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Intranasal Dexmedetomidine for Procedural Distress in Children: A Systematic Review

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abstract

CONTEXT: Intranasal dexmedetomidine (IND) is an emerging agent for procedural distress in children.

OBJECTIVE: To explore the effectiveness of IND for procedural distress in children.

DATA SOURCES: We performed electronic searches of Medline (1946–2019), Embase (1980–2019), Google Scholar (2019), Cumulative Index to Nursing and Allied Health Literature (1981–2019), and Cochrane Central Register.

STUDY SELECTION: We included randomized trials of IND for procedures in children.

DATA EXTRACTION: Methodologic quality of evidence was evaluated by using the Cochrane Collaboration's risk of bias tool and the Grading of Recommendations Assessment, Development, and Evaluation system, respectively. The primary outcome was the proportion of participants with adequate sedation.

RESULTS: Among 19 trials ($N = 2137$), IND was superior to oral chloral hydrate (3 trials), oral midazolam (1 trial), intranasal midazolam (1 trial), and oral dexmedetomidine (1 trial). IND was equivalent to oral chloral hydrate (2 trials), intranasal midazolam (2 trials), and intranasal ketamine (3 trials). IND was inferior to oral ketamine and a combination of IND plus oral ketamine (1 trial). Higher doses of IND were superior to lower doses (4 trials). Adverse effects were reported in 67 of 727 (9.2%) participants in the IND versus 98 of 591 (16.6%) in the comparator group. There were no reports of adverse events requiring resuscitative measures.

LIMITATIONS: The adequacy of sedation was subjective, which possibly led to biased outcome reporting.

CONCLUSIONS: Given the methodologic limitations of included trials, IND is likely more effective at sedating children compared to oral chloral hydrate and oral midazolam. However, this must be weighed against the potential for adverse cardiovascular effects.



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Drs Poonai, Ali, and Hartling and Mr Spohn conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Mr Hendriks conducted the literature search and reviewed and revised the manuscript; Mr Spohn designed the data collection instruments, collected data. (Continued)

WHAT'S KNOWN ON THIS SUBJECT: Painful and distressing procedures are commonly performed in children. Oral and intranasal midazolam, the most commonly used anxiolytics, have limited evidence of benefit. Intranasal dexmedetomidine is a relatively new agent, but its study has been limited by small sample sizes.

WHAT THIS STUDY ADDS: Intranasal dexmedetomidine may provide more effective sedation than chloral hydrate or midazolam. Limited data exist for minor, painful procedures such as laceration repair or lumbar puncture. The benefits of administration must be weighed against the potential for adverse cardiovascular effects.

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In the hospital, painful and distressing procedures including laceration repair, lumbar puncture,¹ intravenous (IV) insertion,²⁻⁶ and venipuncture^{6,7} are common. However, administration of analgesia is inconsistent for painful procedures, and procedural distress is poorly managed.²⁻⁶ In a Canadian survey of >3000 hospitalized children, researchers found that the children received >6 painful procedures per day, and less than one-third of them received analgesia.⁸ Such procedures result not only in the reported pain but also in closely linked procedural distress, which often requires a different approach than analgesia. In addition, other nonpainful diagnostic procedures, such as computed tomography (CT) and MRI, require a child to lie motionless, which can be anxiety provoking across the age spectrum, and often require some level of sedation for younger patients.

To address these issues of sedation and anxiolysis, intranasal therapies for procedural distress can be noninvasively administered⁹ and require less procedural skill than IV insertion.¹⁰ Currently, midazolam is the most commonly used anxiolytic in children because of its rapid onset of action and amnestic properties.¹¹ However, when used via the intranasal route, it has an unpleasant taste, can be irritating to the nasal mucosa,^{12,13} and has adverse effects,^{11,14} underscoring the need for appropriate monitoring. Furthermore, 2 Cochrane reviews have differing conclusions regarding midazolam's effectiveness for children's procedures,^{11,14} suggesting that additional evidence for alternative agents is needed.

Dexmedetomidine is a central α_2 -adrenergic receptor agonist with analgesic and anxiolytic properties, and its use outside the intensive care and preanesthetic setting is gaining popularity.¹⁵ Authors of 3 systematic reviews suggest dexmedetomidine is

effective for procedural distress in children.¹⁵⁻¹⁷ However, they mainly reported effects by IV route, and only 1 explored intranasal dexmedetomidine (IND), focusing on anesthetic premedication.¹⁶ To date, no large trial or review exists to guide the use of IND for procedural distress in children. With the emerging popularity of dexmedetomidine for procedural distress and a desire for less invasive approaches in children, a comprehensive review of IND is needed to guide its use. We sought to summarize the effectiveness of IND for children undergoing painful and distressing procedures.

METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.¹⁸

Eligibility Criteria

We included all published and unpublished randomized trials comparing IND as monotherapy to any comparator for a procedure in children <19 years and reported adequacy of sedation. Trials of both adults and children were included if the authors provided pediatric-specific data. We excluded substudies, crossover studies, abstracts with insufficient information, and studies of anesthetic premedication unless they involved a painful procedure.

The primary outcome was the proportion of participants deemed to be adequately sedated on the basis of the investigators' opinion. Clinically, we believed this to be the most pragmatic, relevant, and feasible approach to describing relief of procedural distress. Methodologically, we believed this to be a consistent way of overcoming differences in sedation scales. Secondary outcomes included the need for additional sedation, onset and duration of sedation, length of stay, analgesia, adverse events, and acceptance of intranasal administration.

Data Sources

A medical librarian (S.H.) developed the search strategy. We performed electronic searches of Medline (1946–2018), Embase (1980–2018), Scopus (2018), Web of Science (2018), Google Scholar (2018), Cochrane Central Register (2018), and Cumulative Index to Nursing and Allied Health Literature (1981–2018). The search was completed in January 2018 and repeated in February and July 2019 without language restriction (Supplemental Tables 2 through 5). Our gray literature search was informed by the Canadian Agency for Drugs and Technologies in Health checklist.¹⁹ We checked reference lists of included trials and systematic reviews. We contacted corresponding authors when data on the primary outcome were missing.

Study Selection and Data Extraction

Two authors (N.P., J.S.) independently screened titles, abstracts, and full texts for inclusion. Disagreements were resolved through discussion. The primary author entered the data into Review Manager version 5.2.11 and GRADEpro Guideline Development Tool version 3.6.

Risk of Bias in Individual Studies

Two authors (N.P., J.S.) independently evaluated methodologic rigor using the Cochrane Collaboration's risk of bias tool²⁰ and outcome-specific ratings of the overall quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.²¹

Summary Measures and Synthesis of Results

A priori, we considered meta-analyses if there was homogeneity in procedures, dosing regimen, and outcome measures. However, meta-analyses were not performed on any outcome because of substantial heterogeneity. Instead, we conducted a descriptive analysis of each study's

design, population, and primary outcome. On the basis of the classification system of Tricco et al,²² we categorized the results of individual studies on the basis of the outcome of adequate sedation as unfavorable (effect in favor of the comparator with $P \leq .05$), neutral (nonstatistically significant difference between interventions with $P > .05$), favorable (effect in favor of the experimental agent [IND] with $P \leq .05$), and indeterminate (unable to judge because of conflicting and multiple primary outcomes). We used ranges to describe onset and duration of sedation and length of stay. We used proportions to describe acceptance of intranasal administration. Agreement between reviewers was described by using raw agreement.

Risk of Bias Across Studies

Publication bias was assessed by using a funnel plot.

Additional Analyses

We evaluated statistical heterogeneity using the I^2 statistic.

RESULTS

Study Selection

Nineteen trials ($N = 2137$) were included. Thirteen involved IND versus a non-IND comparator. Six were used to compare different doses of IND or methods of IND administration (Fig 1).

Study Characteristics

IND was studied for the following nonpainful procedures: ophthalmic examination (3 trials),²³⁻²⁵ transthoracic echocardiography (TTE) (2 trials),^{26,27} auditory brainstem response (ABR) testing (2 trials),^{28,29} CT (3 trials)²⁹⁻³¹ and MRI (2 trials),^{32,33} and visually evoked potentials (VEPs) (1 trial).²⁹ IND was studied for the following painful procedures: IV insertion (6 trials),^{31,34-38} laceration repair (1

trials),³⁹ and dental work (2 trials).^{40,41} All trials were published in English in peer-reviewed journals and included 2137 children (847 of 2093; 40.5% girls) who were age 1 month to 14 years. Demographic statistics excluded Patel et al⁴¹ because these details were not specified. IND was compared to oral dexmedetomidine,⁴¹ chloral hydrate,^{23,26,28,30,33} IND plus oral ketamine,³⁷ intranasal or oral midazolam,^{31,34,39,40} and intranasal or oral ketamine.^{35-37,40} In 6 trials, the authors compared different doses of IND^{24,25,29,32} or methods of IND administration^{27,38} (Table 1).

