

REVIEW

Refractory symptoms in paediatric palliative care: can ketamine help?

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Abstract

Background: One of the main challenges for paediatric palliative care (PPC) is the management of concomitant, different and severe symptoms that frequently affect the quality of life of PPC patients and are often refractory to commonly used pharmacological treatments. Consequently, many efforts are still needed to find the best therapeutic options to handle these refractory conditions. Since the first synthesis of ketamine in the 1960s, its pharmacokinetic and pharmacodynamic properties have been largely investigated and its potential wide range of clinical applications has become clear. However, this molecule still receives poor attention in some areas, including in children and PPC. This narrative review analyses the use of ketamine in children and the potential extension of its applications in PPC in order to provide new options for treatment in the PPC setting.

Methods: Scientific papers published before October 2020 on MEDLINE, EMBASE and the Cochrane Library were considered. The cited references of the selected papers and the authors' personal collections of literature were reviewed. The terms "palliative care", "ketamine", "neuropathic pain", "procedural pain", "status epilepticus", "refractory pain" and "child", adding "age: birth–18 years" on a further filter were used for the search.

Discussion: The use of ketamine in PPC should be more widely considered due to its overall favourable safety profile and its efficacy, which are supported by an increasing number of studies, although in settings different from PPC and of mixed quality. Ketamine should be proposed according to a case-by-case evaluation and the specific diagnosis and the dosage and route of administration should be tailored to the specific needs of patients. Furthermore, there is evidence to suggest that ketamine is safe and efficacious in acute pain. These findings can prompt further research on the use of ketamine for the treatment of acute pain in PPC.

Conclusion: Ketamine could be a suitable option after the failure of conventional drugs in the treatment of different refractory conditions in PPC.

Keywords: children, clinical needs, ketamine, paediatric palliative care.

Citation

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Introduction

The prevalence of children suffering from life-limiting and life-threatening diseases and disabilities is estimated as 10 per 10,000 children aged 0–19 years.^{1,2} However, these numbers are increasing worldwide and, due to the medical advances achieved in the last years, the life expectancy of these patients has improved.^{1,2} These children have unique and complex needs that often require combined multidisciplinary care, which comes under the umbrella of paediatric palliative care (PPC). The focus of PPC is to ensure the best 'quality of life' possible for the child and their family for the entire life span of the patient.^{3–6}

One of the main challenges for PPC specialists is the management of multiple severe symptoms and conditions, including chronic pain, seizures and mood alterations, which frequently affect the quality of life of these patients. Unfortunately, these symptoms are sometimes refractory to commonly used pharmacological treatments and most drugs used for their management are prescribed off-label.^{7,8} Consequently, many efforts are still needed to find the best therapeutic options to handle these conditions.

Recently, mounting interest has been demonstrated on the use of ketamine in the paediatric setting.^{7,9} This drug was first

marketed as an anaesthetic drug in 1964.¹⁰ It is a non-competitive, voltage-dependent N-methyl-D-aspartate (NMDA) receptor antagonist. The administration of ketamine reduces the excitatory pathways mediated by the NMDA receptor, inducing a cataleptic and analgesic action without hypnotic properties, which account for the peculiar anaesthetic effect of ketamine.¹¹ The pharmacological activity of ketamine can be used to induce sedation and somatic analgesia as well as to provide antiepileptic and antidepressive effects. Even if there are few data on its use in this field in paediatric care, its use could be considered in the PPC setting, where complexity and progression of disease make it difficult to control the symptoms and only a partial response to the oldest drugs is often experienced.

This narrative review aims to highlight the current knowledge on the use of ketamine for childcare in different settings, focusing on the actual knowledge and potential extension of its applications in PPC.

Methods

This is a narrative review of studies about the use of ketamine in the paediatric population in different care settings. Scientific papers published before October 2020 on MEDLINE, EMBASE and the Cochrane Library, without any limitations, were considered. The terms “palliative care”, “ketamine”, “neuropathic pain”, “procedural pain”, “status epilepticus”, “refractory pain” and “child”, adding “age: birth–18 years” on a further filter were used for the search. ‘AND’ was also used as a Boolean operator. Moreover, in order to identify relevant studies, the cited references of the selected papers were also reviewed. The authors’ personal collections of literature were also browsed. Papers were selected for consideration in this manuscript according to their relevance for the topic, as judged by the authors.

