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# Nebulized ketamine for managing acute pain in the pediatric emergency department: A case series

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## Abstract:

Administration of sub-dissociative doses of ketamine is used via intranasal (IN) and intravenous routes in the pediatric emergency department for managing acute pain. Due to difficulties in both obtaining intravenous access and compliance with IN medications in children, administration of ketamine via breath-actuated nebulizer can serve as a valuable modality for timely analgesia in children where dosing titration is patient controlled. We describe five pediatric patients who received ketamine via breath-actuated nebulizer at 0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg, with all patients experiencing a decrease in pain score. This case series introduces ketamine inhalation as a modality for managing pain in children.

## Keywords:

Analgesia, ketamine, nebulization, sub-dissociative dose

## Introduction

Pain is a common chief complaint for children presenting to the pediatric emergency department (PED). Ketamine is widely used in the PED for managing a variety of painful conditions as a part of both procedural sedation (full dissociative dose) and as an analgesic (sub-dissociative dose).<sup>[1-2]</sup> Ketamine is a noncompetitive N-methyl-D-aspartate/glutamate receptor complex antagonist that provides a “wind-up” phenomenon at the level of the spinal cord (dorsal ganglion) and central nervous system. This unique property decreases pain by diminishing central sensitization and hyperalgesia.<sup>[1]</sup>

In pediatric patients requiring analgesia, sub-dissociative ketamine (SDK) can be administered via intravenous (IV) (0.1–0.3 mg/kg), subcutaneous (SQ)

(0.1–0.3 mg/kg), and intranasal (IN) routes (1 mg/kg).<sup>[1-7]</sup> Obtaining IV access in children presents many challenges and at times, may be unattainable. Compliance with IN administration for children can be suboptimal. Administration of ketamine via inhalation may serve as an alternative for timely analgesia in the PED. Administration of nebulized ketamine for children has been studied for use in preoperative sedation and acute postoperative management of sore throat, with dosing regimens ranging from 0.5 mg/kg to 2 mg/kg.<sup>[1,8,9]</sup>

This case series comprises the first five patients recruited from an institutional review board-approved prospective randomized, double-blinded controlled study comparing the efficacy and adverse effects of SDK via breath-actuated nebulizer (BAN) for acute pain in the PED at three different dosing ranges. The dosing regimens were based on previous

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studies using inhaled ketamine.<sup>[5-9]</sup> A convenience sample of patients aged 7–17 years, presenting with acute pain (traumatic and nontraumatic) of 5 out of 10 or greater on a verbal numeric pain rating scale, were included in the study.<sup>[10]</sup> Exclusion criteria included altered mental status, pregnancy, airway abnormalities, guardian not available for consent, closed head injury, seizure disorder, use of opioid analgesic, or schizophrenia/bipolar disorder.

As per departmental nursing triage protocol, patients presenting with pain or fever could receive oral acetaminophen (15 mg/kg with maximum dose 650 mg) prior to physician evaluation. After informed consent and assent, patients were randomized to one of the three dosing arms and were allowed up to 15 min to inhale self-administered SDK with the option to stop at any time. If there was any remaining medication, we recorded the actual dose received [Table 1]. Changes in pain score and rates of adverse effects were evaluated via Side Effects Rating Scale of Dissociative Anesthetics and were recorded at 15, 30, and 60-min postinhalation.<sup>[11]</sup>

We present five cases that utilize nebulized ketamine via BAN at three different dosing regimens: 0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg for patients presenting to the PED with an acutely painful condition.

## Case Series

### Case #1

A 10-year-old male with no past medical history (PMH) presented with right shoulder pain after falling. The patient rated his pain as 6/10. On physical examination, he had tenderness to the right clavicle and shoulder with swelling. Imaging demonstrated a midshaft fracture of the right clavicle. The patient was pretreated with acetaminophen and received nebulized ketamine at 1 mg/kg with a change of pain score from 6 to 0. The patient was placed in a sling and referred to an orthopedician.

### Case #2

A 16-year-old male with no PMH presented with right forearm pain after falling on his arm. The patient rated his pain an 8/10 with tenderness, swelling, and mild deformity of the right forearm on the physical examination. Imaging demonstrated an angulated fracture of the proximal radial shaft. The patient was pretreated with acetaminophen and received nebulized ketamine at 1.5 mg/kg with a change in pain score from 8 to 6. The patient was placed in a cast and referred to an orthopedician. Ondansetron was administered secondary to nausea.

