

In Children with Limb Injury Pain, Shall We Use Intranasal Fentanyl or Ketamine?

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Introduction

Pain relief is an essential component in the management of children presenting to the Emergency Department (ED). However, difficulties in obtaining venous access delay the provision of adequate analgesia (1). The intranasal route is both an effective and an easy way of administering drugs and has provided a well-tolerated alternative to the distress caused by intramuscular and intravenous access, especially in children (2, 3). Intranasal fentanyl has been widely reported to be an effective tool in pediatric pain relief along with other opiates (4). However, ketamine has only recently been described for the provision of analgesia in pediatric emergency settings (5-7).

This study by Graudins et al. was conducted to compare the analgesic effectiveness of intranasal ketamine versus fentanyl in pain reduction among children presenting with isolated limb injuries.

Methods and Design (Figure 1)

- **Population Studied:** The inclusion and exclusion criteria of the study are presented in Tables 1 and 2, respectively.
- **Study Design:** Randomized controlled double-blind intention-to-treat equivalence clinical trial.
- **Intervention:** Intranasal ketamine (1 mg/kg) or intranasal fentanyl (1.5 µg/kg) administered via a mucosal atomization device in a standardized volume of 0.03 mL/kg, with a total maximum volume of 1.5 mL divided equally between both nares.
- **Study Outcomes:** The primary and secondary outcomes of the study are presented in Table 3.

Results

The results of the study are presented in Table 4 and the adverse events in Table 5.

Appraisal: This study was unique in evaluating intranasal ketamine versus intranasal fentanyl in children via a comparative trial format. It was conducted under appropriate concealment and blinding. It provides great insight into the use of intranasal analgesics in the pediatric population because this is still a relatively new aspect of pediatric anal-

gesia and highlights the growing need for effective and fast analgesia with the least amount of discomfort, which is crucial in this population.

In this study, the assessment of pain severity was undertaken via different modalities of pain rating scales using a child's self-reporting of pain, which was shown to be superior to observational assessments in estimating pain severity in young children (8). However, the self-reporting of pain depends on the cognitive ability of children and their understanding that their pain severity can be objectively measured on a scale (9). As is evident in this study, pain rating scales were adequately tailored to pre-specified age groups, with younger children using the Face Pain Scale-Revised (FPS-R) and older children using the Visual Analog Scale (VAS), taking into consideration each age group's cognitive abilities, which confirms the appropriate utilization and strength of the methodology. The authors in this trial used an adequate dose of intranasal fentanyl of 1.5 µg/kg, as the average of 1–2 µg/kg, although some other trials had a higher dosing regimen (10, 11). This dosage was comparable to that in the majority of studies conducted on intranasal fentanyl administered via atomization (4, 12-15).

The study sample size was adequate and similar to those in other trials addressing similar questions (12, 13). The study sample size was sufficient to detect a difference of 20 mm on the VAS, which is a clinically significant difference as determined by Powell et al. (16).

The baseline characteristics were similar across both study groups in terms of age, gender, initial pain rating, and ibuprofen given.

The study authors demonstrated that ketamine achieved comparable pain reduction as fentanyl for acute pain from limb injuries, as shown in Table 4. Despite the novelty and strengths of this study, it has some limitations. Almost 80% of the ketamine group (compared with 40% in the fentanyl group) was reported to experience some form of adverse event (Table 5), which the authors described as mild. However, when looking at the figures, it is evident that intranasal ketamine produces almost twice as much side effects as intranasal fentanyl, which, in our opinion, is significant. Ketamine is known to be a dissociative anesthetic; hence, the fact that more patients (55%) in the ketamine group complained of dizziness compared with (10%) in the fentanyl group is not surprising. Dizziness as an adverse event may increase the risk of falls in children with limb injuries, which may necessitate their observation in the ED until the dizziness

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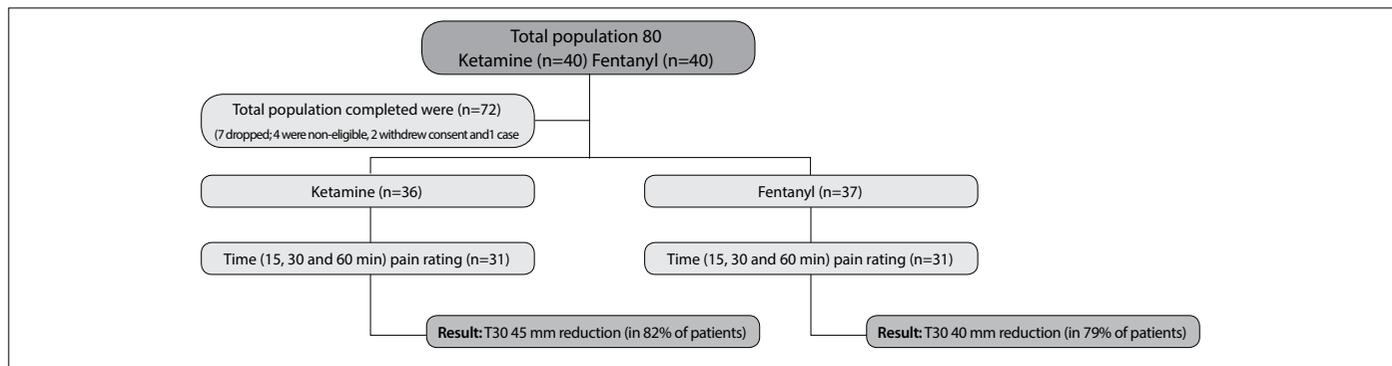


