Systematic Review and Meta-Analysis

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Influence of ketamine versus fentanyl on pain relief for pediatric orthopedic emergencies

A meta-analysis of randomized controlled studies

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Abstract

Introduction: The comparison of ketamine with fentanyl for pain control of pediatric orthopedic emergencies remains controversial. We conduct a systematic review and meta-analysis to explore the influence of ketamine versus fentanyl on pain management among pediatric orthopedic emergencies.

Methods: We have searched PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through September 2020 for randomized controlled trials assessing the effect of ketamine versus fentanyl on pain management for pediatric orthopedic emergencies.

Results: Five randomized controlled trials are included in the meta-analysis. Overall, compared with fentanyl for pediatric orthopedic emergencies, ketamine led to similar change in pain scores at 15 to 20 minutes (standard mean difference = -0.05; 95% confidence interval [CI] = -0.38 to 0.28; $P = .77$) and 30 minutes (standard mean difference = 0.11; 95% CI = -0.20 to 0.42; $P = .49$), as well as rescue analgesia (RR = 0.90; 95% CI = 0.54 to 1.51; $P = .69$), but revealed the increase in nausea/vomiting (RR = 2.65; 95% CI = 1.13 to 6.18; $P = .02$) and dizziness (RR = 3.83; 95% CI = 1.38 to 10.60; $P = .01$).

Conclusions: Ketamine may be similar to fentanyl in terms of the analgesic efficacy for pediatric orthopedic emergencies.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials, SMD = Standard Mean difference.

Keywords: children, fentanyl, ketamine, pain control, randomized controlled trials

1. Introduction

Inadequate pain control has become a major public health concern.[1–5] The pain of children is widely and particularly be underdiagnosed and undertreated for orthopedic emergencies.[6] Children receiving pain medication always suffer from long delays in administration.[7] The intranasal administration route is a more efficient alternative for delivering analgesia due to rapid onset of action, minimal discomfort, and relative simplicity.[8]

Opioids via intranasal administration have been the most commonly used class of analgesics for children presenting with severe pain,[9] but may be limited by genetic predisposition of diminished sensitivity and some adverse effects.[10,11] Ketamine is widely used to facilitate painful procedures and pain control in adults 13 to 20 and children.[12–16] In the PICHFORK trial, intranasal ketamine (1 mg/kg) and intranasal fentanyl (1.5 μg/kg) were documented to have similar and clinically meaningful pain reduction at 30 minutes.[16] Another trial also confirmed the similar pain reduction at 20 minutes with frequent adverse events between 2 drugs.[15]

Recently, several studies have compared the analgesic efficacy of ketamine versus fentanyl for pediatric orthopedic emergencies, but the results are conflicting.[15–18] This systematic review and meta-analysis of randomized controlled trials (RCTs) aims to assess their efficacy on pain control of pediatric orthopedic emergencies.

2. Materials and methods

This systematic review and meta-analysis were performed based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions.[19,20] No ethical approval and patient consent were required because all analyses were based on previous published studies.

2.1. Literature search and selection criteria

We have systematically searched several databases including PubMed, EMbase, Web of science, EBSCO, and the Cochrane library from inception to September 2020 with the following keywords

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Compliance with ethical standards.

Research involving human participants and/or animals was not applicable.

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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"ketamine", and "fentanyl", and "children" or "paediatric," and "orthopedic" or "injury" or "fracture." The reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly in order to include additional eligible studies.

The inclusion criteria were presented as follows: (1) study design was RCT, (2) children had orthopedic emergencies, and (3) intervention treatments were ketamine versus fentanyl.

2.2. Data extraction and outcome measures

Some baseline information was extracted from the original studies, and they include first author, number of patients, age, female, baseline pain and detail methods in two groups. Data were extracted independently by 2 investigators, and discrepancies were resolved by consensus. The primary outcomes were pain score change at 15 to 20 minutes and 30 minutes. Secondary outcomes included rescue analgesia, nausea/vomiting, and dizziness.

