Is the nasal route a viable option for relieving acute pain in pediatric emergency medicine? A literature review

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Abstract

In recent years, the nasal route has increasingly been viewed as an alternative option for the delivery of analgesia, especially when the traditional ways are complicated or time-intensive. However, little is known about the value of this intervention in acute pain management in pediatric emergency medicine.

This evidence-based analysis review aims to assess the current evidence regarding the use, safety, and effectiveness of intranasal analgesics in acutely painful conditions encountered in Pediatric Emergency Departments (PEDs).

A systemic electronic searching of Cochrane library, PubMed, and EMBASE databases from the beginning of each database until October 2018 was conducted using a maximally sensitive searching strategy. Only randomized controlled trials (RCTs) or quasi-randomized controlled trials that evaluated the use of intranasal analgesia for acute pain in children in the Emergency Department and published between January 1990 and October 2018 were included. The methodological quality of the trials was assessed using the Grading of Recommendations Assessment, Development, and Evaluation criteria. Risks of bias within each included study were evaluated according to the Cochrane Risk of Bias Tool for RCTs. This review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Seven RCTs and one quasi-randomized study met the inclusion criteria. Five studies compared an intranasal analgesic and an alternative intervention, two compared intranasal fentanyl against ketamine, and one compared two different concentrations of intranasal fentanyl. All included trials reported reductions in pain scores, especially within the first 10 to 30 minutes post-intervention; however, pain reduction was maintained to 60 minutes in only one study. No evidence of significant adverse events was associated with the administration of any intranasal analgesic in any of the included studies.

This review identified eight articles that discussed the intranasal analgesia as a possible route of analgesia in the PED. While no paper was entirely perfect, the findings support the idea that intranasal analgesia may be an effective analgesic for the treatment of children (3-18 years) with acute moderate to severe pain, and its administration appears to cause minimal adverse effects.

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Introduction

Acute pain is one of the significant symptoms and pervasive source of suffering for children presenting to the Pediatric Emergency Departments (PEDs).[1,2] The prevalence of acute pain in children who present to the PED had been reported as presenting complain in 41% of children who transported by emergency ambulance to four tertiary referral hospitals in a recent study in Ireland.[3] Of 334 children older than four years who studied in another pilot study, 48% had severe pain.[1]

Acute pain in Emergency Department (ED) can be a result of several medical conditions (trauma, injuries, burn, or painful diseases) as well as simple venipuncture and surgical interventions.[4] Murphy *et al*. found that 2071 out of 2635 (78%) of acute pain episodes resulted from traumatic injuries, while non-traumatic conditions reported in 20% of cases.[3]

It has been recognized that sever unrelieved pain has long-term consequences on a child's behavior such as increased anxiety, decreased pain tolerance, and fear of future medical visits.[5-8] The literature also indicates that children may suffer posttraumatic stress disorder symptoms after painful and stressful procedures in the PED.[9] Furthermore, the lack of appropriate and effective analgesia in the ED had associated with higher admission rates, more extended hospitalization, and higher cost to patients and organizations.[10] Therefore, adequate pain control had recommended in several clinical practice guidelines in pediatric emergency medicine.[11,12]

Although several advances have been made in improving pediatric pain management,[13] timely management of acute pain in children continues to be suboptimal in both prehospital and PED.[14-16]

The difficulty of assessing pain in young children, the unfamiliarity of medical staff with new products and techniques, fear of adverse medication effects, staffing limitations, and time constraints[17,18] are the significant barriers to adequate pain management in PEDs. Additionally, some healthcare providers still have been believing that neonates and infants feel less pain than adults, making their pain management ineffectively.[19]

Optimal pain management in children requires both non-pharmacological interventions and adequate administration of pain medications. Different distraction techniques, oral sucrose administration to the neonates, cutaneous stimulation, elevation and immobilization of a fractured limb, and applying protective dressings to burns have shown to have a beneficial effect during different procedures in the PED, especially in younger age groups.[20-22] The administration of systemic analgesia is warranted whenever non-pharmacological approaches are insufficient, or not achieved the needed pain relief lonely. The main aim of systemic analgesic administration is the establishment of useful pain relieving at the first attempt through using an appropriate drug, dose, and route without causing more pain.[23] Nonsteroidal anti-inflammatory drugs and opioids remain the most commonly used drugs for controlling moderate to severe pain in PEDs.[24]

