

Intranasal Ketamine as Analgesia to Treat Refractory Pain in Children in the Outpatient Setting

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Abstract

Ketamine has become a useful analgesic in treating neuropathies, disorders of central sensitization, and hyperalgesia in adults and children. It has been delivered by various routes including intravenous, oral, sublingual, topical, rectal, intramuscular, intrathecal, and intranasal with documented success in the inpatient and acute care settings. This article presents 3 cases in which intranasal ketamine was effectively used to treat refractory pain in children with various oncologic diagnoses that were home receiving palliative or hospice care.

Keywords: Intranasal Ketamine; Refractory Pain; Non-Opioid Analgesia; Outpatient Pediatric Pain Management

Received Date: November 11, 2016

Accepted Date: January 23, 2017

Published Date: January 30, 2017

Citation: Bettini, E., et al. Intranasal ketamine as analgesia to treat refractory pain in children in the outpatient setting. (2017) *J Palliat Care Pediatr* 2(1): 37- 39.



Introduction

Intranasal Ketamine use in Pediatrics

Ketamine has been utilized in the past 50 years as both an anesthetic and analgesic in both children and adults, mainly in the acute care and operative settings. Ketamine is a N-methyl-D-aspartic receptor (NMDA-R) antagonist that is thought to interact with opioid, monoamine, cholinergic, purinergic, and adenosine receptors, as well as having local anesthetic properties^[1,2]. The reduction of persistent pain related to cancer and other chronic illnesses with ketamine is presumed related to the decrease of central sensitization via antagonism of the NMDA-R. Central sensitization leads to persistent pain that results from increased membrane excitability, amplified synaptic transmission, and reduced inhibition of neurons in the dorsal horn^[2]. Chronic pain results in sensitization of central pain pathways and a hyperalgesic state in some patients^[3]. Other anti-nociceptive effects of ketamine may be related to reduction of pro-inflammatory chemicals through inhibition of tumor necrosis factor alpha (TNF-alpha), interleukin 6 (IL-6) gene expression in lipopolysaccharide activated macrophages, and nitric oxide synthase^[1,4]. Due to NMDA receptor antagonism, along with reduction of anti-pro inflammatory chemicals, ketamine is an ideal drug for the treatment pain refractory to opioid management.

Ketamine is metabolized by the CYP2B6, CYP3A4,

and CYP2C9 enzyme pathways in the liver, and has been found to be safe in the setting of renal and hepatic failure with no significant accumulation of the drug^[1]. The drug also has minimal impact on cardiovascular or respiratory function in comparison with many other analgesics^[5], and has been utilized commonly as part of general anesthesia during cardiac surgery. Side effects of ketamine are dose dependent and include dizziness, somnolence, nausea, agitation, hallucination, blurred vision, confusion, and night mares^[2,6].

Ketamine is most often administered via intravenous route in the clinical setting and is widely used for procedural sedation/analgesia, although as previously mentioned, it can be delivered through most means of drug delivery with good bioavailability. Oral dosing is available, however, this route undergoes significant first pass metabolism, which limits its efficacy and onset of action^[6]. Administered intranasally, ketamine avoids first pass metabolism, and can be utilized in patients with limited ability to swallow or without IV access. In a study by Carr and Colleagues^[7], intranasal ketamine showed efficacy in treating breakthrough chronic pain in adults in doses from 10 - 50 mg. A more recent study of intranasal ketamine in adult patients with neuropathy found doses of 0.2 - 0.4 mg/kg to be effective with an onset of action of 60 minutes, duration of 2 - 3 hour analgesic effect^[6]. Intranasal ketamine has been utilized in procedural se-



dation in pediatrics with doses from 3 - 9 mg/kg/dose, but found to be less effective than IV ketamine for adequate sedation^[5-8]; however, the difficulty of establishing intravenous access in young children makes this route less desirable and precludes routine outpatient use. When comparing intranasal fentanyl at 1.5 mcg/kg and intranasal ketamine at 1 mg/kg in children aged 3 - 13 years with limb injuries, pain was reduced in both groups at 15 minutes and 60 minutes following administration. Higher satisfaction with effectiveness of analgesia was reported in the ketamine vs. the fentanyl group (83 vs. 72%)^[9]. Given some evidence of analgesic efficacy, intranasal ketamine was prescribed in 3 cases of children with advanced symptom needs with the goal of improving pain control. Intranasal ketamine was chosen in these cases due to either increasing demand of opioids without further analgesia, or when opioids were completely ineffective in reducing pain.