### Case #3

A 10-year-old male with no PMH presented with left forearm pain after falling on his arm. The patient

**Table 1: Patient characteristics and numerical rating scale pain scores**

Patient #	1	2	3	4	5
Age/sex	10 male	16 male	10 male	15 male	15 male
Chief complaint	Traumatic shoulder pain	Traumatic arm pain	Traumatic wrist pain	Traumatic arm pain	Traumatic knee pain
Final diagnosis	Clavicular fracture	Radial fracture	Radial and ulnar fracture	Elbow effusion	Knee sprain
Pretreatment	Acetaminophen	Acetaminophen	-	Acetaminophen	-
Dose	405 mg	650 mg		600 mg	
Dosage	15 mg/kg	Adult dose		15 mg/kg	
Given	Right before starting	1.25 h before starting		Right before starting	
Weight	27 kg	55 kg	45 kg	Initial 40 kg actual/correct 60 kg	78 kg
Mg/kg/dosing arm	1 mg/kg	1.5 mg/kg	0.75 mg/kg	0.75 mg/kg	1.5 mg/kg
Mg/kg dose inhaled	0.81 mg/kg	1.23 mg/kg	0.56 mg/kg	0.44 mg/kg	0.82 mg/kg
Total dose offered	27 mg	85 mg	33 mg	45 mg	115 mg
Dose inhaled	22 mg	68 mg	25.1 mg	26.1 mg	64.4 mg
Baseline vitals					
HR	94	90	103	68	66
BP	111/55	138/68	121/71	118/76	125/73
RR	18	18	24	24	20
O <sub>2</sub>	99	100	100	100	100
Pain over time					
Baseline	6	8	8	10	7
15 min	1	7	6	7	6
30 min	0	6	6	7	5
60 min	0	6	5	4	3

NRS: Numeric Rating Scale, HR: Heart rate, BP: Blood pressure, RR: Respiratory rate

rated his pain an 8/10. Physical examination showed significant swelling and deformity of the left forearm. Imaging demonstrated a fracture of the distal radius and ulna shafts with volar displacement. The patient received nebulized ketamine 0.75 mg/kg with a change in pain score from 8 to 5. The patient was subsequently treated with IN midazolam at 0.3 mg/kg for anxiety and IV ketamine at 1 mg/kg for procedural sedation to facilitate a closed reduction and cast placement.

#### Case #4

A 15-year-old male with no PMH presented with left elbow pain after falling. The patient rated his pain as 10/10 and had tenderness as well as swelling of the left elbow. Imaging demonstrated a joint effusion, with a possible nondisplaced radial head fracture. The patient was pretreated with acetaminophen and received nebulized ketamine at 0.75 mg/kg with a change in pain score from 10 to 4. The patient was placed in a splint and referred to an orthopedician.

#### Case #5

A 15-year-old male with no PMH presented with left knee pain after playing soccer. The patient rated his pain as 7/10 and had tenderness and swelling to the left knee. Imaging demonstrated a small joint effusion. The patient received nebulized ketamine at 1.5 mg/kg with a change in pain from 7 to 3. The patient was placed in an ace wrap and referred to an orthopedician.

## Discussion

Nebulized analgesia has multiple advantages including (1) provision of rapid, effective, and titratable analgesic delivery; (2) provision of a painless method of delivery; and (3) improvement of overall pain management in the PED.<sup>[12]</sup> BAN is a disposable nebulizer that can generate aerosol during inspiratory flow (breathe actuated), triggering the opening valve, allowing virtually no drug loss to the environment.<sup>[13]</sup> BAN has the potential to provide greater compliance and a safer patient environment and may impact clinical outcomes such as decreased length of stay, improved patient outcome, and reduced hospital/patient costs.

We describe five male patients aged from 10 to 16 years presenting with acute painful conditions between May 2019 and June 2019 who received nebulized ketamine. None of the patients had contraindications to SDK. Three patients received nebulized ketamine at 1.5 mg/kg dose, one patient at 1 mg/kg, and one patient at 0.75 mg/kg. One patient from each dosage arm received a dose of acetaminophen. The dosages of nebulized ketamine, vital signs, and pain scores are presented in Table 1.

Of note, some patients were pretreated with acetaminophen, which could have altered the overall pain scores and made it difficult to interpret the effect of nebulized ketamine. All the patients in this case series presented with musculoskeletal complaints, which makes it unclear if nebulized ketamine will alleviate other forms of acute pain to the same degree.