Multiple options for delivering systemic analgesia have practiced in pediatric medicine, including oral, rectal, topical, subcutaneous, mucosal, parenteral, and inhalation. Despite having many advantages, these traditional routes are not always appropriate or feasible, particularly in PED and prehospital settings. Therefore, the availability of an alternative way, thereby providing analgesia rapidly and safely is an attractive route. The nasal cavity is an easily accessible vascular bed that has many features making it a lovely route for analgesic administration. Six arterial branches serve the nasal cavity, which makes it a much-vascularized surface.[25] Its venous return drains to the internal jugular vein which in turn flows into the right heart chambers,[26,27] enables the intranasal absorbed drug to avoid the gastrointestinal degradation and hepatic first-pass metabolism, resulting in a rapid onset of action similar to those being by intravenous (IV) administration and better than subcutaneous (SC), intramuscular (IM), and rectal one.[28,29] Moreover, the nasal cavity is lined by a mucous membrane that covered by numerous microvilli and its subepithelial cells are bound by a fenestrated epithelium, features converting it to a large and suitable area for fast and reliable drug absorption which minimize the lag time associated with oral drug delivery.[26,30] Furthermore, unlike parenteral drug therapy, nasal drug administration is a simple, painless, non-invasive, self-used, and convenient method.[31]

This review aims to assess the current evidence regarding the use, safety, and effectiveness of intranasal (IN) analgesia in the treatment of the children who presented with acute moderate to severe pain to the PEDs.

Methods of research

Design

This literature review was conducted to identify and evaluate all randomized controlled trials (RCTs) and quasi-randomized trials (QRTs) that assessed the analgesic efficacy of one or more IN analgesic(s) in children who presented with acute moderate to severe pain. The retrieved studies were not sufficiently homogeneous to design systemic review and meta-analysis, so, only qualitative analysis was conducted. This review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[32]

Inclusion and exclusion criteria

All RCTs and QRTs that compared one (or more) IN analgesic agent(s) against a placebo, other IN analgesic, or against alternative analgesic intervention for relieving of acute pain of children in PED or prehospital setting, were included. Only articles published in English, conducted in humans, and published between January 1990 and October 2018 were selected. Conference abstracts, case reports, narrative reviews, editorials, comments, dissertations, animal studies, unpublished or unavailable in English, studies not contained sufficient details regarding the primary outcomes; and those evaluated the efficacy of IN analgesia in a setting outside the PED were excluded. The inclusion and exclusion criteria are summarized in Table 1.

Search strategy

A systemic electronic searching of the Cochrane library, PubMed, and EMBASE databases from the beginning of each database until October 2018 was conducted using a maximally sensitive strategy to identify all relevant literature. Search strategies for each database were shown in Appendix 1. The search strategy was adapted for each database as required, using Boolean operators and wildcards to account for variations across databases. Several keywords including intranasal analgesics, nasal, intranasal, analgesia, acute pain, pain, procedural, young child, chil-

Table 1. Inclusion and exclusion criteria.

Item	Inclusion criteria	Exclusion criteria	Comments
Time span	01 Jan 1990 - 31 October 2018	Before Jan 1990; after October 2018	-
Age limits	Aged 1-18 years	<1 year; over 18 years	One study has a mixed population (children and adults) was excluded
Language	English	Other languages	When the full report had not available in English it had been excluded
Type of study	RCTs and quasi-randomized trials	Case reports, retrospective, cohort, case-control, and narrative review	Only studies conducted in humans were included
Type of publication	Full report	Conference abstracts, editorials, comments, dissertations, and unpublished studies	-
Setting	Trials conducted in EDs and/or prehospital settings	Studies conducted in setting outside the EDs	Studies conducted in mixed ED (pediatric and adults) were included

RCTs, randomized controlled trials; EDs, emergency departments.

dren, pediatric, emergency department, and pre-hospital setting were used independently as well as in various combinations. Moreover, nasal or intranasal term matching with specific medication including fentanyl, sufentanil, alfentanil, remifentanil, ketamine, dexmedetomidine, diamorphine, butorphanol as well as buprenorphine were used too. After that, hand-searching of the reference lists of relevant articles was done to identify other potential references and grey literature.

Population

Children less than 18 years old who presented with an acute pain severity caused by either bone fractures, burns, wounds, emergency medical procedures, or medical illness; who received at least one dose of intranasal analgesia in the PED. This review excluded patients who used IN analgesia for the treatment of postoperative pain in operation rooms, the pain of dental procedures in dental clinics, or as a pretreatment before endoscopies. Patients who received IN analgesics in a setting outside the ED or for indications other than analgesia were also excluded.

Outcome measures

The primary outcome is to determine if the intranasal delivery of analgesia is as effective as other routes of drug delivery in providing analgesia in the PED through comparison to the reduction in pain as measured by a recognized pain score. The minimum clinically significant differences (MCSD) in pain score, which selected by the authors and considered as the cutoff value for establishing the therapeutic importance of the results, were deemed to be significant when they had achieved.

The secondary outcomes were to determine the rate of failure with IN drug delivery as determined by the rate of rescue medication and to compare rates of adverse events with IN drug delivery.

