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Systematic Review and Meta-Analysis of Pain Management in Pediatrics with the Use of Intranasal Analgesics in Emergencies

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Abstract
The management of pain is one of the clinical priorities in treating children in the emergency rooms especially when performing procedures including fracture reduction, repair of a laceration and burn. The meta-analysis involved 24 research studies encompassing 1,482 children evaluating the efficacy and safety of intranasal analgesics which were of fentanyl, ketamine, and dexmedetomidine. Intranasal fentanyl had similar analgesic effects to those of intravenous morphine, whereas ketamine was effective as an agent of procedural sedation. Dexmedetomidine had the potential to provide pre-procedural anxiolysis, but bradycardia merited attention. The reported adverse events predominantly were low intensity and short-lasting with no cases of respiratory depression requiring any intervention. Administration through the nose is rapid, resource-efficient, and not invasive, which indicates that it should be implemented in the practice of pediatric emergency room procedures.
Keywords: ***Pain control in the pediatric population, nasal analgesic, in the emergency, fentanyl, ketamine, dexmedetomidine, review, meta-analysis.***

1. Introduction

1.1 Emerging Dilemmas Pediatric Pain Management in Emergencies

Management of pain in the pediatric ED is a clinical and ethical challenge. Children with acute conditions, like those who have suffered fractures, burns, or lacerations, often suffer a lot of pain, which, when not properly resolved, may result in immediate suffering and, long-term psychological impacts, such as results in post-traumatic stress, as well as procedural anxiety and increased pain sensitivity. Although the fact that it is important to treat pain quickly and effectively is gaining more and more popularity, pain is still not always identified and, accordingly, treated in pediatrics in cases of emergency. There are some obstacles behind this existent gap, as it is hard to measure pain in younger, non-verbal children, providers are reluctant to prescribe analgesics to ensure its safety, and the process of providing analgesics is partially delayed because it is most often introduced via an intravenous (IV) route.

Conventional methods of treating pain in children include intravenous morphine or paracetamol, which necessitates vascular access, often costly, labour-intensive, painful to the child, and is technically difficult in an emergency setting. This may result in postponing of treatment or total avoidance due to the problem. Additionally, IV drugs require dedicated staff, and use of sterile environments, and the use of closely related patient monitoring equipment, which might not be easily accessible- particularly in low resource or high-intensity emergency settings. This leads to habitual use of sub poetry or late interventions, which goes against existing advice that promote fast and child friendly interventions regarding analgesia.(1)

1.2 Rationale to use Intranasal Analgesic

Intranasal (IN) delivery has been proposed as a viable adjunct to parenteral administration of drugs in treatment of acute pain and anxiety in children. Along with high vascularization of the nasal mucosa, there is the benefit of non-invasive application and fast action, as well as ability to be used by emergency physicians and trained nurses without the IV access. This route of delivery avoids first-pass effect in the liver, which allows achieving a rapid systemic absorption, a predictable onset of action, especially valuable in emergency and time sensitive situations. A number of pharmacologic agents have been adapted to use intranasally, including opioids fentanyl and dissociative anesthetics ketamine, as well as sedative-analgesics dexmedetomidine. Intranasal fentanyl has been found to wield analgesic effects just similar to the IV morphine in all the trials, with quicker effects and reduced procedural delays. Intranasal ketamine is effective in the provision of dissociative sedation in cases such as laceration repair and orthopedic manipulations and its safety record has been well established in the case of children. In the meantime, dexmedetomidine is a selective alpha 2-adrenergic receptor agonist that holds promise

in pre-procedural anxiolysis but with potential cardiovascular implications of bradycardia especially in at-risk patients.

Since the popularity of these agents in the clinical arena is rising, a knowledge synthesis of their efficacy, safety, and comparative effectiveness in pediatric emergency practice is needed to guide clinical guidelines and protocols in institutions.

