insomnia, and disturbed appetite [89]. Hence, further investigation is needed to assess the long-term complications of chronic ketamine use.

Conclusions

In summary, ketamine is a unique drug that produces dissociative anesthesia, a trance-like state characterized by catatonia, catalepsy, analgesia, and amnesia. It maintains laryngeal and pharyngeal reflexes, causes bronchodilatation, and does not lead to hemodynamic instability. Due to these invaluable advantages, it is considered the drug of choice for asthma and CHD. In recent years, several research trials and systematic reviews have suggested its efficacy as an analgesic and a sedative, especially in children. It also has several non-anesthetic uses in clinical practice, including refractory depression, PTSD, and generalized anxiety disorder. It is considered an excellent drug for acute and chronic pain, especially when it is due to a neuropathic component. However, the taboo of its side effects as well as its psychological tolerance has limited its use. There is evidence that many of these fears about its side effects are unfounded. Unfortunately, the quality of literature on the drug is still unsatisfactory. We recommend that more studies should be conducted to explore the role of ketamine in the pediatric population and determine its usefulness outside of being an anesthetic.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Li L, Vilisides PE: Ketamine: 50 years of modulating the mind. Front Hum Neurosci. 2016, 10:612. 10.3389/fnhum.2016.00612
2. Lofsey AO, Amir-Jabeh AK, Moarefi P: Anesthesia with ketamine: indications, advantages, and shortcomings. Anesthesiol. 1970, 49:969-74.
3. Mion G, Villevieille T: Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2015, 19:570-80. 10.1111/cns.12099
4. Morris C, Perris A, Klein J, Mahoney P: Anaesthesia in haemodynamically compromised emergency patients: does ketamine represent the best choice of induction agent?. Anaesthesia. 2009, 64:532-9. 10.1111/j.1365-2044.2008.05835.x
5. Kurdi MS, Theerth KA, Deva RS: Ketamine: current applications in anesthesia, pain, and critical care. Anesth Essays Res. 2014, 8:285-90. 10.4103/0259-1162.143110
6. Jamora C, Iravani M: Unique clinical situations in pediatric patients where ketamine may be the anesthetic agent of choice. J Ther. 2010, 17:511-5. 10.1097/MJT.0b013e3181ddc984
7. Griggs C, Goverman J, Bittner EA, Levi B: Sedation and pain management in burn patients. Clin Plast Surg. 2017, 44:335-40. 10.1111/cps.2017.02106
8. Walsh Z, MoftahAfshin TA, Rootman J, et al.: Ketamine for the treatment of mental health and substance use disorders: comprehensive systematic review. BJPsych Open. 2021, 8:e19. 10.1192/bjo.2021.1066
9. Dolansky G, Shah A, Moshos G, Rieder M: What is the evidence for the safety and efficacy of using ketamine in children?. Paediatr Child Health. 2008, 13:507-8. 10.1093/pch/13.4.307
10. Liu Y, Lin D, Wu B, Zhou W: Ketamine abuse potential and use disorder. Brain Res Bull. 2016, 126:68-73. 10.1016/j.brainresbull.2016.05.016
11. Domino EF: Taming the ketamine tiger. 1965. Anesthesiology. 2010, 113:678-84. 10.1097/ALN.0b013e3181ed09a2
12. Lavender E, Hirazawa-Fujita M, Domino EF: Ketamine’s dose related multiple mechanisms of actions: Dissociative anesthetic to rapid antidepressant. Behav Brain Res. 2020, 390:112631. 10.1016/j.bbr.2020.112631

13. Eger EI 2nd: Characteristics of anesthetic agents used for induction and maintenance of general anesthesia . Anesthesiology. 2002, 96:545-53. 10.1097/00000542-199201000-00004

14. Tregra G, Bell A, Cardwell R, Fincher G, Chaud D, Cashion G: What is the nature of the emergence phenomenon when using intravenous or intramuscular ketamine for paediatric procedural sedation?. Emerg Med Australas. 2009, 21:155-22. 10.1111/j.1742-6723.2009.01205.x

15. Pedraza JL, Calvo MB, Lanza JM, Muriel C, Santos Lamas J, Domínguez-Gil A: Pharmacokinetics of rectal ketamine in children. Br J Anaesth. 1989, 63:671-4. 10.1093/bja/63.6.671

16. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pienad M: Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth. 1996, 77:205-7. 10.1093/bja/77.2.205

17. Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM: Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. Eur J Pharmacol. 1997, 20:99-104. 10.1016/S0014-2999(97)80116-3

18. de Wilde SN, Reams GL, Leeder JS, van den Anker JN: Cytochrome P450 SA: ontogeny and drug disposition. Clin Pharmacokinet. 1999, 37:485-505. 10.2165/00003188-199937060-00004

19. Jäbre P, Combes X, Lapostolle F, et al.: Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. Lancet. 2009, 25:295-300. 10.1016/S0140-6736(09)60949-1

20. Lange M, Bökkiing K, van Aken H, Huckenbruch C, Bone HG, Westphal M: [Role of ketamine in sepsis and systemic inflammatory response syndrome]. Anaesthesist. 2006, 55:383-91. 10.1007/s00101-006-1048-x

21. Sehdev RS, Symmons DA, Kirpal K: Ketamine for rapid sequence induction in patients with head injury in the emergency department. Emerg Med Australas. 2006, 18:57-64. 10.1111/j.1742-6723.2006.00802.x

22. Zeiler FA, Teitelbaum J, West M, Gillman LM: The ketamine effect on ICP in traumatic brain injury. Neurocrit Care. 2014, 21:163-75. 10.1007/s12028-015-0995-0

23. Hill GL, April MD, Maddy JK, Schauer SG: Prehospital ketamine administration to pediatric trauma patients with head injuries in combat theaters. Am J Emerg Med. 2019, 37:1459-64. 10.1016/j.ajem.2018.10.046

24. Aye T, Milne B: Ketamine anesthesia for pericardial window in a patient with pericardial tamponade and severe COPD. Can J Anaesth. 2002, 49:283-6. 10.1007/BF03020528

25. Chen TL, Huang FY, Lin SY, Chao CC: Hemodynamic response to ketamine and diazepam in dogs with acute cardiac tamponade. Ma Zui Xue Za Zhi. 1989, 27:19-25.

26. Cortíñas M, Oya B, Caparros P, Cano G, Ibarra M, Martínez L: Premedicación con ketamina-midazolam oral en pacientes no colaboradores en cirugía mayor ambulatoria (Oral ketamine-midazolam premedication of uncooperative patients in major outpatient surgery). Rev Esp Anestesiol Reanim. 2010, 57:479-85. 10.1016/S0034-9556(10)70708-8

27. Mercer SJ: The Drug of War’ – a historical review of the use of Ketamine in military conflicts . J R Nav Med Serv. 2009, 85:145-50.

28. Mulvey JM, Qaidri AA, Macquod MA: Earthquake injuries and the use of ketamine for surgical procedures: the Kashmir experience. Anaesth Intensive Care. 2006, 34:489-94. 10.1111/j.1745-727X.2006.00044.x

29. Rice MJ, Gwertzman A, Finley T, Morey TE: Oral ketamine preanesthetic medication in children . Anesth Analg. 2001, 93:934-8. 10.1213/00000542-199201000-00004

30. Faix BR, Capps R, Neumeister G, Semple T: Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. Br J Anaesth. 1995, 75:698-701. 10.1093/bja/75.6.698

31. Panjahi N, Prakash S, Gupta P, Gogia AR: Efficacy of three doses of ketamine with huvipavacaine for causal analgesia in pediatric inguinal herniotomy. Reg Anesth Pain Med. 2004, 29:28-31. 10.1097/00000542-199201000-00004

32. Cossovel F, Trombetta A, Ramondo A, et al.: Intranasal dexmedetomidine and intranasal ketamine association allows shorter induction time for pediatric sedation compared to intranasal dexmedetomidine and oral midazolam. Ital J Pediatr. 2022, 48:5. 10.1186/s13052-021-01196-0

33. Darkling V, Shende D, Subramanyam MS, Sunder R, Naik A: Oral ketamine or midazolam or low dose combination for premedication in children. Anaesth Intensive Care. 2004, 32:246-9. 10.1111/j.1745-727X.2004.00023.x

34. Marhofer P, Krenn CG, Plochli W, et al.: S(+)-ketamine for caudal block in paediatric anaesthesia . Br J Anaesth. 2000, 84:541-5. 10.1093/oxfordjournals.bja.a013436

