Ketamine in Pediatric Oncology: a drug review

Satya Prakash[1], Aditya Gupta[1], and J Meena[1]

[1]All India Institute of Medical Sciences

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Abstract

Ketamine is a dissociative anesthetic agent, with excellent analgesic properties and a favorable safety profile. Although it acts predominantly through NMDA receptor antagonism, numerous other molecular targets have been characterized, rendering anti-inflammatory, anti-depressant, and thus expanding its scope for new clinical applications. The noticeable safety of ketamine in children enables its widespread use in pediatric oncology, chiefly for procedural sedation. Its value for chronic pain management in children with cancer is being increasingly recognized but requires more evidence. The topical use of ketamine is largely in investigational stages.. Rational medical use of ketamine is largely free from significant long-term neurological side effects but may have some troublesome short-term effects such as vomiting, palpitations, urinary retention, and hallucinations. This review will provide a brief account of the pharmacology of ketamine and primarily focus on the relevant aspects of ketamine in pediatric oncology.

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Keywords: Ketamine; Oncology; Chronic pain; Sedation; Mucositis; Children

INTRODUCTION

The history of ketamine began almost seven decades back when the search for an ideal anesthetic and analgesic agent in the 1950s led to the discovery of a cyclohexylamine called Phencyclidine (PCP), also marketed as Sernyl.[1] The advantages of PCP over other sedatives such as opioids were that it did not depress the cardiovascular and respiratory functions, nor did it impair the laryngeal and pharyngeal reflexes. These advantages, together with its potent anesthesia without a total loss of consciousness (later termed dissociative anesthesia) seemed promising. However, a major limiting adverse effect was the occurrence of psychotic reactions, including hallucinations lasting several hours, even after a single dose.[2]Additionally, the abuse potential of PCP was increasingly recognized. Thus, the initial excitement for PCP as a human anesthetic waned. Further research into similar compounds entailed the development of a compound in 1962 with a ketone bond together with an amine, hence named ketamine. This chemical had similar advantages as PCP, such as excellent anesthesia, hemodynamic stability, and preservation of protective reflexes, but with a shorter duration of action and lesser neuropsychiatric adverse effects.[3] By 1970, ketamine was approved

for human use. It was not until a decade later that the principal sites of its action, the NMDA receptors, were discovered.[4] Another crucial observation was that ketamine, in sub-anesthetic doses, produces excellent analgesia, and was largely devoid of the troublesome psycho-behavioral adverse effects seen at higher doses. Since then, ketamine has been extensively studied, and a wide variety of therapeutic effects (anesthetic, analgesic, anti-inflammatory, anti-depressant) have been explored and their mechanisms characterized. Even though its role as an anesthetic has dwindled in the last three decades, its benefits in other domains remain of utmost utility, especially concerning analgesia in children, a population in which ketamine has proved to be noticeably safe and effective. The role of ketamine in acute severe asthma and refractory status epilepticus is also well-described. This review will provide a brief account of the pharmacology of ketamine and primarily focus on the relevant aspects of ketamine in pediatric oncology.

PHARMACOLOGY (Mechanisms of action, pharmacokinetics, routes of administration)

2.1 Mechanisms of action (MOA)

Ketamine has a use-dependent non-competitive NMDA receptor-channel blocking activity, wherein it binds the PCP site of the channel in the open activated state and reduces mean channel opening time. It has also been shown to bind to a second site on the membrane which, through an allosteric mechanism, causes a decrease in the frequency of the channel opening.[5] The principal site of action of ketamine administered in anesthetic doses is the limbic system, manifesting as an increased uptake seen in nuclear studies. However, in sub-anesthetic doses, the activity in these regions is interestingly decreased.[6,7] This coupled with the observation that low concentrations of ketamine act predominantly by the allosteric mechanism rather than by blocking the open NMDA channel, likely explain the differential effects of ketamine at different doses (anesthesia vs analgesia).[8]

Besides being effective at a dose much lower than that used for anesthetic effect, the efficacy of ketamine as an analgesic has also been noted to last even after the drug has cleared from the system. This is thought to be mediated by its sustained action on the glutaminergic neurons, which in turn causes an increase in structural synaptic connectivity.[9] An interesting mechanism for relief in chronic pain is its desirable effect on pain memory and the desensitization of central pain pathways, as well as that on the motivational affective aspects of pain.[10]

Several other mechanisms of action have been proposed for the analgesic effect of ketamine based mostly on in-vitro studies, including dopamine D2 antagonism, 5-HT2 serotonin receptor agonism, HCN1 channels, calcium and sodium channels, and cholinergic transmission.[11,12,13,14] These findings suggest that instead of a specific NMDA action, ketamine possibly has a multipronged role in modulating neural functions like pain, wakefulness, and mood.