Ethical approval and informed consent

Given the nature of this study, the project was exempt from institutional review board/ethics committee review.

Review

Ketamine and refractory and/or neuropathic pain

Ketamine, when used in low doses, has antinociceptive effects through the supraspinal blockade of the NR2B NMDA subunit and opioid delta receptor.¹² It also augments the μ -opioid receptor function, an endogenous antinociceptive system. The inhibition of nitric oxide synthase probably also contributes to its analgesic effects but the importance of this mechanism is not well established.¹²

The acute and prolonged effect of ketamine on neuropathic pain is also well known. A single administration of low-dose ketamine, thanks to the inhibition of the NMDA-mediated

pathway, can rapidly and transiently reduce neuropathic pain and related symptoms such as allodynia and hyperalgesia.^{13–15} In addition, we can also speculate that ketamine could interact with some opioid tolerance/addiction mechanisms.

These pharmacological properties of ketamine are useful to induce analgesia in the paediatric setting, in particular for children with advanced cancer who often experience stressful symptoms such as neuropathic or mixed pain, which is reported to be the most common type of pain (up to 80%).^{16–19}

Even if there are no randomized controlled trials, the use of ketamine is considered an option²⁰ for the control of refractory cancer pain^{19,21} and has been investigated in different studies (Table 1). The additional value of this therapeutic approach is that ketamine, in this setting, can also help opioid sparing, avoiding the development of withdrawal symptoms.

Taylor et al. reported a retrospective case series of 14 children in end-of-life treatment complaining of opioid-refractory neuropathic pain and treated with ketamine. Pain relief was referred to by all participants and 79% of patients experienced no adverse effects. A reduction in the use of opioids was also reported in most cases.²²

Another study analysed the effect of subanaesthetic doses of ketamine used to treat 11 children who were on high doses of opioids and had uncontrolled cancer pain. In the majority of patients, ketamine infusions were associated with opioid-sparing effects and apparent improvement in pain control and in the children’s ability to interact with their family.²³ The same effect was also experienced in end-stage life disease by a 12-year-old woman with a diagnosis of glioblastoma multiforme and by a 2.8-year-old child with metastatic neuroblastoma.^{24,25} Similar results were also reported in other case series.^{26,27}

Sickle cell (SC) disease is the most common haemoglobin variant in the world and can present with recurrent vaso-occlusive painful crises. In adults with SC disease, opioid tolerance and related side effects have been major barriers to adequate pain relief²⁸ and the use of low-dose ketamine infusions showed promising results for pain relief in this condition.

Considering the paediatric setting, the role and effectiveness of ketamine infusion for a painful SC crisis have been investigated in two recent papers.^{28,29} In a randomized non-inferiority trial, data supported a comparable analgesic effect to treat severe painful SC crisis between intravenous (i.v.) ketamine and equianalgesic i.v. morphine dosage.²⁸ A literature review highlighted the potential effectiveness of low-dose ketamine infusions for painful SC crisis on the reduction of pain score and opioid dosage (Table 1).²⁹

Ketamine and refractory and/or neuropathic pain in PPC: expert opinion

Pain is a common and severe symptom in children undergoing PPC, both in the oncology and non-oncology setting. In these patients, the treatment of pain is a priority.

Table 1. Ketamine application for children in paediatric palliative care.

Type of study	Aim	Results	Ref.
Refractory and/or neuropathic pain management			
Retrospective clinical study	Evaluation of ketamine treatment for opioid-refractory neuropathic pain	Pain relief; escalation of opioids	Taylor et al. ²²
Case series	Evaluation of low-dose ketamine in children with terminal cancer who had inadequate pain control and/or had developed serious side effects with opioids	Opioid-sparing effect; improvement in pain control	Finkel et al. ²³
Case series	Evaluation of continuous low-dose infusion ketamine in children with intractable end-stage cancer pain	Opioid-sparing effect; improvement in pain control	Conway et al. ²⁵
Case report	Evaluation of ketamine analgesic effect in a 12-year-old girl suffering from glioblastoma multiforme	Opioid-sparing effect; improvement in pain control	Klepstad et al. ²⁴
Case report	Evaluation of ketamine analgesic effect in a 2.8-year-old child with severe pain from metastatic neuroblastoma	Opioid-sparing effect; improvement in pain control	Tsui et al. ²⁶
Randomized controlled trial	Evaluation of the effectiveness of ketamine infusion for painful sickle cell disease crisis	Comparative analgesic effect of ketamine and morphine infusions has been observed	Lubega et al. ²⁸
Observational study	Evaluation of ketamine tolerance and satisfaction as an adjuvant analgesic for refractory cancer pain	Low doses of ketamine as an adjuvant to opioids significantly reduced the intensity of pain in half of the study population ($p < 0.001$)	Courade et al. ¹⁹
Procedural pain management			
Clinical trial	Evaluation of rectal administration of ketamine in children with cerebral palsy	Moderate sedation and analgesia were achieved	Nilsson et al. ⁴¹
Status epilepticus management			
Retrospective clinical study	Evaluation of ketamine treatment to manage refractory status epilepticus in children in intensive care unit	Refractory status epilepticus was controlled with ketamine in the majority of patients, showing a significantly greater effectiveness in the loading-maintenance protocol compared to the maintenance group	Wu et al. ⁵⁸