35. Cook B, Grubb DJ, Aldridge LA, Doyle E: Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. Br J Anaesth. 1995, 75:698-701. 10.1093/bja/75.6.698

36. Panjahi N, Prakash S, Gupta P, Gogia AR: Efficacy of three doses of ketamine with huvipavacaine for causal analgesia in pediatric inguinal herniotomy. Reg Anesth Pain Med. 2004, 29:28-31. 10.1097/00000542-199201000-00004

37. Gharde P, Chauhan S, Kisan U: Evaluation of efficacy of intranasal midazolam, ketamine and their mixture as premedication and its relation with bispectral index in children with tetration of fallout undergoing intracardiac repair. Ann Card Anaesth. 2006, 9:25-30.

38. Tavakollian AR, Allahyary E: The comparison of the effect of three anesthetic induction regimens on the arterial oxygen saturation in children with tetralogy of fallout undergoing cardiac surgery. Iran Red Crescent Med J. 2011, 13:702-6.
42. Hong B, Lim CS, Kim YH, Lee JU, Kim YM, Jung C, Jo Y: Comparison of topical ropivacaine with and without ketamine on post-surgical pain in children undergoing tonsillectomy: a randomized controlled double-blind study. J Anesth. 2017, 31:559-64. 10.1007/s00540-017-2355-z

43. Kayyal TA, Wolfwinkel EM, Weimers WM, Capehart SJ, Moxon LA, Buchanan EP, Glover CD: Treatment effects of dexmedetomidine and ketamine on postoperative analgesia after cleft palate repair. Cranio-maxillofac Trauma Reconstr. 2014, 7:131-8. 10.1055/s-0034-1371446

44. Yoon JY, Kim EJ: Current trends in intravenous sedative drugs for dental procedures. J Dent Anesth Pain Med. 2016, 16:89-94. 10.17245/jdampm.2016.16.2.89

45. Losvik OK, Murad MK, Skjerve E, Husuam H: Ketamine for prehospital trauma analgesia in a low-resource rural trauma system: a retrospective comparative study of ketamine and opioid analgesia in a ten-year cohort in Iraq. Scand J Trauma Resusc Emerg Med. 2015, 23:5. 10.1186/s13041-015-0176-1

46. Coulter FL, Hannam JA, Anderson BJ: Ketofol simulations for dosing in pediatric anesthesia. Paediatr Anaesth. 2014, 24:806-12. 10.1111/paen.12386

47. Howes MC: Ketamine for paediatric sedation/analgesia in the emergency department. Emerg Med J. 2004, 21:275-80. 10.1136/emj.2003.005769

48. Mistry RB, Nahata MC: Ketamine for conscious sedation in pediatric emergency care. Pharmacotherapy. 2005, 25:1104-11. 10.1592/phco.2005.25.8.1104

49. Hostetler MA, Barnard JA: Removal of esophageal foreign bodies in the pediatric ED: is ketamine an option?. Am J Emerg Med. 2002, 20:96-8. 10.1053/ajem.2002.31572

50. Sacchetti A, Stander E, Ferguson N, Maniar G, Valko P: Pediatric procedural sedation in the community emergency department: results from the ProSCED registry. Pediatr Emerg Care. 2007, 23:218-22. 10.1097/PEC.0b013e31803e176c

51. Kozer-Langenecker SA, Marhofer P, Sator-Katzenschlager SM, Dieckmann K: (S)-ketamine for long-term sedation in a child with retinoblastoma undergoing interstitial brachytherapy. Paediatr Anaesth. 2005, 15:248-50. 10.1111/j.1460-9592.2005.01425.x

52. Saini V, Samra T: Persistent postoperative hypercyanotic spells in an adult with surgically untreated tetralogy of Fallot: use of ketamine infusion. J Anaesthesiol Clin Pharmacol. 2017, 33:412-5. 10.4103/0970-9185.173524

53. Abdel-Ghaffar H, Salem MA: Safety and analgesic efficacy of pre-emptive intranasal ketamine versus intranasal fentanyl in patients undergoing endoscopic nasal surgery: safety and analgesic efficacy of pre-emptive intranasal ketamine versus intranasal fentanyl in patients undergoing endoscopic nasal surgery. J Anesth. 2012, 8:430-6. 10.7573/jasa.080312.57