Risk of Bias Within Studies

Most trials were judged as low risk of bias for random sequence generation, blinding, incomplete outcome data, and selective reporting (Fig 2). For allocation concealment, most trials were judged as unclear risk of bias. Li et al²⁹ was judged as high risk of bias for incomplete outcome data because 14 of 67 participants receiving 1 $\mu\text{g}/\text{kg}$ of IND withdrew postrandomization with no outcome data reported. Surendar et al⁴⁰ reported vital signs instead of

adverse effects and was judged as unclear risk of bias.

Risk of Bias Across Studies

The overall quality of evidence based on the GRADE system was judged as high (length of stay), moderate (need for additional sedation, duration of sedation, and adverse effects), or low (adequacy of sedation, onset of sedation, and analgesia) (Fig 3).

Adequacy of Sedation

Adequacy of sedation was reported in 18 of 19 trials. A validated sedation instrument was used in 10 trials^{25-27,29-34,36} and included the Observer's Assessment of Alertness/Sedation Scale, Modified Observer's Assessment of Alertness/Sedation Scale, Ramsay Sedation Scale, and the University of Michigan Sedation Scale (Table 1). In 7 trials, the authors used nonvalidated scales to measure sedation.^{24,28,35-37,40,41} In 2 trials, the authors did not report adequacy of sedation but pain during IV insertion using the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale³⁸ and anxiety during early stages of laceration repair using the Yale Preoperative Anxiety Scale.³⁹ The proportion of participants with

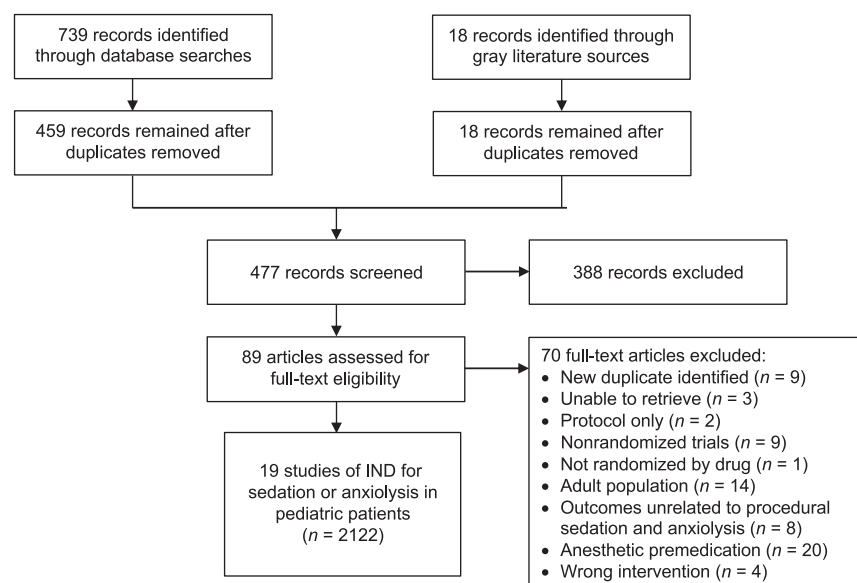


FIGURE 1 Study flow diagram of reasons for exclusion include adult population and/or IV dexmedetomidine.