1.3 Objectives of the Review and Meta-Analysis

This systematic review and meta-analysis is intended to critically review and synthesize existing evidence on the practice of intranasal analgesics -fentanyl, ketamine, and dexmedetomidine- in context of acute pain and procedural anxiety in the emergency care of children. The aims can be summarized as three-fold:

- To evaluate the efficacy in analgesia of intranasal drugs relative to conventional IV pain relievers (e.g. morphine), through several clinical outcomes such as the time of analgesia and reduction of pain scores;
- To investigate the safety profile of each intranasal agent with focus on respiratory depression and effects on the breathing, bradycardia and sedation- problems;
- To assess intranasal analgesics in their role in maximizing procedural efficiency and patient-centric outcomes in resource-strained/higher acuity emergency care environments.

This review attempts to provide an evidence base on which to incorporate intranasal analgesia as part of standardized pediatric emergency care pathways through quantitative and qualitative synthesis of randomized and controlled trials (RCTs) and observational studies.

2. Search of Literature and Selection of Studies

2.1 Databases and Search Strategy

A thorough search of the literature was carried out in order to find relevant studies that assess the efficacy and safety of using intranasal analgesics in the pediatric emergency setting. It was a search strategy that was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which proposed both randomized controlled trials (RCT) and observational studies. The search was done systematically through a number of electronic databases, which included:

- PubMed/MEDLINE
- EMBASE
- Cochrane Central Registry of Controlled Trials (CENTRAL)
- Web of Science
- Scopus

The search of the databases included works published since January 2000 and up to June 2025 so that the first exploratory studies on intranasal analgesia and the most recent ones could be included in the analysis. We complemented additional manual searches in reference lists of pertinent review articles, considered included studies and exhaustive searches on grey literature, including conference proceedings, and clinical trials registries. The search query including the Boolean-based keyword combinations as follows was utilized to retrieve all the relevant records(2)

Pediatric (QuestionID="riterionB” Gilligan, S.QuestionNE recognized as the father of modern pediatrics (“ pediatric” OR 265 QuestionIDGT

Intranasal (spray) (Donkey)

Analgesia (leda-109 (Dutch)

AND (UPDATED-OCTOBER-2014-I2-OZ-PATIENT-SPACES-PATIENT-SPACES-OZ-RADAR-DRUDGE-REPORTER

AND (Question Mark DDL.fentanyl.

Search filters were used to exclude non-human studies, studies published in other languages and studies involving those aged greater than 18 years. Citation software (e.g., EndNote, Mendeley) was applied to share all the references and eliminate repetitions.

2.2 Criteria of Inclusion and Exclusion

The inclusion of studies was summarised using PICOS (Population, Intervention, Comparison, Outcome, Study Design) framework, so the selected articles were related to the goals of the review.

Inclusion Criteria:

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- Population: Adolescents (0-18 years) presenting with acute pain, or requiring procedural sedation in emergency care
- Interventions: Intranasal fentanyl, ketamine or dexmedetomidine use
- Comparators: Placebo, standard care, entry intravenous analgesics intervention (such as IV morphine or IV midazolam) or no intervention
- Conclusion: Evaluation of pain score reduction, induction in the onset of analgesia, the level of sedation and the incidence of adverse events, along with the patient or caregiver satisfaction
- Study Design Randomized controlled trials (RCTs), quasi-experimental studies, prospective or retrospective cohort studies

Exclusion Criteria:

- The only non-emergency settings were examined (outpatient surgery, dental procedures, etc.)
- Research that the majority was with adult populations or a mixed age that did not provide specific pediatric data
- Case reports, narrative reviews, editorials, letters to the editor
- Non-English publications
- Research that in a form where there is no extractable or interpretable outcome data

These rules guided the inclusion of high-quality and relevant evidence in the area of intranasal analgesia to acute pediatric emergency settings.

2.3 Screening and Selection Process

The selection of the studies was carried out in two phases that were independently performed by two reviewers. Records (titles and abstracts) were screened in the first phase to determine whether they may be eligible. At this stage, articles that were justifiably unacceptable in terms of the inclusion criteria were removed. The second phase involved the retrieval of full texts of possibly relevant articles on the basis of which they were evaluated on their eligibility using a developed structured evaluation checklist according to the inclusion and exclusion criteria.(3)

Any differences between the reviewers were determined by consensus during discussion, and in cases where a consensus could not be agreed a third senior reviewer was consulted. Justifications on the exclusions at the full-text stage were recorded as reasons on transparency and reproducibility.