54. Hosseini Jahromi SA, Hosseini Valami SM, Hattamian S: Comparison between effect of lidocaine, morphine and ketamine spray on post-tonsillectomy pain in children. Anesth Pain Med. 2012, 2:17-21. 10.3812/apam.4092

55. Ratanasuwon P, Nonphaichitr S, Pongyiansakul S, et al.: Efficacy of a combination of ketamine and morphine for intravenous patient controlled analgesia in upper abdominal surgery: a prospective, double-blind, randomized controlled trial. J Med Assoc Thai. 2021, 104:1528-34. 10.3755/jmedassocthai.2021.09.12996

56. Minoshima R, Koushi S, Nishimura D, et al.: Intravenous ketamine for adolescent idiopathic scoliosis surgery: a randomized controlled trial. Acta Anaesthesiol Scand. 2015, 59:1260-8. 10.1111/aas.12571

57. Alshahrani MS, Alghamdi MA: Ketamine for sickle cell vaso-occlusive crises: a systematic review. Saudi J Med Sci. 2021, 9:3-9. 10.4103/sjms.sjms_218_20

58. Nieters M, Martini C, Dahan A: Ketamine for chronic pain: risks and benefits. Br J Clin Pharmacol. 2014, 77:557-67. 10.1111/bcp.12094

59. Zgaia AO, Irimie A, Sandesc D, Vlad C, Lisenuc C, Rogobete A, Achimas-Cadariu P: The role of ketamine in the treatment of chronic cancer pain. Clin J Pain. 2015, 31:457-61. 10.1097/AJP.0000000000000300

60. Duan W, Hu J, Liu Y: Ketamine inhibits colorectal cancer cells malignant potential via blockage of NMDA receptor. Exp Mol Pathol. 2019, 107:171-8. 10.1016/j.yexmp.2019.02.004

61. Owens VF, Palmieri TL, Comroe CM, Conroy JM, Scavone JA, Greenhalgh DG: Ketamine: a safe and effective agent for painful procedures in the pediatric burn patient. J Burn Care Res. 2006, 27:211-6; discussion 217. 10.1097/01.BCR.0000204510.67594.A1

62. Groeneveld A, Inxton T: Ketamine. A solution to procedural pain in burned children. Can Nurse. 1992, 88:28-31.

63. Matveychuk D, Thomas RK, Swainson J, Khullar A, MacKay MA, Baker GB, Durum SM: Ketamine as an antidepressant: overview of its mechanisms of action and potential predictive biomarkers. Thr Adv Psychiatr Pharmacol. 2020, 10:204512520916657. 10.1177/204512520916657

64. Fond G, Loundou A, Rabu C, et al.: Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology (Berl). 2014, 231:5663-76. 10.1007/s00213-014-3664-5

65. Dwyer JB, Landeros-Weisenberger A, Johnson JA, et al.: Efficacy of intravenous ketamine in adolescent treatment-resistant depression: a randomized midazolam-controlled trial. Am J Psychiatry. 2021, 178:532-62. 10.1176/appi.ajp.2020.20010018

66. Liriano F, Hatten C, Schwartz TL: Ketamine as treatment for post-traumatic stress disorder: a review. Drugs Context. 2019, 8:1212055. 10.7575/dic.212055

67. Taylor JH, Landeros-Weisenberger A, Coughlin C, et al.: Ketamine for social anxiety disorder: a randomized, placebo-controlled crossover trial. Neuropsychopharmacology. 2018, 43:525-33. 10.1038/s41386-017-194

68. Banov MD, Young JR, Dunn T, Szabo ST: Efficacy and safety of ketamine in the management of anxiety and anxiety spectrum disorders: a review of the literature. CNS Spectr. 2020, 25:331-42. 10.1017/S1092852920001258

69. Kadiyala PK, Kadiyala LD: Anaesthesia for electroconvulsive therapy: an overview with an update on its role in potentiating electroconvulsive therapy. Indian J Anaesth. 2017, 61:573-80. 10.4103/ija.IJA_152_17