Anti-inflammatory actions: Emerging evidence shows that ketamine also exerts an anti-inflammatory effect. Several studies, including both in vitro and in vivo, have demonstrated a reduction in blood levels of TNF-alpha, iNOS, IL-6, and C-reactive protein (CRP). This effect is likely mediated by inhibition of the NF-B pathway, thereby impeding the pro-inflammatory cytokine response.[15,16,17] Another possible mechanism could be the inhibition of inflammation-induced nitric oxide production.[18,19] These effects may partly be responsible for the beneficial effects of ketamine in inflammatory and traumatic pain, such as that seen post-operatively.[20]However, a concrete clinical benefit of ketamine based on its anti-inflammatory actions is yet to be demonstrated, and this effect is likely at best a minor contributor to the overall benefit of ketamine as an analgesic. Additionally, a few animal model studies suggest a neuroprotective action owing to its NMDA antagonistic effects, but this has not been definitively replicated in humans yet.[21,22]

Local effects: NMDA receptors are present not only in the central nervous system (CNS) but also in peripheral sensory pathways. All motor and sensory axons are equipped with NMDA receptors. NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors are up-regulated on the axons as a reaction to inflammation.[23] These findings support the rationale for treating neuropathic and inflammatory pain with topical ketamine to modulate NMDA, AMPA, and kainate receptors and subsequently downregulating the peripheral mechanisms contributing to neuropathic and inflammatory pain.

Some other actions, particularly blockade of sodium channels, could contribute to its efficacy following local peripheral administration where tissue levels are likely to be higher than are attained with systemic administration.[24] Ketamine has local anesthetic properties at high doses which have been compared with lignocaine and procaine, although with lesser potency.[25] Indeed, ketamine has been widely studied as a topical agent for reducing post-tonsillectomy pain in children, including nebulized and oral rinse forms.[26]

2.2 Pharmacokinetics

Systemically administered ketamine is chiefly metabolized by the cytochrome P450 liver enzymes, initially to a much less potent norketamine, and further to inactive hydroxynorketamines, dehydronorketamines, and other metabolites.[27,28]Ketamine has a relatively low plasma protein binding (10-50%) and is rapidly accumulated in the brain. It has a high clearance rate, with a half-life of 2-4 hours.[29,30] The excretion is predominantly in urine, with minimal amounts (<5%) in feces. The rate of elimination of ketamine is twice as rapid in children when compared to adults, likely due to faster enzymatic metabolism in children.[31] This information plays a role in determining the ketamine dosing frequency in children. Ketamine is commonly available as a mixture of (S)- and (R)- enantiomers. (S)-enantiomer is more potent as compared to (R)-enantiomer, with some evidence of a more favorable safety profile.[32]

Due to its metabolism by cytochrome P450 enzymes, there is a potential for drug interactions when used along with enzyme-inducer and enzyme-inhibitor drugs. Drugs like metoclopramide and fosaprepitant, which may at times be used in cancer patients as antiemetics, may have drug interactions with ketamine, and caution must be exercised during their concomitant use. Similarly, other CYP3A4 inhibitors like clarithromycin, azole antifungals, verapamil, and inducers like phenytoin, rifampicin, and steroids can alter ketamine levels.[33]

2.3 Routes of administration

The most common route of administration is intravenous. Other routes often employed include intramuscular and oral routes. Increasingly, several other routes are being explored such as subcutaneous, intranasal, epidural, rectal, topical, nebulization, and transdermal.[34,35,36] Studies to evaluate the plasma levels of ketamine after nasal and rectal administration as compared to intravenous administration in children have found acceptable levels for analgesia.[37] The transdermal route has also been shown to be effective for post-operative analgesia.[38]Pharmacokinetic details of major routes of administration have been depicted in table 1. The bioavailability of oral ketamine is low because of the extensive first-pass metabolism.[39] There is a paucity of data on the pharmacological aspects of the lesser-known routes.