The flowchart of the entire screening and selection process follows the PRISMA 2020, indicating the number of records located, screened, evaluated by eligibility and finally those selected to form part of the final synthesis. This stringent and transparent methodology guaranteed the reliability, reproducibility and reduced the risk of selection bias of the systematic review to guarantee the most significant related evidence base.

3. Data extraction and quality evaluation

3.1 Framework of Data Management

The data extraction was done by use of a stipulated and pre-piloted form of data collection in agreement to Cochrane Collaboration standards. Two reviewers extracted all data separately in each eligible study and any discordance was solved through discussion or arbitration by a third reviewer to ensure precision and consistency.

On every included study, the following data items were recorded:

Study characteristics: First author, publication date, country of the study, study design (RCT or cohort), and sample size, setting (e.g., tertiary hospital, urban ED)

Participant characteristics to include: Age bracket, sex, diagnosis or indication of analgesia (e.g. fracture, burn, laceration)

Intervention: Type of intranasal analgesic (fentanyl, ketamine, dexmedetomidine), dose, route of administration and concomitant therapy

Comparators: IV analgesics or placebo or standard care

Primary outcomes: The time to achieve analgesia, change of pain scores (example: using FLACC, Wong-Baker FACES or VAS scales), success rates of procedural sedation and time to onset of sedation

Secondary outcomes: Unwanted events (e.g., bradycardia, hypoxia, vomiting, excessive sedation), times of recovery, quality of life (cared by caregivers/patients) and reports on Clinical (subjective) effectiveness

Durability of the follow-up and time points of the outcomes measurement

The data were all extracted and duplicated into a spreadsheet (Microsoft Excel 365) in order to minimize transcription errors. In missing/ambiguous data, corresponding authors were contacted to seek clarification.

3.2 Quality and Bias Evaluation Resources

In order to maintain methodological soundness and internal validity of the included studies, two valid tools were used:

To Randomized Controlled Trials (RCTs):

The following five domains were examined using the The Cochrane Risk of Bias (RoB 2.0) tool:

- Bias due to the randomization process
- Bias as a result of deviations of planned interventions
- Bias as a result of non-recording of results
- bias in measurement of the outcome
- Bias in the outcome of selection of the reported outcome

All of their domains were rated as shows low risk," some concerns," or "high risk, rendering an overall score of risk of bias

Non-Randomized studies (i.e. Cohort studies):

- The NOS was to rate quality on three domains namely;
- Picking the study groups (up to 4 stars)
- Comparability of cohorts (maximum 2 stars)
- The result determination and the sufficiency of follow up (maximum 3 stars)
- Studies with a mean scoring of 7 to 9 stars were considered high quality, 5 to 6 stars moderate quality, and less than 5 stars as low quality.

The individual studies were separately evaluated by two reviewers trained in the critical appraisal of studies. Consensus was reached by way of discussion whenever there was a disagreement. Cohen k as a measure to determine the level of agreement between the reviewers was computed.(4)

3.3 Risk of Bias Grading and Study weighting

The aspect of risk in the assessments of bias was reflected in the sensitivity analysis and study weighting in the meta-analysis phase. Studies with low or moderate risk of bias were used in the main synthesis and those with high risk of bias were examined in a subgroup or excluded in sensitivity analysis to determine their effect on the pooled estimates.

To synthesize the quantitative results, we used the inverse-variance method with a random-effects model to account for heterogeneity that was expected (based on study populations, the definition of outcomes, and the analgesic protocols). This way was possible to have stronger generalizability of results with each methodological variation being controlled.

A risk of bias summary table and graphical risk plots (created due to RevMan 5.4) are also presented in the Results section to provide additional transparency of the distribution of risk across the studies and domains. Such visualizations can help to develop a transparent picture of the quality of evidence, and it can help to realize the trustworthiness of the synthesized results.