2.3. Quality assessment in individual studies

The methodological quality of each RCT was assessed by the Jadad Scale which consisted of 3 evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points).[21] One point would be allocated to each element if they were conducted and mentioned appropriately in the original article. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score ≤ 2 was considered to be of low quality. The study was thought to be of high quality if Jadad score≥ 3.[22]

2.4. Statistical analysis

We assessed standard mean difference (SMD) with 95% confidence interval (CI) for continuous outcomes (pain score change at 15–20 min and 30 min), and risk ratio (RR) with 95% CI for dichotomous outcome (rescue analgesia, nausea/vomiting, and dizziness). Heterogeneity was evaluated using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity.[23] The random-effects model was used for all meta-analysis. We searched for potential sources of heterogeneity when encountering significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting 1 study in turn or performing the subgroup analysis. Owing to the limited number (<10) of included studies, publication bias was not assessed. Results were considered as statistically significant for $P < .05$. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics and quality assessment

Figure 1 showed the detail flowchart of the search and selection results. 154 potentially relevant articles were identified initially. Finally, five RCTs were included in the meta-analysis.[15–18,24]

The baseline characteristics of 5 included RCTs were shown in Table 1. These studies were published between 1998 and 2019, and the total sample size was 528. Ketamine and fentanyl were administered by intranasal[15–18] or intravenous approaches.[24] The doses of ketamine ranged from 0.5 mg/kg to 1.5 mg/kg, while the doses of fentanyl ranged from 0.5 μg /kg to 2.0 μg /kg. The pain of children was caused by extremity injury,[15–17] fracture or joint reduction,[24] other musculoskeletal injury.[18]

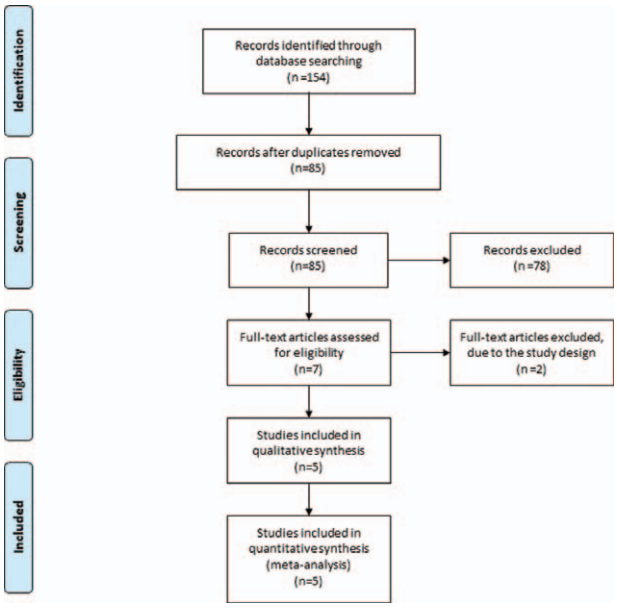

Figure 1. Flow diagram of study searching and selection process.

Among the 5 included RCTs, four trials reported pain score change at 15 to 20 minutes,[15–17,24] two trials reported pain score change at 30 minutes,[16,17] two trials reported rescue analgesia,[15,17] four trials reported nausea/vomiting,[15–17,24] and 5 trials reported dizziness.[15–18,24] Jadad scores of the 5 included studies varied from 3 to 5, and all 5 studies have high-quality based on the quality assessment.

3.2. Primary outcomes: pain score change at 15 to 20 minutes and 30 minutes

The random-effect model was used for the analysis of primary outcomes. The results found that compared to fentanyl for pediatric orthopedic emergencies, ketamine was associated with similar change in pain scores at 15 to 20 minute (SMD = -0.05; 95% CI = -0.38 to 0.28; $P = .77$) with significant heterogeneity among the studies ($I^2 = 68\%$, heterogeneity $P = .03$, Fig. 2), and 30 minute (SMD = 0.11; 95% CI = -0.20 to 0.42; $P = .49$) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $P = .81$, Fig. 3).

3.3. Sensitivity analysis

There was significant heterogeneity for pain score change at 15 to 20 minute. As shown in Figure 2, the study conducted by Kennedy et al showed results that were almost out of range of the others and probably contributed to the heterogeneity.[24] After excluding this study, the results suggested that compared with fentanyl for pediatric orthopedic emergencies, ketamine resulted in similar decrease in pain scores at 15 to 20 minute (SMD = 0.12; 95% CI = -0.14 to 0.37; $P = .37$) and no heterogeneity remained ($I^2 = 0$, $P = .65$).

Table 1

Characteristics of included studies.