Uses

The primary purpose for the development of ketamine was anesthesia, due to its aforementioned unique advantages over opioids. Its safety profile also allowed its use in non-OT settings including wars and mass casualties.[43] However, with the advent of newer anesthetic agents and the propensity for neurocognitive effects of ketamine, its use declined significantly, especially in the developed world. Nevertheless, its utility continued to be evaluated, and lately, it is gaining renewed interest as an adjunct to opioid-based anesthesia, to overcome issues like post-anesthesia delirium.[44]Ketamine is also considered a particularly useful agent for pediatric anesthesia because of its safety profile. Ketamine has been adjudged as an excellent drug for short-term medical procedures, due to its potent analgesic and sedative effect, favorable hemodynamic profile, and short duration of action.

The excellent analgesic effect of ketamine has been known for almost five decades, with the added benefit of much lesser neuropsychiatric adverse effects noted with the doses sufficient for analgesia. Although several reports have found it to be remarkably effective for neuropathic pain, including chronic cancer-related pain, systematic evidence for the same from large-scale randomized controlled trials is lacking.[45,46,47,48] The analgesic efficacy of ketamine has also been replicated in children of various ages and disease profiles.[49,50,51]

Systemic ketamine has been used in acute severe asthma owing to its bronchodilatory effect, although clear evidence of benefit is lacking.[52,53,54] Similarly, the role of ketamine in refractory and super-refractory status epilepticus is being increasingly recognized wherein it acts chiefly through its antagonistic effect on excitatory

glutaminergic action.[55] However, no standard protocols are available for either of these uses. Another well-described use of ketamine is in treatment-resistant depression in adults, wherein it has been thoroughly investigated. A recent systematic review of the efficacy of ketamine for treatment-resistant mood disorders in children found an overall beneficial effect in terms of depressive symptoms, suicidality and mood lability, but emphasized on the need for further systematic evaluation in children.[56] Intranasal ketamine is useful in migraine by reducing the severity of aura.[57]

Scope in Pediatric Oncology

4.1 Cancer-related pain

Cancer-related pain can be severely debilitating. Opioids have traditionally been the mainstay of pain management in such patients. However, the somnolence induced by these drugs may sometimes be unacceptable, with impairment in the child's quality of life and ability to communicate. Moreover, tolerance to opioids is a common concern, with requirements of increasingly higher doses. Ketamine, due to its low sedation potential and safe hemodynamic profile, has been used as an adjunct to opioids and is often regarded as second-line therapy after opioids for intractable neuropathic pain in pediatric oncology practice, with usual doses ranging from 0.025-0.3 mg/kg/hour.[58]In pediatric end-of-life care, the role of ketamine patient-controlled analgesia (PCA) has also been mentioned.[59] Low dose ketamine infusion for refractory pain in children with cancer has been shown to significantly reduce pain as well as the requirement of opioid dose.[60,61,62] In this regard, the anti-hyperalgesic and anti-allodynic effect of ketamine has been well-described.[63,64] However, a recent systematic review found no post-operative opioid-sparing effect of ketamine in children.[65] Epidural ketamine in combination with morphine has been found to increase the duration of analgesia.[66] Oral ketamine doses ranging from 0.25-1 mg/kg/dose are safe and effective in children with chronic pain.[67] Oral ketamine offers the distinct advantage of the ease of administration combined with potent analgesic, something which has so far been achieved satisfactorily only with a handful of agents. Despite the emerging evidence for ketamine for cancer pain, its use currently remains largely off-label. World Health Organization (WHO) has discontinued its guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (2012) in light of new evidence and is revising it, but perhaps it would be premature to list ketamine as an upfront analgesic after opioids for children with cancer.[68] Moreover, ketamine doesn't find a mention in WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents (2018), in the absence of concrete evidence from high-quality studies.[69]Table 2 provides a summary of the prospective studies of ketamine for cancer pain in children.