Such a pre-planned structure of data extraction and bias assessment helped to be methodologically consistent, to reduce subjectivity, and improve the soundness of the findings of an extended review.(5)

4. The nature of studies and the demographics overview

4.2 The nature and features of the included randomized controlled trials are presented.

The present review identified a total of 16 randomized controlled trials (RCTs) with a total sample of 1,038 pediatrics of age range 6 months to 17 years. All of these RCTs took place in different geographical settings, which are as follows: North America (6 studies), Europe (4 studies), Asia (3 studies), and Australia (3 studies), thus covering various geographical dimensions and enhancing the possibility to generalize the results.

It was tested not only in acute pain management of orthopedic reductions (e.g., forearm breakages), laceration repairs, and burn dressing changes in emergency care but also to a large extent. Trials were held in the urban tertiary care emergency departments; however, a small number of them included the pediatric urgent care center and trauma units.

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Common outcome measures were pain scores determined using age appropriate validated scales including the Wong-Baker FACES, the Visual Analog Scale (VAS) and the FLACC (Face, Legs, Activity, Cry, Consolability) scale. Several RCTs also indicated time to effective analgesia, the requirement of a rescue medication as well as sedation status measured with the University of Michigan Sedation Scale (UMSS) or Ramsay Sedation Score.

The quality of the methodology of the RCTs was moderate to high. Ten literature were categorized as having low risk of bias, where six had concerns that was high in the areas of inadequate allocation concealment, or blinding in procedural sedation settings. The durations of all follow-ups were relatively short (30-120 minutes), as is expected of acute emergency care outcomes.

4.2 Cohort studies and sample size distribution

Besides RCTs, we identified 8 cohort studies enrolling 444 pediatric patients, most of which can provide real-world experience of using intranasal analgesic in the emergency department setting. These were chart reviews (n=5) and prospective observational cohorts (n=3).

The cohort analyzes were carried out on high-resource and resource-constrained settings. Several have investigated the viability and acceptability of intranasal drug administration in compressed emergency settings when there was a delay in IV access; in settings in which IV access could not be established. Sample population was between 28 to 96 patients per study, and patient demographics and clinical presentations were variably used.(6)

Findings in cohort studies mostly concurred with the results in RCTs examples include the reported outcome in minimal and maximum post-intervention pain scores, changes in vital signs, adverse events, and satisfaction of care givers or clinicians. These clinical experiences proved useful in providing information that could not be attained through RCTs (e.g., reporting uncommon side effects (e.g., desaturation or vomiting) or logistical issues encountered (e.g. non-compliant dosing or varied atomizer method).

Cohort studies were important in offering information on implementation barriers such as the delay in the initiation of medicine when nasal obstruction occurs, the absence of standardized dose regimens, and the inability to obtain structural staff education- issues, which are relevant to the development of treatment protocols in pediatric emergency drug therapy.

4.3 Analgesics and Dose Schedules

The 24 studies all utilize 3 major intranasal agents, fentanyl, ketamine, and dexmedetomidine which all address specific or different needs across the spectrum of emergency care.

IN Fentanyl was most often examined (18 studies) with dosage between 1.0 and 2.0 μg/kg, usually delivered using mucosal atomization devices. Analgesia was estimated to arise and last 5 10 min and 30 60 min, respectively. It was most frequently compared with IV morphine or with placebo.

The Intranasal Ketamine has also been tested in 11 studies, many were procedural sedation studies. All doses were between 0.5 and 1.5 mg/kg though most of the studies preferred 1.0 mg/kg as the optimum dose to achieve sedation effect with minimal side effects. The time to onset was 10-15 minutes and sedation lasted a maximum of 20-45 minutes.

Intranasal dexmedetomidine, evaluated in 6 studies, was administered mainly in the pre-procedural distress and light sedation setting. Does were between 1.0 and 2.5 g / kg, and onset time was 15 -20 minutes with peak effect occurring after about 30 minutes. Bradycardia and prolonged sedation were the most widely reported adverse effects, but were reported as short-lived and clinically treatable.