NO.	Author	Ketamine group					Fentanyl group					Pain cause	Jada scores
		Number	Age (yr)	Female (n)	Baseline pain	Methods	Number	Age (yr)	Female (n)	Baseline pain	Methods		
1	Frey 2019	44	11.8±2.6	18	74.7±15.3	intranasal ketamine (1.5 mg/kg)	42	12.2±2.3	18	72.0±18.6	intranasal fentanyl (2 μg/kg)	traumatic limb injuries	5
2	Quinn 2018	11	9.77±2.51	1	8 (5–10)	intranasal ketamine (1 mg/kg)	11	9.58±2.92	3	8 (6–10)	intranasal fentanyl (1.5 μg/kg)	pediatric emergency department with acute moderate to severe pain	3
3	Reynolds 2017	43	–	17	73±26	intranasal ketamine (1 mg/kg)	44	–	16	69±26	intranasal fentanyl (1.5 μg/kg)	suspected isolated extremity fractures	4
4	Graudins 2015	36	9 (6 to 11), median (IQR)	14	80 (70 to 100)	intranasal ketamine (1 mg/kg)	37	7 (6 to 9.5), median (IQR)	13	80 (69 to 96)	intranasal fentanyl (1.5 μg/kg)	limb injuries	4
5	Kennedy 1998	130	9.7±3.27	42	–	intravenous ketamine ≤0.5 mg/kg every 3 min until a decreased response to verbal or painful stimuli occurred or a maximum first reduction dose of 2 mg/kg	130	9.7±3.01	36	–	fentanyl ≤0.5 ug/kg every 3 min until a decreased response to verbal or painful stimuli occurred or a maximum first reduction dose of 2 ug/kg (maximum, 100 ug)	emergency fracture or joint reduction	4

IQR = interquartile range.

3.4. Secondary outcomes

In comparison with fentanyl for pediatric orthopedic emergencies, ketamine showed no obvious impact on rescue analgesia (RR = 0.90; 95% CI = 0.54 to 1.51; $P = .69$; Fig. 4), but led to the increase in nausea/vomiting (RR = 2.65; 95% CI = 1.13 to 6.18; $P = .02$; Fig. 5) and dizziness (RR = 3.83; 95% CI = 1.38 to 10.60; $P = .01$; Fig. 6).

4. Discussion

This meta-analysis included 5 eligible RCTs involving the 528 children, and found that ketamine and fentanyl demonstrated similar reduction in pain scores at 15 to 20 minute and 30 minute, and rescue analgesia for pediatric orthopedic emergencies. In addition, ketamine may increase the incidence of nausea/vomiting and dizziness than fentanyl, but these adverse events were minor, transient and well tolerant.

Opioid inhibits the transmission of acute pain via targeting a limited number of specific receptors. Repeated stimulation of the opioid pathway leads to physiologic tolerance, and patient have high risk of dependence, addiction, and opioid hyperalgesia. The development of chronic pain may occur.[25] In contrast, ketamine targets multiple pain pathways simultaneously and avoids hyperactivity in a single pain circuit. Ketamine is superior

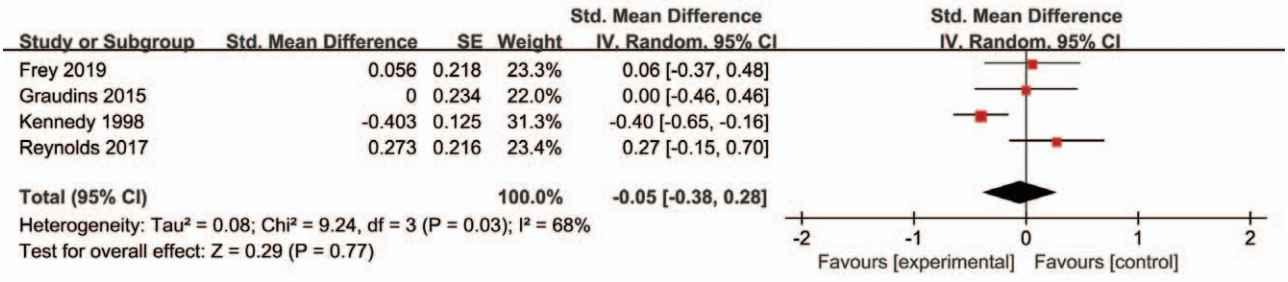

Figure 2. Forest plot for the meta-analysis of pain score change at 15–20 min.