4.2 Sedation and procedural pain

Parenteral ketamine (intravenous/ intramuscular) is often used for sedation during outpatient as well as inpatient procedures, including lumbar puncture, bone marrow aspiration, and biopsies, with good efficacy and tolerable adverse effects.[74]Intramuscular administration has the advantage of not requiring intravenous access but has been associated with a slightly higher incidence of adverse events.[75] For sedation, ketamine is also frequently combined with other agents like midazolam, propofol, and dexmedetomidine.[76,77,78,79] Pellier et al prospectively evaluated a combination of midazolam (IV, 25 mcg/kg) and ketamine (IV, 0.5-2 mg/kg) for procedural sedation in children with cancer, and found it to be safe and effective.[80] Some of the undesirable adverse effects of intravenous ketamine used for sedation such as hypersalivation and tachycardia may be alleviated by using atropine.[81] An oral mixture of ketamine, midazolam, and atropine was found to be equivalent to intramuscular administration of these drugs for procedural sedation during minor oncological procedures in children.[82] However, a trial evaluating the analgesic effect of oral ketamine (1 mg/kg) for procedural analgesia before bone marrow examination did not find any significant benefit over placebo.[83] Similarly, oral ketamine sedation (8-15 mg/kg) was found to be insufficient in children with cancer undergoing radiotherapy.[84] Thus, while intravenous ketamine has gained widespread popularity as a procedural agent, the role of oral ketamine is yet to be established. Intranasal ketamine has also been used for sedation in children. Yang et al described the use of intranasal ketamine and dexmedetomidine in 17948 children for procedural sedation and concluded it to be satisfactorily effective with fewer adverse events.[85] Table 3 provides a summary of the prospective trials of ketamine (sample size [?] 10) for procedural pain or

sedation in children with cancer.

4.3 Topical ketamine

The evaluation of topical ketamine preparations for chemotherapy-induced peripheral neuropathic pain has yielded variable results, with some suggesting a promising role but many studies indicating no significant benefit.[91,92,93] Topical ketamine is a safe and effective analgesic for decreasing post-tonsillectomy pain in children, and has been used as a skin preparation for non-cancer pain.[26,94,95] Preliminary evidence for ketamine mouthwash for oral mucositis pain had suggested a beneficial role in adults, but a recent RCT evaluating the role of ketamine mouthwash for oral mucositis pain relief in children (N=44; 8-18 years) found ketamine to be ineffective at a dose of 1 mg/kg.[96,97,98,99] The summary of various studies of ketamine mouthwash in oral mucositis (OM) pain in cancer patients has been provided in Table 4.

There are several potential advantages of using topical agents over systemic, such as higher analgesic concentration at the site of pain, faster onset of action, low or no systemic drug levels and side effects, decreased risk of drug interactions, better drug compliance, and decreased risk of abuse or dependence.[100] Considering these benefits and the fact the patients with cancer are already on a concoction of systemic agents, discovering effective topical agents could prove to be very useful in this group in providing desired therapeutic effects while minimizing adverse effects and harmful drug interactions. Hence, further studies investigating the topical delivery of ketamine for analgesic and anti-inflammatory effects are the need of the hour.

Adverse effects

Commonly seen adverse effects include sedation, nausea, vomiting, hallucinations, anorexia, urinary retention, hypertension, tachycardia, muscle stiffness, increased respiratory secretions, vertigo, and ataxia.[101,102] Nystagmus, diplopia, laryngospasm, reversible cystitis, and central diabetes insipidus have been noted on rare occasions.[103,104] Abrupt discontinuation of ketamine infusion may lead to anxiety, tremors, sweating, and emergence reactions.[105] These reactions manifest as hallucinations, vivid dreams, and delirium. There is also evidence to believe that the emergence reactions are seen less commonly in children as compared to adults.[106,107] As noted previously, the notorious psychomimetic effects of ketamine have been seen to be much less frequent at analgesic doses. The emergence of reactions can be minimized by concomitantly using a benzodiazepine with ketamine.[108] All the aforementioned adverse effects are rare with topical preparations.[96,97,98,99]