Data management, collection, and analysis

Once collected, the obtained articles were exported to Mendeley Desktop bibliographic software for storage. After removal of duplicates, each title and abstract of the remaining studies were assessed for relevance. The full copies of all relevant studies were screened and evaluated for selection according to the inclusion criteria. Principles of the Grading of Recommendation, Assessment, Development, and Evaluation system were used to assess the methodological quality of each trial.[33] Risks of bias within each included study were evaluated according to the Cochrane Risk of Bias Tool for RCTs.[34] The following criteria were taken into consideration: random sequence generation; allocation concealment; blinding of personnel, participants and outcome assessment; incomplete outcome data; selective reporting; and other bias. The relevant data were extracted from the selected studies using a pre-specified data extraction form (Appendix 2) which recorded many specified items like the methodological character of the study, participant's characteristics, inclusion and exclusion criteria, main features of intervention and comparison agents, and relevant outcomes. The descriptive data were tabulated within tables, and after that, the consistent findings brought together as a narrative review.

Results

Results of the search

The primary search of electronic databases and other sources yielded a total of 363 publications. After the removal of duplicates and screening of the titles and abstracts of all remaining studies, 27 full papers were retrieved for possible inclusion. When the full texts had been examined, 19 articles were excluded, and only eight randomized trials met the inclusion criteria. Figure 1 summarizes the study selection process. This review was performed based on those eight articles.[35-42]

Included studies were published between 1999 and 2018, and were conducted in Australia (n=4), United State (n=2), and the United Kingdom (n=2). All included studies contained two comparison arms. Three IN analgesics were evaluated in these clinical trials: fentanyl (INF), diamorphine (IND), and ketamine (INK). Borland (2007),[35] Kendal,[37] Younge,[40] Fenster,[41] and Wilson[42] compared IN analgesics *vs* alternative interventions, while Graudins[38] and Reynolds[39] compared INF against INK, and Borland (2011)[36] compared two different concentrations of INF. Table 2 showed the main methodology characteristics of included studies.

A typically included study asked verbal children to score their pain intensity immediately before the administration of the study drug and then at multiple time points after the intervention. Every subject was shown age-appropriate pain scale and asked to rank his pain by pointing to the face that he feels is most consistent with his current pain level, and verbalizing the number that corresponds to their pain on the numeric rating scale. Pain intensity at each subsequent follow-up point was compared with the baseline reading to measure the amount of pain reduction.

Six studies described the reduction in pain intensity over time as the primary outcome measure while remaining[39,40] as a secondary outcome. With the exception of Fenster *et al.*,[41] all the investigators ask the patients, their parents, and/or attending physician/nurse to measured pain intensity at 0-time (baseline) and compared it to several follow-up measurements (*e.g.*, at 5, 10, 15, 20, 30, or 60 minutes) post IN drug administration. Instead, Fenster *et al.* assigned an Observational Scale of Behavioral Distress–revised (OSBD-R) score to each of the following predetermined phases of abscess incision and drainage: i) pre-analgesic

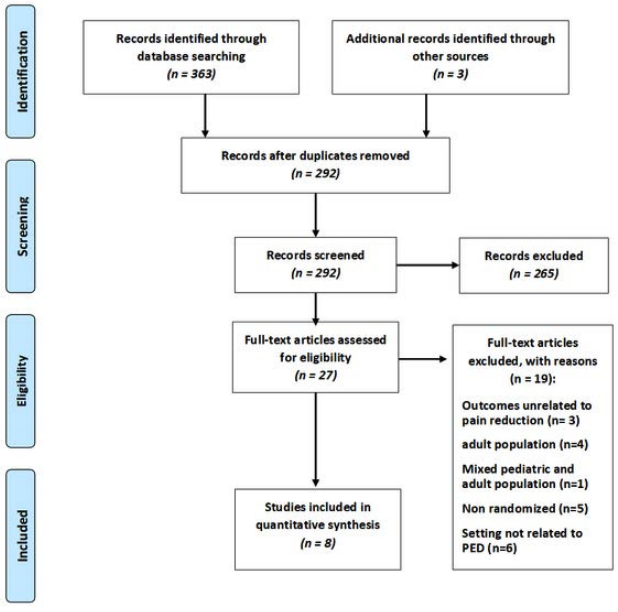

Figure 1. Study selection process. Flow chart of retrieved, excluded and analyzed trials. PED, Pediatric Emergency Department.

Table 2. Methodology characteristics of included studies.