TABLE 1 Characteristics of Included Trials

Source, Trial Design, Country, Indication for Sedation	Age Range (Analysis Sample Size)	Comparisons	Measure of Effectiveness of Sedation	Results	Summary
Cao et al., ²³ parallel group RCT, China, ophthalmic examination	3–36 mo (n = 141)	IND 2 µg/kg; oral chloral hydrate 80 mg/kg	Proportion with “successful sedation to complete the examination” based on the Observer’s Assessment of Alertness/Sedation score ≤4	IND 2 µg/kg 61 of 71 (85.9%) versus oral chloral hydrate 45 of 70 (64.3%) (P = .003)	Favorable for IND 2 µg/kg versus oral chloral hydrate 80 mg/kg
Chen et al., ²⁵ parallel group RCT, China, ophthalmic examination	6–24 mo (n = 100)	IND 2 µg/kg; IND 3 µg/kg	Modified Observer’s Assessment of Alertness/Sedation score	No significant difference in mean (SD) sedation scores between IND 2 µg/kg (2.6 [2.1]) and IND 3 µg/kg (2.7 [1.9]) (P > .05)	Neutral for IND 2 µg/kg vs IND 3 µg/kg
Gan et al., ²⁴ parallel group RCT, China, ophthalmic examination	5–36 mo (n = 60)	After failure of oral or rectal chloral hydrate 80 mg/kg; IND 1 µg/kg; IND 2 µg/kg	Proportion with “successful ophthalmic examination” based on 4-point Likert scale score of 1	IND 2 µg/kg 28 of 30 (93.3%) versus IND 1 µg/kg 20 of 30 (66.7%) (P = .02)	Favorable for IND 2 µg/kg versus IND 1 µg/kg
Ghai et al., ³¹ parallel group RCT, India, IV insertion and CT	1–6 y (n = 59)	IND 2.5 µg/kg; oral midazolam 0.5 mg/kg	Sedation level based on Groningen Distress Scale (IV insertion) and proportion with “adequate sedation” based on Ramsay Sedation score ≥4 (CT)	IV insertion: significantly lower median (IQR) scores with IND 2.5 µg/kg (1 [1]) versus oral midazolam 0.5 mg/kg (2 [1]) (P = .04) Completion of procedure not reported CT: IND 2.5 µg/kg 20 of 30 (67%) versus oral midazolam 0.5 mg/kg 7 of 29 (24%) (P = .002)	Favorable for IND 2.5 µg/kg versus oral midazolam 0.5 mg/kg
Gupta et al., ³⁴ parallel group RCT, India, IV insertion	1–8 y (n = 60)	IND 1 µg/kg; intranasal midazolam 0.2 mg/kg	Proportion that allowed IV insertion without crying and Observer’s Assessment of Alertness/Sedation score ≤4	IND 1 µg/kg 24 of 30 (80%) versus intranasal midazolam 0.2 mg/kg 16 of 30 (53%)	Favorable for IND 1 µg/kg versus intranasal midazolam 0.2 mg/kg
Gyanesi et al., ³⁵ parallel group RCT, India, IV insertion	1–10 y (n = 150)	IND 1 µg/kg; intranasal ketamine 5 mg/kg; intranasal saline	Proportion with satisfactory IV cannulation based on de novo “ease of cannulation score” ≥4	IND 1 µg/kg 20 of 52 (38%) versus intranasal ketamine 5 mg/kg 18 of 52 (35%) (P = .46) versus intranasal saline 1 of 46 (2%) (P < .01 for both agents versus saline)	Neutral for IND 1 µg/kg versus intranasal ketamine 5 mg/kg
Ibrahim, ³⁶ parallel group RCT, Saudi Arabia, IV insertion and MRI	4–10 y (n = 58)	IND 3 µg/kg; intranasal ketamine 7 mg/kg	IV insertion: proportion with “satisfactory acceptance” based on de novo 4-point scale value ≥3 MRI: sedation failure rate based on the Modified Ramsay Sedation Scale	IV insertion: IND 3 µg/kg 27 of 29 (93%) versus intranasal ketamine 7 mg/kg 27 of 29 (93%) (P = .45) ^a ; MRI: IND 3 µg/kg 4 of 29 (14%) versus intranasal ketamine 7 mg/kg 6 of 29 (21%) (P = .48); all successfully completed MRI	Neutral for IND 3 µg/kg versus intranasal ketamine 7 mg/kg for both IV insertion and MRI
Li et al., ²⁹ parallel group RCT, China, diagnostic procedures ^b	1 mo–13 y (n = 213)	After failure of oral chloral hydrate 50 mg/kg; IND 1, 1.5, 2 µg/kg	Adequate sedation based on the Modified Observer’s Assessment/Alertness Scale score from 0 to 3	IND 1 µg/kg 56 of 67 (84%) versus IND 1.5 µg/kg 66 of 74 (89%) versus IND 2 µg/kg 51 of 53 (96%) (P = .03 ^c)	Favorable for higher doses of IND
Li et al., ²⁷ parallel group RCT, China, TTE	2–36 mo (n = 280)	IND 3 µg/kg using either a MAD or nasal drops	“Successful sedation” based on a University of Michigan Sedation Scale score from 2 to 4	IND 3 µg/kg via MAD 113 of 137 (83%) versus drops 120 of 142 (85%) (P = .57)	Neutral for IND 3 µg/kg via MAD versus drops
Miller et al., ²⁶ parallel group RCT, United States and China, TTE	3–36 mo (n = 150)	IND 2 µg/kg; IND 3 µg/kg; chloral hydrate 70 mg/kg	Adequate sedation based on a Ramsay Sedation score ≥3	IND 2 µg/kg 50 of 50 (100%) versus IND 3 µg/kg 48 of 50 (96%) versus chloral hydrate 70 mg/kg 48 of 50 (96%) (P = .36)	Neutral for IND 2 µg/kg and 3 µg/kg versus chloral hydrate 70 mg/kg