70. Kastner T, Walsh K, Shulman L, Alam F, Flood S: Ketamine and the core symptoms of autism. Int J Disabil Hum Dev. 2016, 15:1211-7. 10.1515/ijdh-2015-0005

71. Rosati A, L’Erario M, Ivento L, Cecchi C, Pisanò T, Mirabile L, Guerrini R: Efficacy and safety of ketamine in
refractory status epilepticus in children. Neurology. 2012, 79:2355-8. 10.1212/WNL.0b013e318278b685

72. Canbay O, Celebi N, Sahin A, Celliker V, Ozgen S, Appar U: Ketamine gargle for attenuating postoperative sore throat. Br J Anaesth. 2008, 100:490-5. 10.1093/bja/aen623

73. Kanbak M: Ketamine in porphyria. Anesth Analg. 1997, 84:1395. 10.1097/00000539-199706000-00056

74. Lee J, Lee J, Lim H, Son JS, Lee JR, Kim DC, Ko S: Cartoon distraction alleviates anxiety in children during induction of anesthesia. Anesth Analg. 2012, 115:1168-73. 10.1213/ANE.0b013e31824b469

75. Zapantis G, Csóka I, Csányi E, Horváth G, Eriš I: Evaluation of ketamine systemic absorption from topical preparations. Short Communication. Acta Biol Hung. 2006, 57:387-9.

76. Dallimore D, Herd DW, Short T, Anderson BJ: Dosing ketamine for pediatric procedural sedation in the emergency department. Pediatr Emerg Care. 2008, 24:529-33. 10.1097/PEC.0b013e3181860bb5

77. Green SM, Rothrock SG, Lynch EJ, et al.: Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. Ann Emerg Med. 1998, 31:688-97. 10.1016/s0196-0644(98)70226-4

78. Stukus KS, Przybylowicz RW, Backes CH Jr, Cohen DM: Ventricular tachycardia after ketamine sedation for fracture reduction. Pediatr Emerg Care. 2014, 30:730-2. 10.1097/PEC.0000000000000237

79. Bhutta AT: Ketamine: a controversial drug for neonates. Semin Perinatol. 2007, 31:303-8. 10.1053/j.semperi.2007.07.005

80. Green SM, Roback MG, Krauss B: Laryngospasm during emergency department ketamine sedation: a case-control study. Pediatr Emerg Care. 2010, 26:798-802. 10.1097/PEC.0b013e3181f8737

81. Green SM, Johnson NE: Ketamine sedation for pediatric procedures: part 2, review and implications. Ann Emerg Med. 1990, 19:1033-46. 10.1016/s0196-0644(05)82569-7

82. Green SM, Krauss B: Clinical practice guideline for emergency department ketamine dissociative sedation in children. Ann Emerg Med. 2004, 44:460-71.

83. Breccelj J, Trop TK, Orel R: Ketamine with and without midazolam for gastrointestinal endoscopies in children. J Pediatr Gastroenterol Nutr. 2012, 54:748-52. 10.1097/MPG.0b013e31824f04af

84. Dahmani S, Delivet H, Hilly J: Emergence delirium in children: an update. Curr Opin Anaesthesiol. 2014, 27:309-15. 10.1097/ACO.0000000000000076

85. Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, Krystal JH: Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Arch Gen Psychiatry. 2000, 57:270-6. 10.1001/archpsyc.57.5.270

86. Green SM, Clark R, Hostetler MA, Cohen M, Carlson D, Rothrock SG: Inadvertent ketamine overdose in children: clinical manifestations and outcome. Ann Emerg Med. 1999, 34:492-7. 10.1016/s0196-0644(99)8051-1

87. Moore E, Mayes R, Hartkin M, Miller JL, Johnson PN: Extended duration ketamine infusions in critically ill children: a case report and review of the literature. J Pediatr Intensive Care. 2021, 10:221-7. 10.1555/j.ajpmn.2021.344

88. White MC, Karsli C: Long-term use of an intravenous ketamine infusion in a child with significant burns. Paediatr Anaesth. 2007, 17:1102-4. 10.1111/j.1460-9592.2007.02329.x

89. Pearce JI, Brousseau DC, Yan K, Hainsworth KR, Hoffmann RG, Drendel AL: Behavioral changes in children after emergency department procedural sedation. Acad Emerg Med. 2018, 25:267-74. 10.1111/ace.13332