Study ID/Design/Setting	Intervention	Sample size and sampling	Population	Grade of evidence
Borland *et al*., 2007:[35] Double-blind RCT in a single tertiary PED, Australia	Active INF (1.4 mcg/kg) plus 1 mL IV saline as placebo vs Active IVM (0.1 mg/kg) plus 1 mL IN saline as placebo	n=67; Convenient sample	Children aged 7-15 years with clinically deformed closed long-bone fractures.	High
Borland *et al*., 2011:[36] Double-blinded RCT in a single tertiary hospital, Australia	Two doses of SINF (50ug/mL) at 1.5 ug/kg vs 2 doses of HINF (300 ug/mL) at 1.5 ug/kg	n=189; Convenient sample	Children aged 3-15 years who presented to the ED with clinically deformed closed long bone fractures.	High
Kendall *et al.*, 2001:[37] Open-label RCT in eight EDs, United Kingdom	IND Spray at dose of 0.1mg/kg vs IMM at dose of 0.2mg/kg	n=413; Convenient sample	Children aged 3-16 years who presented with closed long bone fractures of limbs.	High
Graudins *et al.*, 2015:[38] Double-blind RCT in 2 EDs, Australia	INK at a dose of 1 mg/kg vs INF at a dose of 1.5 ug/kg	n=80; Non-consecutive convenient sample	Children aged 3-13 years and weighing less than 50 kg, with isolated limb injury.	High
Reynolds *et al.*, 2017:[39] Double-blind RCT, United States	INK at a dose of 1mg/kg vs INF at a dose of 1.5 ug/kg	n=87; Convenient sample	Children ages 4-17 years (n=87) with a suspected single extremity fracture.	High
Younge *et al.*, 1999:[40] A prospective, randomized, open-label, pilot study at single ED, Australia	Single dose INF at 1 ug/kg vs IMM (0.2 mg/kg)	n=47; Consecutive sampling	Children aged 3-10 years who presented with a clinical fracture of the upper or lower limbs.	Moderate
Fenster *et al.*, 2018:[41] Single-blind, RCT in a single urban PED, United States	INF (2 g/kg) vs IVM (0.1 mg/kg)	n=20; Convenient sample	English and Spanish-speaking children aged 4-18 years who presented with a cutaneous abscess required incision and drainage in PED	Low
Wilson *et al.*, 1997:[42] Quasi-RCT in single ED, United Kingdom	IND at dose of 0.1 mg/kg vs IMM at dose of 0.2 mg/kg	n=58; Consecutive sample	Children age 3-16 years presenting to ED with limb fracture.	Very low

RCT, Randomized Controlled Trial; PED, Pediatric Emergency Department; ED, Emergency Department; INF, Intranasal Fentanyl; IV, Intravenous; IVM, Intravenous Morphine; IN, Intranasal; SINF, Standard Intranasal Fentanyl; HINF, High Concentration Intranasal Fentanyl; IND, Intranasal Diamorphine; IMM, Intramuscular Morphine; INK, Intranasal Ketamine.

administration; ii) 10 minutes after analgesic administration but pre-procedural; iii) lidocaine infiltration; iv) skin incision; v) abscess drainage; and vi) 10 minutes after procedure completion. All trials assessed pain intensity by single or combined validated scales. Seven studies reported results as the difference between the median/mean pain scores of both groups at each time point, while one study compared and reported the cumulative percentages of patients' pain scores over time according to Wong-Baker Faces (WBF) pain scale.[37] The participant's tolerance to the drug administration was reported in four studies,[35,37,40,41] and the occurrence of adverse events and assessment of the failure rate of IN analgesia after administration was documented in all included trials. This outcome was reported as a number or percentage of the patient who needs *rescue* analgesia during the emergency room stay.

Patients' characteristics

The patient population in the included trials was heterogeneous. Sample sizes were varied widely, ranging from 20 to 413 patients. Each of the eight selected studies evaluated IN analgesia in pediatric patients (aged between 3 to 18 years) who had presented with moderate to severe acute pain to the EDs. All trials investigated pain in suspected limb fractures except Fenster who studied pain of cutaneous abscess incision and drainage. All the trials reported comparable baseline characteristics and presenting pain between control and intervention arms. Exclusion criteria found to be similar for all included studies (*e.g.*, no consent, head injury or trauma impairing judgment, known allergy to opiates, blocked/traumatized nose, parenteral or IN opioid analgesic use before arrival, participants requiring immediate IV access, and inability to perform pain scoring).

Risk of bias in included studies

The included trials had various methodological methods (Table 2). Four trials conducted as double-blind, two as open-labeled, one as single labeled, and one as a quasi-RCT. Judgments about each bias item for every study were summarized in Figures 2 and 3.

Effects of interventions

A summary of the main findings of the included trials is presented in Table 3.

Reduction in pain score

All included trials reported significant reductions in pain scores especially within the first 10 to 30 minutes post-intervention, however, pain reduction was maintained to 60 minutes in only one study for both intervention agents, IN fentanyl (INF) and IN ketamine (INK).[38]

Borland *et al*. (2011)[36] found an equivalent effect in reducing pain when two doses of standard INF (50 ugs/mL) were compared with 2 doses of highly concentrated (300 ugs/mL) at dose of 1.5 ug/kg, with the trend to increased oral additional agents in the more diluted solution. Each intervention demonstrated a statistically and clinically significant decrease in pain scores (median reduction for both groups 40 mm, P=0.000) over the study time (at 10, 20- and 30-minutes) post initial dose.