TABLE 1 Continued

Source, Trial Design, Country, Indication for Sedation	Age Range (Analysis Sample Size)	Comparisons	Measure of Effectiveness of Sedation	Results	Summary
Neville et al. ³⁹ parallel group RCT, United States, laceration repair	1–5 y (n = 38)	IND 2 µg/kg; intranasal midazolam 0.4 mg/kg	"Not anxious" at the time of wound washout based on the Yale Preoperative Anxiety Scale score ≤30	IND 2 µg/kg 7 of 20 (35%) versus intranasal midazolam 0.4 mg/kg 1 of 18 (6%) (OR 3; 95% CI 1–12); completion of procedure not reported	Neutral for IND 2 µg/kg versus intranasal midazolam 0.4 mg/kg
Patel et al. ⁴¹ parallel group RCT, India, dental procedures	4–9 y (n = 44)	IND 2.5 µg/kg; oral dexmedetomidine 4 µg/kg; oral dexmedetomidine 5 µg/kg	"Safe and successful" based on a de novo 5-point scale for response to treatment and adequate sedation, physiologic parameters, and adverse effects with a value ≤2	IND 2.5 µg/kg 9 of 11 (82%) versus IND 2 µg/kg 3 of 11 (27%) versus oral dexmedetomidine 4 µg/kg 0 of 11 (0%) versus oral dexmedetomidine 5 µg/kg 0 of 11 (0%) (P = .05 ^c)	Favorable for IND 2.5 µg/kg versus all other comparators
Qiao et al. ³⁷ parallel group RCT, China, IV insertion	2–5 y (n = 135)	IND 2.5 µg/kg; oral ketamine 6 mg/kg; IND 2 µg/kg plus oral ketamine 3 mg/kg	"Successful venous cannulation" based on de novo 5-point sedation scale value ≤2	IND 2.5 µg/kg 20 of 42 (47%) versus oral ketamine 6 mg/kg 28 of 41 (68%) versus IND 2 µg/kg plus oral ketamine 3 mg/kg 33 of 41 (80%) (P = .006 ^c)	Unfavorable for IND 2.5 mg/kg versus combination of IND 2 µg/kg plus oral ketamine 3 mg/kg and oral ketamine 6 mg/kg
Reynolds et al. ⁴² parallel group RCT, United States, ABR testing	6 mo–8 y (n = 85)	IND 3 µg/kg; chloral hydrate 50 mg/kg	"Satisfactory sedation" based on ability of audiologist to complete the procedure by placing electrodes within 30 min	IND 3 µg/kg 39 of 44 (89%) versus chloral hydrate 50 mg/kg 27 of 41 (66%) (P = .18)	Favorable for IND 3 µg/kg versus chloral hydrate 50 mg/kg
Surender et al. ⁴⁰ parallel group RCT, India, dental procedures	4–14 y (n = 84)	IND 1.5 µg/kg; intranasal midazolam 0.2 mg/kg; intranasal ketamine 5 mg/kg	"Satisfactory sedation" for the first 30 min of the procedure based on a de novo 5-point scale (4 or 5)	IND 1.5 µg/kg 18 of 21 (86%) versus IND 1 µg/kg 17 of 21 (81%) versus intranasal midazolam 0.2 mg/kg 13 of 21 (62%) versus intranasal ketamine 5 mg/kg 14 of 21 (67%) (P = .24 ^b)	Neutral for IND 1.5 µg/kg and IND 1 µg/kg versus intranasal midazolam 0.2 mg/kg and intranasal ketamine 5 mg/kg
Tug et al. ³² parallel group RCT, Turkey, MRI	1–10 y (n = 60)	IND 3 µg/kg; IND 4 µg/kg	"Adequate sedation" based on Ramsay Sedation score ≥5 and no need for rescue sedation for MRI at 45 min	IND 3 µg/kg 9 of 30 (30%) versus IND 4 µg/kg 21 of 30 (70%) (P = .002)	Favorable for IND 4 µg/kg versus IND 3 µg/kg
Xie et al. ³⁸ parallel group RCT, China, IV insertion	2–5 y (n = 106)	IND 2 µg/kg using MAD; IND 2 µg/kg using drops	Response to IV insertion based on FLACC score	Median (IQR) FLACC score for IND 2 µg/kg using MAD was 1 (3.5) versus IND 2 µg/kg using drops was 3 (4) (P = .02); all participants had completed IV insertions	Favorable for IND 2 µg/kg using MAD versus IND 2 µg/kg using drops
Yuen et al. ³⁰ parallel group RCT, China, CT	Age range not specified (n = 196)	IND 3 µg/kg; oral chloral hydrate 50 mg/kg	"Adequate sedation" based on University of Michigan Sedation Scale score ≥3	IND 3 µg/kg 64 of 87 (74%) versus oral chloral hydrate 50 mg/kg 81 of 107 (76%) (P = .74)	Neutral for IND 3 µg/kg versus oral chloral hydrate 50 mg/kg
Zhang et al. ³³ parallel group RCT, China, MRI	1–6 mo (n = 150)	After failure of oral chloral hydrate 50 mg/kg; IND 1 µg/kg; IND 2 µg/kg; oral chloral hydrate 25 mg/kg	"Successful sedation" based on the Modified Observer's Assessment of Alertness/Sedation Scale score ≤3	IND 1 µg/kg 47 of 50 (94%) versus IND 2 µg/kg 49 of 50 (98%) versus oral chloral hydrate 25 mg/kg 40 of 50 (80%) (P < .01)	Favorable for IND 1 µg/kg and 2 µg/kg versus oral chloral hydrate 25 mg/kg