All the five patients experienced a variable degree of improvement of pain from baseline postmedication administration with side effects of varying degrees in severity. Four out of the five patients had dizziness of varying severity with resolution by 60 min. One patient had a modest sense of unreality that lowered to a weak sense by 60 min. The same patient had modest mood changes with gradual resolution by the end of data collection. Three patients had some form of discomfort, with the highest being bothersome. Two out of three patients had resolution of discomfort by the end of data collection, with the last patient having a gradual decrease from bothersome to weak discomfort [Table 2]. For agitation and sedation monitoring, only one patient reported feeling some drowsiness that worsened to light sedation but then resolved by 60 min [Table 3].

All patients had a variable degree of improvement of pain with side effects of varying degrees in severity. Previous studies have shown improvement of pain and decreased need for rescue analgesia in children treated with inhaled SDK.<sup>[5-8]</sup> Based on a review of the existing literature and the findings of our case series, it would seem that SDK via BAN has the potential to provide some alleviation of pain with varying side effects.

## Conclusion

This case series describes the utilization of SDK via BAN at three different dosing regimens for pediatric patients presenting with acute painful conditions.

We believe that inhalation of ketamine via BAN for managing pain in the PED may be an additional modality to the analgesic armamentarium of PED clinicians in providing rapid, effective, and noninvasive pain relief. Completion of a prospective, randomized study will allow for further evaluation of efficacy and safety of nebulized ketamine along with potentially identifying an optimal dose for analgesia in the PED.

#### Prior publication

This case series has no prior publications nor has been presented in any conference or seminar at this time.

#### Consent to participate

Members of the research department or authors of the study obtained consent by providing information verbally and written about nebulized ketamine along with risk factors. Parents and patients were allowed to ask questions and consider enrolling in the study. All patients' parents

**Table 2: The severity of side effects rating scale of dissociative anesthetics by patient and time**

Level of severity						
Adverse effect	Time point (min)	0 – No change	1 – weak	2 – modest	3 – bothersome	4 – Very bothersome
Dizziness	15	Patient 1	Patient 5	-	Patient 2	Patients 3, 4
	30	Patient 1	Patient 3, 5	Patients 2, 4	-	-
	60	Patients 1–5	-	-	-	-
Unreality	15	Patients 1, 3–5	-	Patient 2	-	-
	30	Patients 1, 3–5	-	Patient 2	-	-
	60	Patients 1, 3–5	Patient 2	-	-	-
Mood change	15	Patients 1, 3–5	-	Patient 2	-	-
	30	Patients 1, 3–5	Patient 2	-	-	-
	60	Patients 1–5	-	-	-	-
Discomfort	15	Patients 1, 5	Patients 3, 4	-	Patient 2	-
	30	Patients 1, 3–5	-	Patient 2	-	-
	60	Patients 1, 3–5	Patient 2	-	-	-

**Table 3: Patients reporting agitation or sedation according to Richmond agitation–sedation scale**

Time point	15 min	30 min	60 min
Level of sedation			
-5 Unarousable	-	-	-
-4 Deep sedation	-	-	-
-3 Moderate sedation	-	-	-
-2 Light sedation	-	Patient 1	-
-1 Drowsy	Patient 1	-	-
No effect			
0 Alert and calm	Patients 2–5	Patients 2–5	Patients 1–5
Level of agitation			
+1 Restless	-	-	-
+2 Agitated	-	-	-
+3 Very agitated	-	-	-
+4 Combative	-	-	-

provided consent and were continuously monitored during treatment and throughout hour posttreatment. The physicians, parents, patients, and nurses were all blinded to the dose given to the patients and the drug was provided by the pharmacist by a predetermined randomized list. Copy of the study and consent was given to the families.

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#### Author contributions statement

SM and JZ contributed to the conception and design of the work. AR, SM, and JZ took responsibility in the literature review. AR, MF, and JZ assisted in consenting and data collection/processing. All authors were involved with the organization/supervision of the article; contributed to the analysis of data, interpretation of the data, drafting/writing of the manuscript; and reviewed/approved the final version to be published.

#### Ethical approval

This case series was approved by the hospital's, Maimonides Medical Center, institutional review board (IRB), and the ethical committee on May 9, 2019.

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#### Conflicts of interest

None Declared.

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