Some studies comparing INF to parenteral morphine (IV or IM) and reported that INF was an effective alternative to the use of morphine in the management of pain in children who had limb fractures or procedure pain. Both Younge[40] and Fenster[41] is favoring INF against morphine. Younge reported a significant reduction in pain scores at 10 min after INF administration. The median WBF pain score was 1 in the INF group *vs* 2 in IM morphine (P=0.014), while no significant difference observed in other time points. Despite this analgesic effect of INF, which lasted for 30 min period, the analgesia was not perfect, as only 11% of children were pain-free at 10 min and 22% at 30 min. Likewise, Fenster reported that INF was superior to IV morphine for the procedural analgesia as a whole as well as for the lidocaine infiltration and abscess drainage phases while it was non-inferior during abscess incision and 10 minutes post procedure phases. The total mean OSBD-R was 5.48 in INF *vs* 19.9 for IVM (mean difference: -13.4, 1-tailed 97.5% CI: −24.24 to −2.67). In contrast, in his high-quality, randomized, and double-blind trial, Borland (2007)[35] found no statistically significant differences in Visual Analogue Scale (VAS)

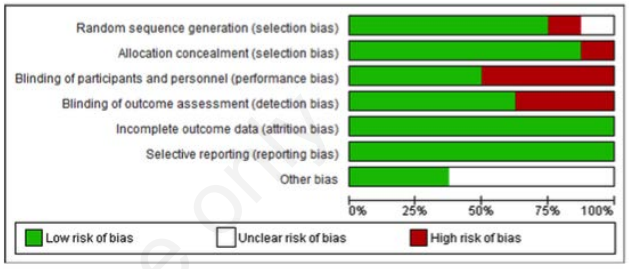

Figure 2. Risk of bias: review authors' judgments about each risk of bias item presented as percentages across all included studies.

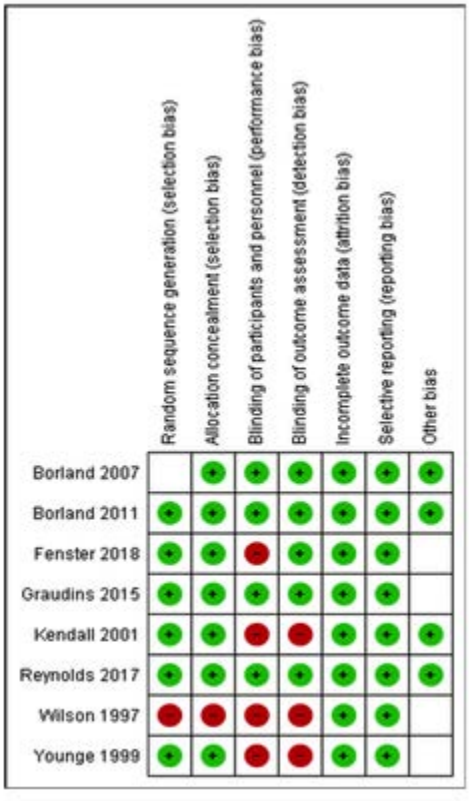

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Table 3. Summary of the main findings of the included trials.