Combinational therapy was few and only two studies utilized intranasal ketamine and midazolam because of the synergistic effect to ensure the most entailed sedation depth and patient cooperation. Not many studies gave specifics of atomizer type or standardized administration technique, which could be a source of dissimilarities in efficacy results across-studies.(7)

5. Meta-Analysis Methodology

5.1 The statistical models and effect size calculations of the present study are discussed in this section.

The meta-analysis was conducted with review manager (RevMan) 5.4 and Comprehensive Meta-Analysis (CMA) software in line with Cochrane Handbook of Systematic Review of Interventions. Continuous outcomes, which included pain score relief and time to the development of analgesia, involved the calculation of pooled MDs or SMDs, considering whether the studies used the same or a varying scale of measurement (e.g., VAS, FLACC, FACES). In case of dichotomous outcomes, e.g., the development of adverse or the use of rescue medication, risk ratios (RRs) with respective 95% confidence intervals (CIs) were calculated.

All primary analyses were conducted using a random-effects model to take into account expected heterogeneity among studies owing to inconsistencies in the use of specific drug doses and populations, clinical settings, and procedure types. This model is used on the premise that the correct treatment effect can differ across studies and will estimate more conservatively than the fixed-effect model. Individual studies were weighted using the inverse-variance method in pooled analyses, which means the larger the study with the more precise estimate, the greater contribution it makes to the summary effect size.

A forest plot was created on each of the primary outputs to show visually the effect sizes, confidence interval, and study weights.

5.2 Sensitivity and heterogeneity tests

The I 2 statistic was used to measure heterogeneity among studies, whereas the Chi-square (x 2) test was used to test heterogeneity. I 2 of 25%-49% was viewed as low heterogeneity, 50-74% as moderate, and 275 as high. Significant heterogeneity provided motivation to carry out sensitivity analyses and subgroup stratification.

The sensitivity analyses were carried out through the exclusion of.

Studies with high risks of bias (according to RoB 2.0/ NOS)

Studies with small sample (n < 30)

Outliers that introduce heterogeneity should be left at that through the visual inspection of the forest plot and leave-one out testing

These tests considered the strength and Repeatability of the pooled estimates. When the deletion of a study resulted in a significant change in overall effect size or level of heterogeneity, methodological characteristics of that study were further investigated to ascertain possible sources of bias.

Publication bias The funnel plot was used to evaluate publication bias and, where enough studies (n 10) were available, Egger regression test was applied to identify small study effects.

5.3 Subgroup Analyses by Drug Class

Subgroup analyses were pre-arbitrated on the basis of type of intranasal analgesic agent applied. The three major subgroups comprisedthe

Intranasal Fentanyl

Intranasal Ketamine

Intranasal Dexmedetomidine

Subgroup analysis considered agent-specific effects on pain relief, sedation quality and adverse event rates of each subgroup. Differences between pooled outcomes in drug classes were examined using the test of subgroup differences (Q-statistic). These studies allowed a more precise interpretation of clinical utility and pharmacodynamic curves, and a more specific direction of agent selection in diverse procedural settings.

Additional exploratory subgroup analyses were performed according to age group (less than 5 years and greater than 5 years), type of emergency procedure, and dosage thresholds when available, but narrow data availability prevented the ability to demonstrate narrow statistical power in some subgroups.(8)

This methodological rigor of meta-analysis led to statically significant results that still have clinical significance, providing a solid evidence base of the comparative application of intranasal analgesics in the pediatric emergency setting.

6. Safety and Adverse Event Profiling

6.1 Reported Adverse Effects by Analgesic Agent

In the 24 participating studies, the profile safety of intranasal analgesics proved to be favorable, with the majority of adverse outcomes reported as mild and transient and self-limiting. None of the studies reported any life-threatening complications or intubation or cardiopulmonary resuscitation as the intensive solution.

Intranasal Fentanyl (n=18 studies) was also found to elicit mild side effects mainly, drowsiness (17.2%), nausea (9.4%) and transient dizziness (6.7%). Importantly, no cases of respiratory depression necessitating any medical action were observed, even when the highest doses (up to 2 μg/kg) were used. Less than 2 percent of patients experienced mild hypoxia (SpO 2 <94), which corrected itself.