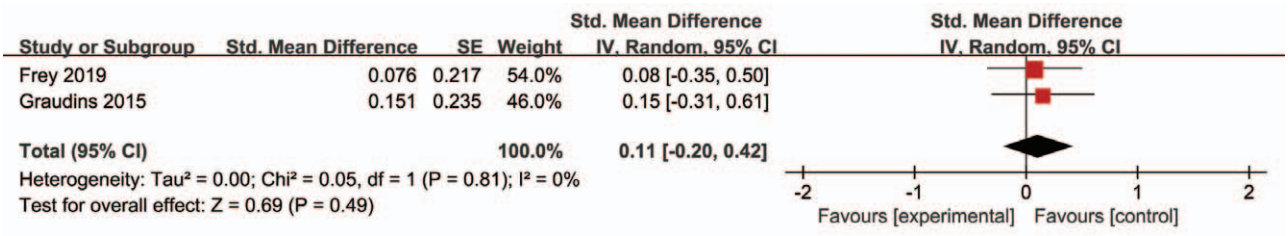

Figure 3. Forest plot for the meta-analysis of pain score change at 30 min.

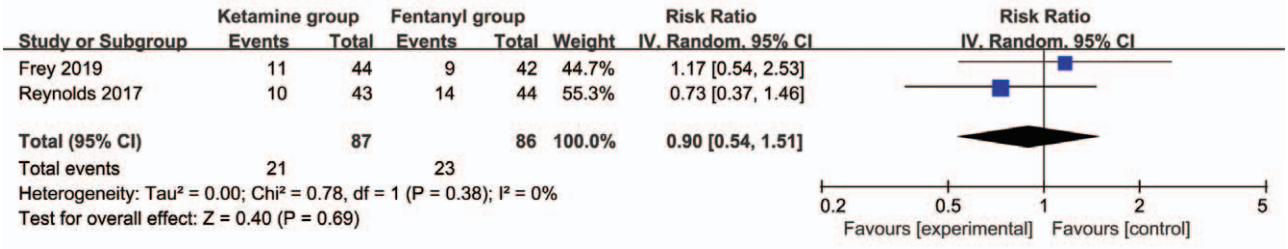

Figure 4. Forest plot for the meta-analysis of rescue analgesia.

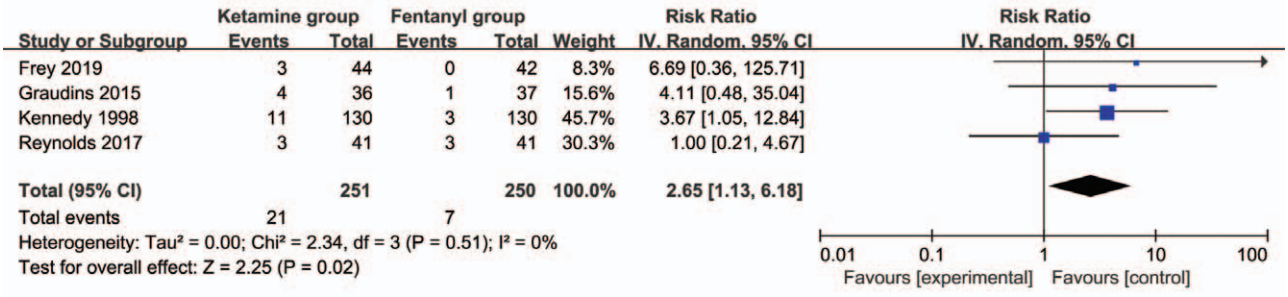

Figure 5. Forest plot for the meta-analysis of nausea/vomiting.

to opioid in terms of reducing wind-up pain and opioid hyperalgesia, and preventing central sensitization and chronic pain through its complex pharmacology.[26–28]

Multiple studies have compared the effectiveness of non-narcotic and narcotic analgesics.[29–32] Among the 5 included RCTs,[15–18,24] the doses of ketamine ranged from 0.5 mg/kg to 1.5 mg/kg, while the doses of fentanyl ranged from 0.5 μg /kg to 2.0 μg /kg. The analgesic efficacy of ketamine and fentanyl increases in a dose-dependent manner, and the maximum doses are recommended to be 100 mg of ketamine and 100 μg of fentanyl.[17] The higher doses of ketamine (1.5 mg/kg vs 1 mg/kg) and fentanyl (2 μg/kg vs 1.5 μg/kg) did not reveal superior pain relief (mean reductions of 31 mm and 32 mm at 30 minutes for ketamine and fentanyl, respectively)[17] compared to the PICHFORK study[16] (median reductions of 45 mm and 40 mm at 30 minutes for ketamine and fentanyl, respectively) and another study (mean reductions of 44 mm and 35 mm at 20 minutes for ketamine and fentanyl, respectively).[15] These suggest that ketamine at 1 mg/kg and fentanyl at 1.5 μg/kg may be sufficient for the analgesia of pediatric orthopedic emergencies.