Study ID	Primary outcome		Secondary outcome		Comments	Conclusion
	Measurement	Findings	A requirement for rescue analgesia	An occurrence of adverse events		
Borland *et al*., 2007:[35] (INF *vs* IVM)	Reduction in pain intensity using VAS score at 0, 5, 10, 20 and 30 minutes	No statistically significant differences at each time points. The combined VAS score showed a statistically significant reduction at all intervals post analgesia except at 30 min	Two patients in the IVM group required rescue analgesia	No serious adverse events. No significant difference	MCSD defined as a change in pain score of 13 mms.	INF provided an analgesic effect similar to IVM
Borland *et al*., 2011:[36] (SINF *vs* HINF)	Reduction in pain intensity using VAS score at 0, 10, 20- and 30-minutes	No statistically significant difference at any time points. Each agent demonstrated a statistically and clinically significant decrease in pain scores over the study time	Rescue analgesia was given in 35% of patients.	Side-effects were minimal. No significant difference	A difference greater than ±10 mms in VAS being clinically significant	The efficacy of two concentrations of INF was equivalent
Kendall *et al.,* 2001:[37] (IND vs IMM)	Cumulative percentages of pain scores (WBF scale) at 0, 5, 10, 20, and 30 minutes	Pain scores improved over time in both groups and were lower in the IND group at 5, 10, and 20, but not after 30 minutes	No difference between the groups	No serious adverse events. Frequencies of all adverse events were similar	Large sample size	IND is a safe and effective in acute pain relieving
Graudins *et al.*, 2015:[38] (INK *vs* INF)	Median pain reduction (FPS-R or VAS) at 30 minutes	Similar pain reductions at all points Reductions exceeded 20 mm in 82% for INK and 79% for INF	Additional analgesia was given for 14% of INK group *vs* 32% of INF	The difference rate was significant between groups with higher in INK group	MCSD defined as a decrease in pain score of 20 mms	INK is an effective analgesic for acute severe pain
Reynolds *et al.*, 2017:[39] (INK *vs* INF)	Mean difference in pain reduction (FPS-R or VAS) at 20 minutes	No significant difference at any time points. No difference in the proportion of patients achieving a clinically significant reduction in pain at 20 minutes	16% of participants need rescue analgesia in INK group *vs* 18% in INF	No serious effects. The cumulative number of side effects was 2.2 times higher in the INK group.	The difference in pain score of 20 mms have chosen as MCSD; Small sample size	Both INK and INF are effective analgesics for acute pain
Younge *et al*., 1999:[40] (INF *vs* IMM)	Compared to the median pain scores (WBF scale) at 0, 5, 10, 20 and 30 min	INF achieved lower pain scores than IMM at 10 min. No significant difference at other points	One child (4.1%) receiving INF required rescue analgesia	No serious adverse effects. No significant difference. Better tolerance for INF	MCSD not defined; Small sample size	INF provides similar analgesic effects to IMM with better tolerance
Fenster *et a*l., 2018:[41] (INF *vs* IVM)	Mean differences in pain score between the 2 groups at 6 times points using OSBD-R scale	Difference between total scores (procedure as a whole) was – 13.45 favoring INF No Statistical difference at abscess incision, and post-procedural phases.	Four patients (40%) receiving IVM had treatment failures	No significant difference.	1.8 change in OSBD-R scores considered as MCSD. Small sample size	INF is superior to IVM for reducing procedural pain
Wilson *et al*., 1997:[42] (IND *vs* IMM)	Compared summed of median reduction in pain score (WBF and VAS) at 5, 10, 20, 30 minutes	The IND group showed a larger change in the summed medians of the pain scores but not significant	One in each group required rescue analgesia	No significant adverse effects were noted.	Improper randomization. MCSD not defined	IND seems to be an effective analgesic in acute pain

INF, Intranasal Fentanyl; IVM, Intravenous Morphine; SINF, Standard Intranasal Fentanyl; HINF, High Concentration Intranasal Fentanyl; IND, Intranasal Diamorphine; IMM, Intramuscular Morphine; INK, Intranasal Ketamine; VAS, Visual Analogue Scale; WBF-R, Wong-Baker Faces-Revised; FPS-R, Faces Pain Scale-Revised; OSBD-R, Observational Scale of Behavioral Distress-Revised; MCSD, Minimum Clinically Significant Difference.

scores between the two treatment arms for each time point. However, when the VAS scores were combined (to form an overall score for each time point), he found statistically significant reductions at 5 minutes post analgesia of 20 mm (P=0.000), at 10 minutes of 4 mm (P=0.012), and at 20 minutes of 8 mm (P=0.000) but no further significant reductions beyond this time point.

Two trials studied IN diamorphine (IND) at a dose of 0.1 mg/kg against IM morphine at a dose of 0.2 mg/kg and favored IND. Kendall[37] reported that the onset of pain relief was faster in the diamorphine spray group than in the morphine group and found statistically significant lower pain scores in the spray group at 5, 10, and 20 minutes after treatment but not after 30 minutes. Similarly, Wilson[42] reported that the IND group showed a broader change in the summed medians of the pain scores than the IM morphine group (9 *vs* 8) at 30 minutes, though this was not statistically significant.

When compared head to head, IN ketamine and fentanyl have been found to have similar pain reduction in children with moderate to severe pain from limb injury in 2 trials. Graudins *et al*.[38] found similar pain reductions between groups at all points (*i.e*., 0, 15, 30, and 60 minutes after intervention). At the primary endpoint of 30 minutes, he had found clinically significant reductions in VAS ratings with approximately 80% of subjects in both groups exceeding the defined MCSD of 20 mm. Further, both treatments provided a considerable analgesic effect to 60 minutes post administration. Similarly, Reynolds *et al*.[39] demonstrated no difference in efficacy between the two drugs either at 20 min or at other time points. However, thirty (77%) subjects in the ketamine group and 35 (80%) in the fentanyl group achieved a clinically significant reduction in pain at 20 minutes (risk difference=-3% [95% CI =-20% to 15%]; P=0.77) but no difference in the magnitude of change in pain score over time between the two treatment groups.