OR, odds ratio; RCT, randomized controlled trial.

^a P value reflects between-group differences in overall 4-point scale.

^b Includes CT, ABR, and VEPs.

^c P value reflects overall difference between groups.

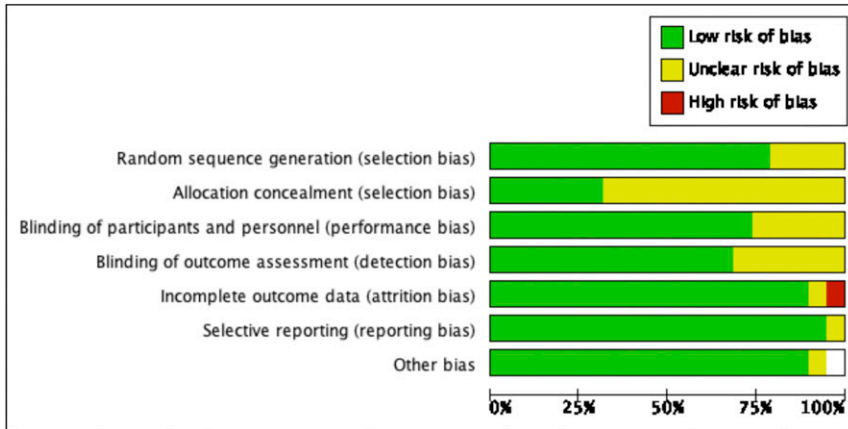


FIGURE 2
Review authors' judgements about each risk of bias item presented as percentages across all included studies.

adequate sedation was 33 of 41 (80.4%) for IND plus oral ketamine, 1086 of 1362 (79.7%) for IND, 241 of 318 (75.7%) for chloral hydrate, 28 of 41 (68.3%) for oral ketamine, 59 of 102 (57.8%) for intranasal ketamine, 30 of 69 (43.4%) for intranasal midazolam, 7 of 29 (24.1%) for oral midazolam, and 0 of 22 (0%) for oral dexmedetomidine. IND was deemed "favorable" versus chloral hydrate in 3 trials,^{23,28,33} oral midazolam in 1 trial,³¹ intranasal midazolam in 1 trial,³⁴ and oral dexmedetomidine in 1 trial.⁴¹ IND was deemed "neutral" versus chloral hydrate in 2 trials,^{26,30} intranasal midazolam in 2 trials,^{39,40} and intranasal ketamine in 3 trials.^{35,36,40} IND was deemed "unfavorable" versus oral ketamine and a combination of IND plus oral ketamine in 1 trial.³⁷

Adequacy of Sedation for Painful and Nonpainful Procedures

For painful procedures,^{31,34-41} IND provided adequate sedation to 145 of 237 (61.2%) vs 151 of 321 (47.1%) participants among comparators. For nonpainful procedures,²³⁻³³ IND provided adequate sedation to 862 of 1025 (84.1%) vs 250 of 347 (72.0%) participants among comparators. Limiting the comparison of painful versus nonpainful procedures to trials using validated instruments, IND versus comparators provided

adequate sedation to 24 of 30 (80%) vs 16 of 30 (53.3%) participants (painful) and 874 of 1021 (85.6%) vs 214 of 277 (77.3%) participants (nonpainful), respectively.