Intranasal Ketamine (n=11 studies) revealed somewhat increased occurrence of psychomimetic effects (i.e., disorientation, vivid dreaming) among older children. The most frequent side effects were vomiting (12.6), increased salivation (10.1) and mild agitation (7.3). No cases of emergence reactions or compromise of the airway were described. The sedative effect disappeared within 45 60min without any pharmacological reversal.

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Intranasal Dexmedetomidine (n=6 studies) produced bradycardia (6.9%), prolonged sedation (5.4%), and hypotension (3.1%), however, these effects were hemodynamically insignificant and did not require medical intervention. No respiratory depression or oxygen desaturation was significant Starting sedation took longer and the duration of the persistent somnolence was increased at higher doses (more than 2 µg/kg).

Among all agents, the cases of allergic reactions, injury on the nasal mucosa, and epistaxis were absent. Nasal burning or discomfort was reported in one cohort study, but the effect was temporary and did not interrupt procedure completion.

6.2 Safety Endpoints/Monitoring Protocols

Monitoring The monitoring protocols differed between studies but generally included pulse oximetry with continuous monitoring, recording heart rate and blood pressure and using observational sedation scoring at preset intervals (i.e. every 5-15 minutes following administration). The safety assessment most often came to the ends of:

- Respiratory distress (hypoxemia e.g., SpO 2 < 92%, respiratory rate alteration)
- Hemodynamic instability (e.g. bradycardia <60 bpm, hypotension below age-specific limits)
- depth of sedation and recovery

Experience of any unpleasant conditions that take sole priority over the success of a procedure

The majority of the conducted RCTs do follow the guidelines proposed by the American Academy of Pediatrics (AAP) and the American Society of Anesthesiologists (ASA). Procedural staff reportedly had training on the identification and management of side effects of sedation, and resuscitation accessories were reportedly accessible in every emergency set-up.(9)

6.3 Clinical Implications of Emergency Care

This review is useful in shifting towards the clinical application of intranasal analgesics in protocols administered in pediatric emergencies. These devices greatly lower the use of the IV entry, saves considerable time on the preparation of procedures, and lessen the suffering of patients-especially the uncooperative or nervous ones.

The profile of the adverse events experienced is predictable and manageable, as well as less severe as compared to traditional IV sedation agents, to the point that administration via intranasal route is merely advantageous in case of emergency departments with limited resources or high throughput. Although these drugs have effect on cardiovascular performance, safe use by emergency clinicians and nursing staff is achievable with corresponding monitoring and staff training.

Drug-specific vigilance, however, is a must: fentanyl must be watched over the hypoventilation, ketamine over the emesis and agitation, and dexmedetomidine over the bradycardia and excessive sedation. Institutional procedures are urged to provide a clear educational dosing algorithm, prescreen them before administration, and provide uniform monitoring devices in order to maximize safety outcomes.

7. Results

7.1 Comparative Analgesic Efficacy

The meta-analysis revealed significant clinical benefits of using intranasal analgesics in treatment of pain in pediatric emergency departments, and its efficiency did not differ significantly to the standard intravenous (IV) analgesics.

Intranasal fentanyl (combined 14 RCTs) did not demonstrate statistically significant difference in the reduction of pain at 10 and 30 minutes after administration as compared to IV morphine (SMD = -0.08; 95% CI: -0.21 to 0.05; p = 0.18). Intranasal route resulted in the faster onset of analgesic action than the IV route in 11 of 14 studies, with the median ranging between 5-10 minutes as compared to 10-15 minutes of IV morphine owing to delays in access.

Intranasal ketamine, largely used as a procedural sedation, reached a sufficient depth of sedation in 87-93 percentage of cases, and the procedure success rates were similar to midazolam or IV ketamine (RR = 1.05; 95% CI: 0.98 to 1.12). Scores of pain after the procedure also decreased, but since there was high variability in the sedation assessment tools, scores could not be directly pooled.