A requirement for rescue analgesia

All included trials reported the use of rescue analgesia in a proportion of 0 to 35.4% of patients who received IN analgesia. Data on the specific rescue agent and protocol used were reported in only five studies[35-38,42] and were not specified in most studies regarding the used doses. The majority of studies offered rescue analgesia from 20 min onwards after the intervention. Only Reynolds's trial presented data on the amount of rescue analgesia consumed by the patients.

Borland (2011)[36] was the only one who described a statistically significant difference in the number of patients who required rescue analgesia. In this trail, rescue IV morphine was given to 67 of 189 patients (42 patients [41.1%] received SINF, *vs* 25 [27.4%] received HINF). The SINF group had significantly (P=0.028) more additional analgesia than HINF. Fenster found that the number of patients requiring rescue analgesia in the IN group was lower as compared to its comparator groups (0 *vs* 4). However, the sample size of this study was tiny. In contrast, Graudins and Reynolds concluded that patients who received IN Fentanyl required more rescue analgesia than those received IN ketamine but with no statistically significant difference. The rate of rescue analgesia was 32% in INF *vs* 14% in INK in Graudins's trial. Fifteen patients in Reynolds study required additional opioid rescue analgesia during the ED stay; seven patients in the ketamine group (16%) and eight patients in the fentanyl group (18%; risk difference=-2% [95% CI=-18% to 14%]). No differences or data reported in the remaining studies.

An occurrence of adverse events with intranasal drug delivery

Based on patients or parental perceptions, tolerance of IN analgesic was found to be significantly better than tolerance of intramuscularly administered morphine in three trials.[37,40,42] All included trials reported a minimum or no side effects for IN analgesia. No one study reported any serious adverse events (*e.g*., opiate toxicity) or death.

The most common reported side effects were bad taste, drowsiness, nausea, vomiting, and itching nose. The frequencies of adverse events were similar between IN analgesia and alternative intervention groups. For example, 24% of patients who received IND spray in the Kendall trial had some adverse events compared to 19% of patients who received IM morphine. Although 84 serious adverse events were reported in this study, all were mild except for one in the spray group that was considered severe (abdominal pain and vomiting). However, two studies reported significantly higher incidences of adverse events when compared IN interventions to each other. All patients (100%) of IN ketamine group *vs* 61% of the IN Fentanyl group in Reynolds trial and 78% *vs* 40% in Graudins's trial were found to have some adverse events.

Discussion

This literature review located and assessed eight published articles (7 RCTs and one QRC) that evaluated the safety and efficacy of IN analgesic for acute pain in children in PEDs.

Summary of evidence

Based on the findings of this review, three IN analgesics found to be safe, have equivalent or superior analgesic effects, and better tolerance than parenteral morphine in children who presented to PED with limb fracture or cutaneous abscess required incision and drainage. Besides, this review found that the associated adverse effects were infrequently reported and, when present, were minor and transient and did not need any intervention. No evidence of significant adverse events (*e.g*., opiate toxicity, anaphylaxis) or death was associated with the administration of any IN analgesia in any of the included studies.

The current evidence seems to show that IN fentanyl, diamorphine, and ketamine have an accepted efficacy for the treatment of moderate to severe traumatic and procedural pain in the PED. Similar results were also reported in a Cochrane review in 2014.[28] Based on three trails, Murphy *et al.*[28] concluded that INF might be an effective analgesic in painful conditions. Likewise, another systemic review by Poonai[43] supports the result of this review regarding the effectiveness of IN ketamine. He concluded that IN ketamine administration is well tolerated and without serious adverse effects during procedural sedation and analgesia in children.

The majority of trials enrolled children aged three years or more with clinically deformed closed long bone fractures. No data in included studies investigate the use of any one of retrieved nasal analgesics in children less than three years.

It is important to note that all studies demonstrated equivalence in pain scores reduction at all intervals during the ED stay; however, significant pain relief was not last beyond 10 min,[40] 20 min,[35] and 30 minutes.[36,37,42] Though, pain rating reduction was maintained to 60 minutes in two studies.[38,39] Additionally, it is thought that slower absorption of intranasal medications in comparison to IV administration, would most likely make their efficacy slower than IV analgesics, especially 5 minutes post analgesia. However, the results of Borland (2007)[35] and Fenster[41] studies showed no statistically significant difference in median pain score between the two agents at any of the studies time points, including 5 minutes. Therefore, intranasal analgesia may decrease the time to pain relief

and the time to analgesia administration.

As the studies comparing IN ketamine and fentanyl analgesia are sparse and limited, existence of 2 high-quality pieces of evidence in this review regarding head to head comparisons of IN ketamine *vs* IN fentanyl, make us confident to conclude that there is a no significant difference in pain reduction when the various forms of IN analgesia would compare for control of acute pain in PED. However, adverse effects seem to be more frequent with ketamine.