Case Report

Case 1

A 7 year-old female patient was diagnosed with a disseminated Juvenile Pilocytic Astrocytoma (JPA), and was being treated with oral chemotherapy. She presented to the pediatric pain medicine clinic with pain in her right cheek and eye following a suspected herpes zoster (HSV) infection, and was diagnosed with herpes induced trigeminal neuralgia. The pain had many characteristics of classic neuropathy with intermittent and stabbing and shooting pain from her right eye into her ear on the same side. The patient was started on amitripty line at night with some relief, and gabapentin was titrated to 30 mg/kg/day with further alleviation of pain. However, the patient continued to have pain flares that occurred during times of infection. The pain during these flares was significant causing the patient to stay home from school and withdraw from friends and favorite activities. A trial of intranasal ketamine was done in the clinic at 0.5 mg/kg/dose. Pain relief from an 8/10 to a 0/10 was achieved after 2 doses that were spaced 30 minutes apart. The child reported some minor dizziness, but no other side effects were noted. Vital signs, which included blood pressure, pulse oximetry, and heart rate were monitored in clinic and remained stable during this trial, and the patient was able to ambulate independently following administration of the drug. Intranasal ketamine at 0.5 mg per spray was ordered for home use during pain flares to be taken up to 2 sprays every 6 hours as needed. The parents reported that the spray was utilized 1 - 2 times per month with resolution of pain with primarily the first spray, with rare use of the second 0.5 mg/kg dose. Side effects were limited to minor dizziness that had minimal effect on function.

Case 2

A 17 year-old male patient with osteosarcoma with metastasis to the right scapula was noted to have neuropathic pain radiating down his arm, and to his shoulder and axilla. This pain was described as shooting and burning with allodynia noted on exam. This patient was followed by palliative care while inpatient and outpatient, as well as home hospice utilizing concurrent care legislation for children. He was treated with methadone around the clock, and oxycodone for break through pain. Gabapentin was prescribed as an adjuvant with minor reduction in neuropathy symptoms, and was later discontinued due to nau-

sea. The patient was administered ultra-low dose ketamine via IV at 0.1 mg/kg/hr for 48 hours during an inpatient admission with further resolution of neuropathic pain. Intranasal ketamine was prescribed at 0.5 mg/kg with instruction to take 1 - 2 sprays every 6 hours as needed after discharge home. On the next admission 1 week later for chemotherapy, the parent and patient report that the intranasal ketamine was utilized 3 times that week for pain that was refractory to the break through oxycodone with typical reduction of pain from an 8 - 10/10 to a 5 - 6/10. Side effects were reported to be minor somnolence, dizziness, and nausea that last approximately 1 hour after administration.

Case 3

An 11 year-old male patient with disseminated choroid plexus carcinoma was receiving hospice care at home at end of life. The patient was on long-term high dose opioids, which included methadone every 6 hours, oxycodone every 4 hours, fentanyl transdermal, and morphine sublingual for break through pain. He continued to complain of severe wide spread pain, and was requiring greater use of break through morphine doses. However, the patient was reluctant to take additional morphine for fear of hastening death. Hyperalgesia was also suspected and the patient was started on intranasal ketamine at 0.5 - 1 mg/kg/dose every 6 hours as needed. He received 2 doses in the last 3 days of life with notable reduction in non-verbal pain behaviors and agitation. The ketamine was utilized comfortably despite the patient no longer being alert in the final two days of life.

Discussion

Recently the use of opioids in chronic pain management has come under scrutiny due to an increase in overdose deaths nationwide. This along with the possibility of causing hyperalgesia at high dosing has made many clinicians look outside of the opioid class for chronic malignant and non-malignant pain management. The NMDA antagonist ketamine has proved to be an effective analgesic in chronic refractory pain in both adults and children, however, has been underutilized in pediatrics to date. This is especially true for the use of ketamine delivered by methods other than IV and outside of acute care. Ketamine administration via intranasal route shows promise in allowing for rapid analgesia in chronic malignant and non-malignant pain with minimal side effects in children within the outpatient setting. These cases demonstrated that ketamine can safely be utilized to treat opioid refractory pain in children within the home setting. However, further research with a randomized control trial is necessary to reach a conclusion on the safety and efficacy of intranasal ketamine in pediatric patients.

Conclusion

Intranasal ketamine at 0.5 mg to 1 mg/kg per dose every 6 hours was found to be effective and safe in this series of 3 pediatric cases. There were no noted adverse cardiovascular consequences or dysphoric reactions in this small limited case series. Side effects were minimal and the drug achieved the goal of significant pain improvement with few doses. For each of these cases, the cost of the ketamine was covered by either hospice or the patient's private insurance. The drug was formulated into a 10% aqueous solution utilizing ketamine 100 mg/ml in

normal saline 0.9%. The solution was placed in an atomizer with each spray measured to deliver a 0.5 mg/kg dose. A randomized controlled study is warranted in order to fully study the safety and efficacy of intranasal ketamine as analgesia for children with chronic refractory pain or hyperalgesia.

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