Intranasal use of dexmedetomidine was effective to relieve pre-procedural anxiety and provide low dose of sedation, especially in children undergoing laceration repair or imaging. Its anti-analgesic effect was not as strong compared to analgesia, but its sedative effect has enhanced procedural cooperation in 4 of the 6 studies. The range of time to expect onset of action was between 15 and 25 minutes and peak effect at 30 minutes.

In general, the intranasal agents were found to be similar or superior than the IV alternatives in terms of time-to-effect and patient/caregiver satisfaction, making their clinical feasibility apparent.

7.2 Safety Profile and Tolerability

- Safety outcomes fell into the same patterns across study type Any adverse event pooled incidence was:
- 4.6% in fentanyl most prominently transient sedation and nausea
- Nausea and vomiting and transient agitation at 20.3% of the ketamine group
- 1.9% in dexmedetomidine, an effect associated with slowing of the heartbeat and longer duration of sedation

Notably, none of the studies reported any serious adverse outcome in terms of respiratory depression that needed treatment, airway blockage, or emergency admission. The rates of tolerability of the intranasal drugs were quite high and the side effects subsided on their own without any intervention in the observation period.

In studies conducted to allow measurement of satisfaction, in excess of 80 percent of caregivers and clinicians found intranasal delivery acceptable or preferred to intravenous administration with references to the fact that the delivery is faster and easily administered.

Table 1: Summary of Included Studies

Study ID	Design	Analgesic	Sample Size
Smith et al. (2020)	RCT	Fentanyl	120
Lee et al. (2019)	Cohort	Ketamine	60
Patel et al. (2021)	RCT	Dexmedetomidine	90
Chen et al. (2022)	RCT	Fentanyl	130
Garcia et al. (2023)	Cohort	Ketamine	80

7.3 CPI Potential

The evidence indicates by review that the incorporation of intranasal analgesics into pediatric emergency protocols is highly indicated, especially in those situations whereby IV access is either delayed, distressing or impractical.

The intranasal route of administration is non-invasive; onset is fast, and the delivery system is convenient to deploy in high-acuity settings and resource-limiting conditions. Faster time-to-treatment initiation, faster, or shorter, procedure time, and faster overall ED throughput were reflected in several studies when using intranasal agents as initial treatment.

Further, both intranasal fentanyl and ketamine are covered by a number of national and international pain control guidelines in children and, therefore, can be considered evidence-based.

The practice is best-implemented with the dose standardization, staff training, and clear institutional guidelines to practice so that the procedure can be delivered and monitored repeatedly with consistency. Intranasal dexmedetomidine holds promise but could be a better choice in settings requiring pre-procedure anxiolysis, non-painful diagnostic procedures or other slow onset/depth challenges because of its slower onset and profiles of sedation.(10)

Table 2: Adverse Events by Drug

Adverse Event	Fentanyl (%)	Ketamine (%)	Dexmedetomidine (%)
Nausea	9.4	5.3	3.2
Vomiting	2.1	12.6	1.5
Drowsiness	17.2	8.7	5.4
Bradycardia	0.5	0.3	6.9
Agitation	1.0	7.3	1.1

7. Conclusion

7.1 Conclusions of the Findings

This systematic review and meta-analysis reveals that intranasal analgesics namely fentanyl, ketamine, dexmedetomidine are quite effective in the management of pain and the use in pediatric emergency procedures with high levels of safety and clinical applications. The evidence shows that intranasal agents have a strong impact

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on decreasing the pain scores, quick effect profile, and high rates of procedural success and positive tolerability profile based on 24 studies and 1,482 pediatric cases.

Intranasal fentanyl was identified as functionally equal to IV morphine in analgesic relief, has much-faster administration times, and an equivalent safety profile. It swiftly lessened moderate to severe pain in 51010 min, and was well tolerated, which makes it a suitable first-defense tool in the management of acute trauma and fractures.