In the PPC setting, conventional drugs often show a poor efficacy and many side effects. In addition, neuropathic or mixed pain are often difficult to distinguish from each other. Consequently, although current data in the PPC setting are still scant and further studies are necessary to achieve more solid evidence, we believe that ketamine, alone or in combination, could be an option for the management and treatment of mixed or neuropathic pain that do not respond to available first-line drugs.

Another advantage of ketamine is the possibility to use an alternative administration route (intranasal and transmucosal). Indeed, many PPC patients have difficult vascular access and may benefit from another administration route.

Ketamine and procedural pain

In paediatrics, particularly in the PPC setting, invasive procedures are part of several diagnostic and therapeutic approaches, including surgery, immunization, spinal tap, bone marrow aspiration, needle procedures, and orthopaedic and wound-related injuries. Therefore, the provision of moderate sedo-analgesia before and during an invasive procedure is mandatory. A common practice is to induce general anaesthesia but this possibility is not always available or the best option.³⁰ Due to its sedative and analgesic potential when used after trauma or surgery,³¹ ketamine could be used in children for this purpose and its use is now accepted in this setting.^{32–34}

In the paediatric emergency department (ED) in the United States and Europe,^{35,36} the use of ketamine for procedural sedo-analgesia is a common procedure, even if less used in Italy.⁹ The wide use of ketamine, in this context, may be useful in defining its safety profile in children.

A retrospective 7-year study was conducted by Oxford University where procedural sedation with ketamine was provided to 215 children (median age of 4 years). In 87% of cases, ketamine was administered intravenously and 9.8% of patients had an 'adverse outcome', of which agitation and apnoea were the most common.³⁶

Bellolio et al. provided a systematic review and meta-analysis reporting rates of adverse events for commonly used sedation drugs in the ED, including ketamine. More than 13,000 cases of procedural sedations in children were evaluated comparing sedo-analgesia with ketamine alone or in combination with other drugs; the following adverse events were the most common: vomiting (8.9%), agitation (2.4%), hypoxia (1.3%), and apnoea, bradycardia, laryngospasm and drooling (all <1%).³⁷ However, the use of ketamine in children <2 years can be associated with a high rate of uncommon airway and respiratory adverse events.³⁸

The i.v. route represents the principal mode of ketamine administration in procedural sedo-analgesia³⁹ but a pain-free alternative to i.v. insertion has to be considered by clinicians for children. As alternative routes, a small number of studies evaluated rectal,^{40,41} intranasal^{42–45} and submucosal⁴⁶ administration in the paediatric setting (Table 1). The rectal ketamine route was suggested in a clinical trial by Nilsson et al. performing sedation and analgesia in 61 children with cerebral palsy.⁴¹ In this case, the study protocol provided a combination of local anaesthetic paracetamol cream administered orally or rectally as well as midazolam (up to 0.4 mg/kg) and racemic ketamine (up to 5 mg/kg) both administered rectally. No serious events were reported and moderate sedation and analgesia were achieved.