Differing Doses of IND and Routes of Nasal Administration

Authors of 6 trials compared different doses or routes of IND administration. Gan et al²⁴ found that 2 µg/kg provided adequate sedation to significantly more participants undergoing ophthalmologic examination than 1 µg/kg [28 of 30 [93%] vs 20 of 30 [67%], respectively; $P = .02$). Chen et al²⁵ found that 2 and 3 µg/kg provided a similar degree of sedation for ophthalmologic examination, successfully sedating 49 of 50 (98%) and 50 of 50 (100%) participants, respectively. Tug et al³² found 4 µg/kg of IND provided adequate sedation to significantly more participants undergoing MRI than 3 µg/kg (20 of 30 [66.7%] vs 7 of 30 [23.3%], respectively; $P = .003$). Li et al²⁹ found that higher doses of IND (1 vs 1.5 vs 2 µg/kg) provided adequate sedation to increasingly more participants undergoing CT scan, ABR testing, or VEPs (56 of 67 [83.6%], 66 of 74 [89.2%], and 51 of 53 [96.2%], respectively; $P = .03$). Li et al²⁷ found no differences in adequate sedation for 3 µg/kg of IND

by mucosal atomizer device (MAD) or nasal drops (113 of 137 [82.5%] vs 120 of 142 [84.5%], respectively; $P = .57$). Xie et al³⁸ found that the median (interquartile range [IQR]) FLACC scores were significantly better with 2 µg/kg of IND via a MAD versus nasal drops for IV insertion (1 [0.4] vs 3 [4]; $P = .02$, respectively)].

Need for Additional Sedation

Five trials reported on the need for additional sedation.^{26,28,31,36,39} Additional sedation was provided to significantly fewer participants in the IND (22 of 223; 9.9%) versus comparator groups (47 of 167; 28.1%).

Onset of Sedation

Onset of sedation was reported in 11 trials* and ranged from 7 to 31 minutes for IND and 7 to 44.2 minutes for comparators. Onset of sedation varied by dose of IND: 1 µg/kg (14.3-19 minutes),^{24,29,33,34,40} 1.5 µg/kg (18.1-20 minutes),^{29,40} 2 µg/kg (8.8-25 minutes),^{23-26,29,33,38,41} 2.5 µg/kg (7-20.6 minutes),^{37,41} 3 µg/kg (13-31 minutes),^{25-28,30,32,36} and 4 µg/kg (30 minutes).³²

Duration of Sedation

Duration of sedation was reported in 6 trials^{23,25,26,33,36,40} and ranged from 41 to 91.5 minutes for IND and 77 to 85.9 minutes for comparators.

Length of Stay

Length of stay was reported in 4 trials^{23,24,26,39} and ranged from 76.8 to 156 minutes for IND and 95 to 144 minutes for comparators.

Analgesia

Analgesia was reported by using the FLACC scale by Surendar et al⁴⁰ in children undergoing dental procedures and Xie et al³⁸ in children undergoing IV insertion. The FLACC scale is scored from 0 to 10, with higher scores denoting greater pain.⁴³

* 23,25,26,28,30,33,34,36,37,40,41

Certainty Assessment							No. Patients		Effect		Certainty	Importance
No. Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	IND	Other sedatives	Relative (95% CI)	Absolute (95% CI)		
Adequacy of Sedation												
18	Randomized trials	Not serious ^a	Serious ^c	Serious ^c	Not serious	None	1086 of 1362 (79.7%)	398 of 622 (64.0%)	Not pooled	See comment	⊕⊕○○ Low	Critical
Need for Additional Sedation												
5	Randomized trials	Not serious ^a	Not serious	Serious ^c	Not serious	None	22 of 223 (9.9%)	47 of 167 (28.1%)	Not pooled	See comment	⊕⊕⊕○ Moderate	Critical
Onset of Sedation												
11	Randomized trials	Serious ^d	Serious ^d	Not serious	Not serious	None	IND range 7 to 31 minutes; intranasal comparator range 7 to 44.2 minutes				⊕⊕○○ Low	Important
Duration of Sedation												
6	Randomized trials	Serious ^d	Not serious	Not serious	Not serious	None	IND range 41 to 91.5 minutes; intranasal comparator range 77 to 85.9 minutes				⊕⊕⊕○ Moderate	Important
Length of Stay												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	IND range 76.8 to 156 minutes; intranasal comparator range 95 to 144 minutes				⊕⊕⊕⊕ High	Important
Analgesia												
1	Randomized trials	Not serious	Serious ⁱ	Not serious	Serious ^g	None	Overall significant difference in the mean (SD) FLACC score during dental procedures between IND 1 µg/kg (3.8 [0.8]), IND 1.5 µg/kg (3.7 [0.9]), intranasal midazolam (5.6 [1.1]), and intranasal ketamine (3.5 [0.7]) ($P < .001$).				⊕⊕○○ Low	Important
Adverse Effects												
18	Randomized trials	Serious ^{h,k}	Not serious	Not serious	Not serious	None	67 of 127 (9.2%)	98 of 591 (16.8%)	Not pooled	See comment	⊕⊕⊕○ Moderate	Critical
Acceptance of IN Administration												
4	Randomized trials	Serious ^k	Not serious	Not serious	Not serious	None	IND well accepted by 199 of 264 (75.4%) participants with no reports of aborting administration because of refusal. Authors of 1 study reported intranasal midazolam was well accepted by 42 of 42 (100%) participants.				⊕⊕⊕○ Moderate	Important