As mentioned above, the frequencies of adverse events were limited, and when they occurred were all relatively mild. Based on this finding, we could conclude that the IN analgesia has an acceptable safety profile. However, the majority of included studies have small sample sizes, make this conclusion unconfident. Therefore, a large, multicenter study in children would be required to determine the exact rate of their side effects. Besides, safety studies have not been conducted to look at long-term effects on the nasal mucosa.

Due to incomplete data regarding the specific rescue agent used were not specified in most studies, various time points at which rescue was offered, and a lack of enough data on the amount of rescue analgesia consumed by patients, it was unable to evaluate the potential impact rescue analgesia had on the reported outcomes of this review. Even though the majority of studies offered rescue analgesia either at 20 min or 30 min after administration of the intervention drug, this finding suggested that physicians should expect that patients who receive IN analgesia may require to receive rescue analgesia after 30 minutes due to the short duration of action. Further, as two trials[35,41] reported that the percentage of patients requiring rescue analgesia in the INF groups was significantly lower than their comparator groups, it should be noted that those trial used either higher dose (2ug/kg) or concentration (300 mg/mL) of fentanyl.

Admittedly, among presented studies, it does not exist a standard dosage per Kg (minimum effective dosage of which would be the suggested one to obtain the best result with less adverse events) in children. Furthermore, also at higher dosages IN therapy remains safe with lower side effects.

Quality of included evidence

The overall quality of the included evidence ranged from *very low* to *high*. Some limitations were noted in the design and implementation of all included studies. Despite Kendall's trial[37] downgraded by (-1) as has a high risk of detection and performance bias, the significance levels for tests of difference in outcomes between groups were upgraded to high quality. Younge's study[40] was limited in design by the open nature of the trial and did not meet all the criteria for a good quality study, suggesting a likely potential source of bias. The comparative efficacy of the two drugs in Reynolds' study[39] was an exploratory measure as the study was not powered to detect a difference in this outcome. Borland (2007)[35] used a convenience sample for enrolments that were dependent on the identification of suitable participants at triage. No record was kept of potential participants who were not enrolled so that no conclusion can be drawn about potential selection bias. Enrolment in Borland (2011)[36] was not compulsory but was actively encouraged by study investigators. Not all patients were able to be screened for inclusion in the study, and this might affect external validity. However, based on reported similarities between cohorts of included and non-included patients, this potential source of selection bias was minimized. Despite prior specific criteria for inclusion, there was potential selection bias based on the need for opiate analgesia. Fenster's study has a high risk of detection bias, as the treating physician was not blinded to the study drug, and it has significant imprecision due to few participants were enrolled in each arm. Finally, Wilson describes a non-random component in the sequence generation process, the patients were randomized according to their hospital number, without blinding of participants or outcome assessors, made it at very high risk for selection, performance, and detection bias. Neither indirectness of evidence nor unexplained heterogeneity or inconsistency of results were identified in any included study. The overall risk of publication bias was thought to be low in all included studies.

Limitations

This literature review has certain limitations. Only trials that were written in the English language were included. To obtain the highest possible internal trial validity, only double-blinded RCTs or quasi-RCT were chosen, this could potentially result in a high trial exclusion rate and might be a limitation of this review. However, in the inclusion of trials with no adequate blinding, the risks of false-negative and false positive results are difficult to assess and could potentially result in an inaccurate conclusion. Further, the majority of the included studies were either open-label, single-blinded, had a small sample size, or conducted in a single center. Another limitation was in the quality of the studies and the use of a single reviewer to grade them. Five of the studies were high quality while remaining studies were either moderate,[40] low,[41] or very low-quality[42] evidence. Furthermore, the authors were not contacted regarding some missed trial information. Due to significant heterogeneity in the methodology and outcomes assessment of the included studies, hence only a narrative synthesis of the results was reported.

Studies evaluate pain scores applied up to 30 minutes from drug administration and not later. In this way, the antalgic effect of the drug can only be evaluated in the initial acute phase of the pain but not in the following one: comparison, for example, with morphine, is applicable only for initial 30 minutes when fentanyl has the fastest action but for the prolonged half-life of morphine its IV or IM action after 30 minutes is probably higher than IN drugs. Therefore, also, evaluation time has to be considered as a limitation of the study to the real evaluation of the antalgic effects of drugs.

I believe that the findings of this review are valid and widely applicable. However, all included trials were conducted in developed countries. Therefore, the findings may not be generalizable to all PED pediatric patients in all countries.

Conclusions

This review identified eight articles that discussed the IN analgesia as a possible route of analgesia in the PED. While no paper was entirely perfect, the findings support that IN analgesia may be an effective analgesic for the treatment of the children (3-18 years) with acute moderate to severe pain, and its administration appears to cause minimal adverse effects.

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