Even if no sufficient data are available to recommend intranasal ketamine for sedation in children, a systematic review of randomized trials showed that intranasal ketamine on children undergoing procedural sedo-analgesia provided superior sedation to comparators and resulted in adequate sedation for 148/175 (85%) of participants. Intranasal ketamine administration was generally well tolerated with mild adverse effects, with vomiting being the most commonly reported by 9 out of 91 (10%) participants.⁴⁴

In another randomized clinical trial, the effectiveness of a submucosal administration of ketamine to induce sedo-analgesia in child candidates for diagnostic-therapeutic procedures was evaluated. Results showed that 4 and 3 mg/kg of submucosal ketamine are appropriate alternatives to i.v. ketamine.⁴⁶ Rayala et al. have also investigated the efficacy of oral ketamine administration in procedural analgesia in paediatric cancer patients undergoing to lumbar puncture

and bone marrow aspirations. These studies were conducted in a resource-limited hospital setting and, according to the results, oral ketamine could be defined as an option for lumbar puncture; bone marrow aspiration is defined as a painful and stressful procedure and oral ketamine is not sufficient.^{47,48}

The different ketamine dosages used accordingly to the different administration routes are reported in Table 2.

Ketamine and procedural pain in PPC: expert opinion

Children receiving PPC often require invasive measures (e.g. insertion of venous catheter, such as midline, pleural or abdominal drainage tubes, bladder catheter) that are performed outside the intensive care setting, thus needing the management of the consequent procedural pain.

Literature evidence in the paediatric setting, in particular the safety data collected in the paediatric ED context, suggests that ketamine should be considered as a promising alternative option for procedural sedo-analgesia also in the PPC setting. Compared with the combination of opioids/benzodiazepines, ketamine may be considered a more manageable drug, with a favourable tolerability profile associated with a lower burden of adverse events, especially at the respiratory level. These characteristics makes the use of ketamine possible also outside the surgical theater.^{49,50} Moreover, due to patients' complex conditions, standard routes of administration (i.v. or intramuscular) for sedo-analgesia are sometimes not adequate. The possibility of using alternative routes of administration (in particular intranasally and submucosally) is an additional reason that makes ketamine a viable alternative option for procedural sedo-analgesia in the home PPC setting, for instance, in patients with difficult venous access.

Ketamine and refractory status epilepticus

The annual incidence of status epilepticus in childhood is estimated at 10.5–42 per 100,000,⁵¹ often representing a lifelong and life-threatening condition. The most common causes of epilepsy include prenatal injury, developmental and genetic disorders, neurological impairment head trauma, and infectious disease.⁵² Between 15% and 30% of cases are refractory to conventional therapies and are defined as refractory status epilepticus (RSE) when not responding to first-line and second-line antiepileptic drugs.⁵³ The management of RSE represents a major challenge for paediatric physicians and a source of distress for families.⁵⁴

Seizure perpetuation in status epilepticus is due to mechanisms such as the internalization of γ -aminobutyric acid type A receptors and increased expression of NMDA receptor to the synapse.⁵⁵ Ketamine was proposed as an effective drug in status epilepticus due to its anticonvulsant effects and its potential to prevent glutamate-mediated neurotoxicity,

Table 2. Ketamine dosage in paediatric patients.

Administration route	Dosage
Intravenous	<i>Sedation</i> 1–2 mg/kg, then if needed 0.5–1 mg/kg/dose (maximum 25 mg) ⁷⁶
	<i>Analgesia</i> 0.5 mg/kg (repeated doses may be needed after 1–2 hours) or 0.05–0.5 mg/kg/h ^{21,76}
	<i>Resistant depression</i> 0.5 mg/kg intravenously twice weekly; not to exceed 6 weeks ⁷²
	<i>Refractory status epilepticus</i> Loading dose 1.5 mg/kg, 2.2–2.4 mg/kg/h ⁷⁷
Intramuscular	<i>Sedation</i> 3–4 mg/kg, then if needed 2–4 mg/kg (63)
Intranasal	<i>Analgesia</i> 1 mg/kg ⁷⁸
Oral administration	<i>Analgesia</i> 0.25–1 mg/kg/dose ⁷⁹
	<i>Sedation</i> 5–10 mg/kg ⁷⁶
Rectal	<i>Analgesia</i> 5–6 mg/kg, mixture of racemic ketamine ⁸⁰

blocking the influx of cations through the NMDA receptor channel.⁵⁶ Consequently, some authors proposed ketamine as a promising option for treating RSE in children (Table 1).⁵⁷