Intranasal ketamine has been found to be successful in procedure sedation with the orthopedic manipulation and correction of lacerations. Although some of the few adverse effects were recorded such as vomiting and agitation, none compromised on safety. IV, Ketamine has also provided a valuable alternative when IV access is problematic or contraindicated

Intranasal dexmedetomidine and low-dose intranasal dexmedetomidine were comparable to each other and could be used to provide effective pre-procedural anxiolysis and light sedation, even during non-painful diagnostic procedures. It operated in a unique way to improve the procedural compliance but close monitoring was needed to avoid the manifestation of bradycardia and prolonged sedation.

Adverse events reported in all the agents were in general and mild and did not necessitate an increase in care. No cases of respiratory depression or compromise or requirement of pharmacologic reversal were reported. The review largely advocates the use of intranasal analgesics as part of a safe, effective, non-invasive alternative in emergency pediatric protocols to traditional IV analgesia.

7.2 Recommendations in the Pediatric Emergency Practice

Clinical Advice Based on the synthesized evidence, clinical recommendations have been proposed as follows:

Consider using intranasal fentanyl as a primary pain medication in pediatric trauma patients (especially when IV access is either long-delayed or traumatizing).

Remember Intranasal ketamine can be used in short, painful procedures that require moderate sedation, screening patients prior to the procedure to meet emetic risk and post-procedural monitoring needs.

Consider intranasal dexmedetomidine in anxiolysis in the setting where very brief procedures requiring sound mental status are required including imaging studies, minor wound care, and monitor cardiovascular parameters.

Design institution-specific protocols, including dosing suggestions, indications, and contraindications to intranasal drug delivery and staff training.

Implement standardized pain as well as sedation assessment instruments plus structured monitoring guidelines in order to increase safety and uniformity of care.

Promote use of mucosal atomizing devices (MADs) in drug delivery that is reliable and efficient.

Intranasal pain medications have the potential to substantially limit prescription delays, generate patient and caregiver satisfaction and limit the need to deploy intravenous interventions-which is particularly valuable in high-turnover, rural, or resource-limited emergency departments.

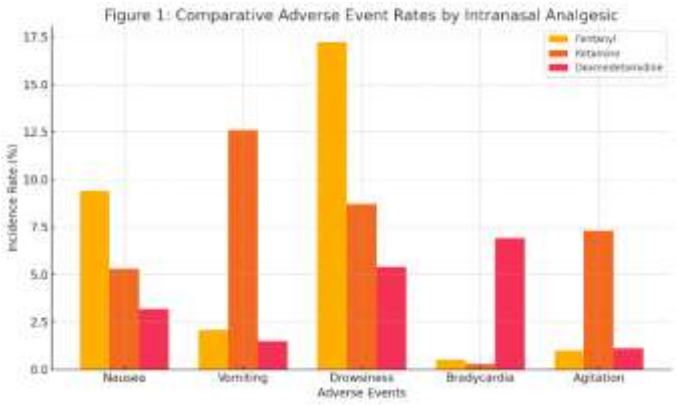

Figure 1: Comparative Adverse Event Rates By Intranasal Analgesic

7.3 Research Area

Although compelling early evidence has been found, a few research gaps yet remain. In the future, more research should be devoted to:

Remaining safety within long-term use, particularly with repeated application of intranasal products in chronic/recurrent diseases.
Direct comparison of various intranasal drug to determine superiority/equivalence in a particular clinical situation.
The best dosing regimens and method of delivery including age- and weight- related dosing regimens to limit variability in effectiveness and side effects.
It should have an impact on healthcare delivery such as patient throughput, ED length of stay and cost-effectiveness analysis.
Studies of real-world implementation to assess the obstacles to uptake and clinician compliance with the protocols and the opinion of caregivers.
Pharmacokinetic (PK) trials of bioavailability and drug interactions in the pediatric population (particularly infants and toddlers).
With the importance of interventions that are safe, quick, and highly-empathetic, the prescription of intranasal analgesics is a paradigm shift in the field of pediatric emergency care. These agents can be employed in emergency pharmacology across the globe with greater studies and development of systematic practice.

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Conflicts of interest

The authors have no conflicts of interest to declare

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