Figure 1. Study methods and design

Table 1. PICHFORK study inclusion criteria

1	Children between the ages of 3 and 13 years, weighing <50 kg
2.	Isolated musculoskeletal limb injuries
3.	Pain ≥ 6 on an 11-point pain scale [0=none, 10=worst pain] at triage
4.	Consideration of INF as the usual method of analgesia according to hospital guidelines
Study participants must have met all four inclusion criteria	

Table 2. PICHFORK study exclusion criteria

1.	Inability to obtain informed consent from parent or guardian
2.	Treatment with serotonergic antidepressants
3.	Previous administration of parenteral or intranasal analgesics or opioid analgesics
4.	Opioid antagonist use
5.	Allergy to ketamine, fentanyl, or ibuprofen
6.	Aberrant nasal anatomy or acute or chronic nasal problems or nasal trauma that may preclude adequate intranasal delivery
7.	Presence of multiple trauma or head injury with loss of consciousness or cognitive impairment
Study participants were excluded if any of the above criteria were present	

Table 3. Outcomes measured

Primary outcome	
1.	Median reduction in pain rating at 30 min after administration of the study drug
Secondary outcomes	
1.	Reduction in pain rating at 15 min and 60 min
2.	Pain reduction equal to or greater than 20 mm
3.	Subjective improvement and satisfaction
4.	University of Michigan sedation score
5.	Adverse events
6.	Need for and timing of rescue analgesia

Table 4. Primary outcome results

	Fentanyl	Ketamine
Median reduction in pain rating 30 min after administration of the study drug	40 mm (20-45)	45 mm (20-60)
Median (interquartile range) mm		
Difference in medians (95% CI) (ketamine to fentanyl)	5 (-10 to 20)	
	Fentanyl	Ketamine
Number of subjects achieving a reduction in pain rating of >20 mm at 30 min	27/34 (79%)	28/34 (82%)
Number (Percentage)		
Difference in medians (95% CI) (ketamine to fentanyl)	3 (-16 to 22)	

Table 5. Adverse events

	Fentanyl	Ketamine
Adverse events encountered for each group	15/37 (40%)	28/36 (78%)
Number (Percentage)		
Difference in medians (95% CI) (ketamine to fentanyl)	38 (-58 to 16)	

subsidies, which may increase the length of stay in the ED (See comment in PubMed Commons below17). Moreover, caring for these patients may require additional personnel with transport, etc., which increases the utilization of resources in the ED.

In the ketamine group 30% complained of drowsiness compared with 13% in the fentanyl group, and 10% complained of hallucination compared with 0% in the fentanyl group. With respect to other adverse events, ketamine recorded a higher percentage for all other adverse events measured in this trial in contrast to fentanyl. In our opinion, the results obtained from this study highlighted the higher profile of adverse events associated with ketamine than that with intranasal ketamine in comparison with intranasal fentanyl. Intranasal fentanyl has widely been used over the past years, and for quite some time now, and it has been proven by several studies to be a safe and effective me of analgesia with limited side effects (10, 11, 18).

The intranasal route of drug administration for pain relief has been well established in the literature. However, atomized intrana-

sal administration when compared with intranasal drops has been associated with higher satisfaction in terms of greater acceptance and fewer aversive reactions in children. Moreover, it was associated with a more rapid onset and recovery than administration via intranasal drops (19). Alternatively, nebulized administration of drugs has shown a lot of promise recently, which may prove very helpful in EDs that have not yet acquired atomization devices. Nebulized fentanyl has been compared with IV fentanyl (20) and IV morphine (21) and showed good results with comparable efficacy in pain relief. Because fentanyl is a highly lipophilic drug, this makes its use via nebulization, which depends mainly on pulmonary absorption, an effective substitute. However, higher doses are required (3–4 µg/kg), bearing in mind the amount of the drug lost to the environment and the non-absorptive tissue encountered in the respiratory tract. On the other hand, one should be aware that the long-term effect of fentanyl on the lung parenchyma and vasculature has not been established, and this poses a relatively higher risk than the nasal mucosa (22). Moreover, the time needed for a drug to be nebulized is several minutes in contrast to a few seconds for atomization. To date, we are not aware of any study that has assessed nebulized versus atomized fentanyl for pain relief in children in a comparative trial format, and this is a question that needs to be answered. Unlike fentanyl, nebulized ketamine has not yet been studied and this is also an area for further research.

When comparing the traditional method of pain relief via IV administration versus intranasal administration, the cost of a mucosal atomization device is around \$4, whereas the cost of a cannula for the IV administration of medication is \$0.50 to \$1. In addition, the time needed to secure a cannula, personnel, failed attempts, and wasted cannulas may narrow the cost gap between the expenses of the two modalities of pain relief. Atomization has the advantage of eliminating the anxiety-provoking experience of needles, let alone the minimal pain associated with intranasal administration, and consequently the higher patient and family satisfaction.

Conclusion

This study provides valuable information about the efficacy of intranasal analgesia in the pediatric population and the alternative drugs that might be used. Intranasal fentanyl, with its lower profile of adverse events, remains a preferable choice for intranasal analgesia in children with limb injuries.

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