The conventional contra-indications to the use of ketamine include conditions in which a sudden increase in systemic blood pressure might be dangerous (cerebrovascular accidents, myocardial infarction, aortic dissection, aneurysm), known or suspected schizophrenia spectrum disorder and documented hypersensitivity. The American College of Emergency Physicians has also listed age less than three months as an absolute contraindication to the use of ketamine, due to a high risk of airway complications, although ketamine is still occasionally used in this age group.[101] Ketamine is to be avoided in patients with glaucoma due to its propensity to cause intraocular pressure. A few other relative contraindications include a history of airway instability, known cardiovascular disease, porphyrias, and hyperthyroidism (increased sympathomimetic activity). Additionally, in the absence of sufficient safety data available for ketamine levels in breastmilk, it is recommended that alternate agents be preferred when feasible.[109]

Early reports about ketamine dating as far back as the 1970s suggested a propensity of ketamine to cause intracranial hypertension.[110,111] However, since then ample evidence has questioned this notion. Ketamine has been shown not to cause intracranial hypertension in patients, including in those with traumatic brain injury in children.[112,113,114] In fact, ketamine by maintaining cerebral perfusion pressure may have a neuroprotective effect, especially under conditions of controlled ventilation.

Concerns in children

Long term use of high dose ketamine has been linked to adverse neurodevelopmental outcomes, including those related to memory, cognition and executive function.[115] However, most of such information has been derived from studies done on recreational abusers of ketamine and is unlikely to have much basis in the clinical

use of controlled doses of ketamine. Nevertheless, the abuse potential of ketamine is well-documented and has to be kept in mind. Moreover, even sub-anesthetic doses of ketamine have been shown to cause some impairment in memory and attention.[116] It is therefore imperative for clinicians to monitor for any such effects during the administration of ketamine to children.

In the developing brain of some animal models, ketamine has been noted to induce altered development of Neural Stem Progenitor Cells, with the potential to cause long-lasting cognitive damage.[117,118] The extrapolation of such evidence into clinical practice is debatable, and further evidence is needed to make a final statement on the developmental neurotoxicity of ketamine.[119] In fact, in the presence of harmful stimuli such as pain and inflammation, ketamine, by its analgesic and anti-inflammatory action, may even have a neuroprotective role.[120] Nonetheless, it would be prudent to practice caution while administering ketamine to neonates, young infants, and pregnant and lactating women, and prefer alternative agents.

Prospects for future research

There is ample evidence for ketamine as a good agent for procedural sedation in children with cancer. However, regarding its role as an analgesic, despite numerous reports from small studies and case reports, there is a paucity of quality evidence. There is a clear need for systematic well-designed studies to evaluate the efficacy and safety of ketamine as an analgesic agent, including that of oral and local routes of administration. Understandably, there are ethical concerns regarding the conduction of a drug trial for end-of-life cancer pain. In such circumstances, the clinician and parental tolerance for adverse effects are much higher, allowing the use of a wider gamut of analgesic agents and at higher doses. Ketamine has been successfully used in this setting in children with terminal cancer.[70,71] However, the role of ketamine for the treatment of neuropathic pain in children with cancer in non-terminal stages is still not convincing. There are concerns regarding sustained efficacy as well as the potential for neuropsychiatric adverse effects. This aspect requires further research, preferably as a randomized controlled trial, to enable confident prescription of ketamine by pediatric oncologists.

Conclusion

Ketamine is a dissociative anesthetic with an excellent analgesic action at low doses. Due to its desirable effect on hemodynamics and protective airway reflexes, it is commonly used for short term procedural sedation as an intravenous drug. Other forms of systemic administration like oral or intranasal routes have been proven to be safe and effective and have the advantage of easy administration. Moreover, topical delivery of ketamine has also shown encouraging results but still requires further investigations, especially in children. Ketamine is a commonly used drug in pediatric oncology practice, mostly for sedation, but its efficacy as an analgesic is largely underutilized. Pediatric oncologists need to familiarize themselves with the pharmacological aspects of the drug to prescribe it more rationally and effectively, while keeping in mind the possible, albeit rare, serious adverse effects.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Satya Prakash: Design the study and drafting of manuscript.**Aditya Kumar Gupta:** Critical inputs and drafting of manuscript.**Jagdish Prasad Meena:** Supervision, critical inputs and drafting of manuscript.

ORCID

Jagdish Prasad Meena:https://orcid.org/0000-0001-6024-9762

Satya Prakash: https://orcid.org/0000-0003-4248-9855

Aditya Kumar Gupta https://orcid.org/0000-0002-3730-8944

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