Adverse events between ketamine and fentanyl were common, minor and acceptable.[15,16] Approximately half of adverse occurred within the first 15 minutes after administration, and higher doses of drugs may have fewer adverse events (63 total adverse events in 47 of 86 patients [54.7%] compared to 91 adverse events in 43 of 73 children [58.9%] in the PICHFORK study and 170 adverse events in 66 of 82 patients [80.5%] in the study conducted by Reynolds et al).[15–17] Drowsiness, dizziness, and nausea/vomiting were the most common adverse events. In this meta-analysis, ketamine may have increased incidence of nausea/vomiting and dizziness compared to fentanyl. These adverse events were mild and well tolerable.

Considering the equally analgesic efficacy of intranasal ketamine and fentanyl in children, intranasal ketamine may be preferred by clinicians. Ketamine is useful in children who have known adverse events with opioids. Intranasal fentanyl may develop opioid tolerance as a result of chronic painful conditions, poor opioid sensitivity owing to genetic predisposition.[11,33] In addition, intranasal ketamine can avoid the use of opioids in children before administration of procedural sedation.

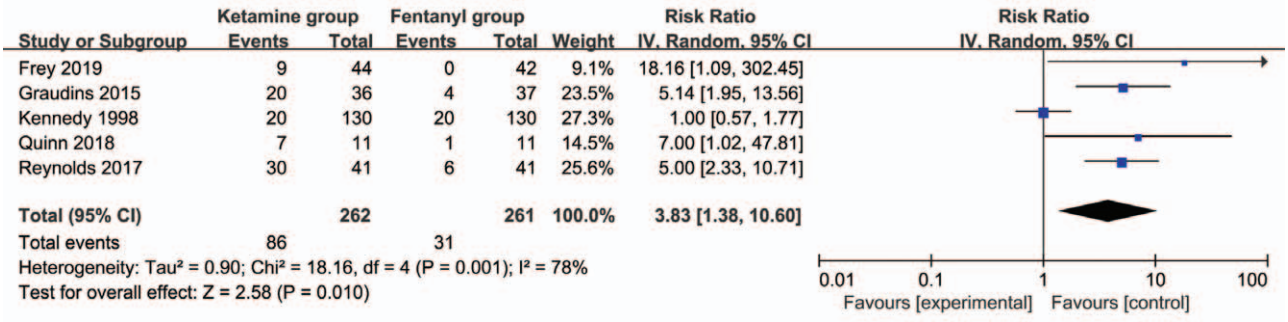

Figure 6. Forest plot for the meta-analysis of dizziness.

Regarding the sensitivity analysis, significant heterogeneity remained for pain score change at 15 to 20 minute. After excluding the study that was conducted by Kennedy et al and involved intravenous ketamine, no heterogeneity remained. These suggested that different approaches (i.e. intranasal and intravenous approaches) affected the pooling results and intravenous ketamine may have better analgesic efficacy than intranasal ketamine.

Several limitations exist in this meta-analysis. First, our analysis is based on only 5 RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, there is significant heterogeneity, which may be caused by different doses and approaches of analgesia. For instance, ketamine and fentanyl were administered by intranasal[15–18] or intravenous approaches.[24] Finally, the pain intensity of children varied during pediatric orthopedic emergencies, which may also have some influence on the pooling results.

5. Conclusion

Ketamine may have equal analgesia for pediatric orthopedic emergencies compared to fentanyl.

Author contributions

Conceptualization: Jin Qiu.
Data curation: Jin Qiu.
Formal analysis: Jin Qiu.
Supervision: Jin Qiu.
Validation: Jin Qiu, Mian Xie.
Writing – original draft: Mian Xie.
Writing – review & editing: Mian Xie.

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