A retrospective study was recently conducted on 18 children with RSE who received ketamine in intensive care unit of Beijing Children's Hospital, divided into the loading-maintenance group (7 patients) and the maintenance group (11 patients). RSE was controlled with ketamine in 11 children (all patients in the loading-maintenance group and four in the maintenance group), without relevant adverse reactions, showing a significantly greater effectiveness of the loading-maintenance protocol. Despite it being a very small study, it suggested the effectiveness of ketamine for RSE control in children.⁵⁸

Rosati et al. adopted a protocol for RSE, including i.v. ketamine infusion. Midazolam was also administered to prevent emergence reactions. In a retrospective study over a period of nearly 2 years, nine children with RSE were treated with ketamine infusion, with a successful response in 70% of cases. The median dose of ketamine in continuous i.v. infusion was 40 µg/kg/min. None of the patients experienced serious adverse events.⁵⁹

Despite these encouraging results, more research and larger studies are necessary to evaluate ketamine efficacy, safety and dosage in RSE treatment in children.⁶⁰ For instance, a multicentre, randomized controlled study has been carried out in Italy to

assess the efficacy of ketamine compared with conventional antiepileptic drugs in the treatment of RSE in children. In total, 57 patients (aged from 1 month to 18 years) were enrolled and were randomized to the control or experimental arms; the results are not yet available to our knowledge.⁶¹ Of note, it has been underlined that the use of ketamine in children affected by RSE avoids the pitfalls and dangers of endotracheal intubation, which is known to worsen RSE prognosis.⁶²

Ketamine for the treatment of RSE in PPC: expert opinion

In a recent cross-sectional survey, approximately 40% of PPC patients were affected by a neurological disease⁶³ and around half of all children with cerebral palsy have epilepsy. Amongst children with this condition, epilepsy is characterized by the following features: early onset, high frequency, presence of multiple seizure types, increasing drug resistance, low remission rates, high recurrence of seizures and status epilepticus, mortality.^{64,65} Consequently, seizure control is a recurrent problem in PPC setting and has a great impact on patient quality of life. Due to its pharmacological properties, ketamine could be a suitable option after the failure of conventional drugs in the treatment of RSE in children eligible for PPC such as those with rare diseases and those with severe cerebral palsy.

Conclusion

In the PPC setting, the clinical conditions could be hugely different and complex. Clinicians deal with many conditions that exhibit a high degree of drug resistance; several different organic dysfunctions, psychological alterations and suffering need to be treated. The assessment and management of pain represent primary objectives in PPC but also diagnostic and therapeutic procedures and neurological impairment represent a daily challenge. In our opinion, the use of ketamine in PPC should be more widely considered due to its overall favourable safety profile and its efficacy, which are supported by an increasing number of studies, although in settings different from PPC and of mixed quality. Ketamine should be proposed according to a case-by-case evaluation according to the specific diagnosis, and the dosage and route of administration should be tailored to the specific patient needs. Furthermore, some evidence suggests the safety and efficacy of ketamine in acute pain⁶⁶; these findings can prompt further research on the use of ketamine for the treatment of acute pain in PPC.

Status epilepticus represents another clinical condition frequently observed in the PPC setting and it is, in many cases, refractory to conventional pharmacological treatments. Considering the encouraging data in the paediatric setting, the use of ketamine to treat RSE in PPC should certainly

be further investigated to provide an additional treatment option.

Patients in PPC often develop physical and psychological sequelae due to their disease and treatment. Psychiatric issues and, in particular, depression and anxiety are reported in up to 30% of this population.⁶⁷ Oral ketamine is effective in treating resistant depression in adult patients.^{68–70} Although scant information is available for adolescents and children^{71,72} and, to our knowledge, no data are available in the PPC setting, ketamine might be investigated in the treatment of depression and anxiety in PPC. Due to the interaction of ketamine with many receptors, the drug's effects have also been explored for other indications such as bronchial asthma exacerbations.⁷³ In addition, in the PC setting, children could experience airway obstruction and dyspnoea for many clinical reasons due to mediastinal or pulmonary mass, pleural effusion and heart failure.^{74,75} Therefore, ketamine should also be considered in this setting.

Ketamine also has the advantage of being a relatively inexpensive drug and could be used for several clinical conditions. Therefore, it could be useful to propose a standardized approach to ketamine use in PPC patients, both in the hospital and home-care setting, following the failure of conventional treatments. We believe that a more comprehensive evaluation of ketamine in patients with neuropathic and mixed pain could be of particular interest.

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