FIGURE 3

GRADE evidence profile. ^a We chose not to downgrade for allocation concealment (selection bias) because although most trials were judged to have an unclear risk of bias, in all cases, this was because of insufficient details provided. ^b Significant heterogeneity ($I^2 = 72\%$) is partially explained by different comparators. ^c Use of a nonstandardized tool to determine level and adequacy of sedation in at least 1 study limits the degree to which the results can be applied broadly. ^d Use of nonstandardized tools to define the onset of sedation was prevalent across trials. ^e This was downgraded for consistency because of the large range in this outcome, which was in turn likely due to heterogeneity in measurement instruments, dose, and comparators. ^f We were unable to assess this given only 1 study reporting this outcome. ^g The total sample size was <200 participants. ^h Li et al²⁹ was judged to have high risk of bias for incomplete outcome data because 14 of 67 participants in the IND 2 µg/kg arm withdrew post-random assignment and did not return to the sedation center. ⁱ Surendar et al⁴⁰ did not report adverse effects but reported vital signs during sedation that appeared to be within physiologic parameters, and the risk of bias was deemed to be unclear. ^j Adverse effects were not defined by using standardized or objective criteria. ^k Use of nonstandardized tools to assess tolerability of intranasal sprays limits the degree to which the results can be applied broadly.

Using a pairwise comparison, Surendar et al⁴⁰ reported that mean (SD) FLACC scores for 1 µg/kg of IND (3.8 [0.8]), 1.5 µg/kg of IND (3.7 [0.9]), and 5 mg/kg of intranasal ketamine (3.5 [0.7]) were significantly lower than 0.2 mg/kg of intranasal midazolam (5.6 [1.1]) (P value not reported). Xie et al³⁸ reported a lower median (IQR) FLACC score for 2 µg/kg of IND by MAD (1 [3.5]) versus nasal drops (3 [4]) ($P = .02$).

Adverse Events

Adverse events were reported in all trials except Surendar et al.⁴⁰ Across the remaining 18 trials, the most common adverse events of IND, IND

plus another sedative, or non-IND comparator were bradycardia (32 of 1484 [2.2%], 0 of 41 [0%], and 6 of 595 [1%], respectively), hypotension (18 of 1484 [1.2%], 0 of 41 [0%], and 9 of 595 [1.5%], respectively), oxygen desaturation (7 of 1484 [0.5%], 0 of 41 [0%], and 12 of 595 [2%], respectively), and vomiting (6 of 1484 [0.4%], 3 of 41 [7.3%], and 47 of 595 [7.9%], respectively). No trials used objective criteria to define adverse events. No trials reported the occurrence of upper airway obstruction, apnea, death, the delivery of positive pressure ventilation, chest compressions, vasoactive medications, endotracheal

intubation, or neuromuscular blockade.

Acceptance of Intranasal Administration

The authors of 4 trials reported acceptability of intranasal administration. Zhang et al³³ reported all 94 participants tolerated IND “without crying.” Xie et al³⁸ reported 25 of 49 (51%) vs 22 of 57 (38.6%) participants “calmly accepted” IND using a MAD versus drops, respectively. Patel et al⁴¹ reported acceptance of IND was “fair to excellent” in 16 of 22 (72.7%) participants. Surendar et al⁴⁰ reported IND and intranasal

midazolam were “well accepted” by all 84 participants.

Agreement Between Reviewers

Two independent reviewers (N.P., J.S.) agreed 102 of 114 (89.5%) times on risk of bias assessments, 366 of 430 (85.1%) times on abstract screening, and 74 of 79 (93.7%) times on full-text screening.

Publication Bias

The funnel plot for adequacy of sedation revealed some asymmetry (Supplemental Information).

DISCUSSION

In this review, the overall quality of evidence for adequacy of sedation was low. Although our findings suggest that IND likely provides adequate sedation to a greater proportion of children than conventional sedatives (oral midazolam and chloral hydrate), trial results could not be pooled, and larger and more methodologically rigorous trials are needed before widespread implementation. Clinicians considering the use of IND to alleviate procedural anxiety in children must weigh the benefit of superior sedation against the potential for adverse cardiovascular effects, which require further rigorous study to fully assess the risk.

We chose to include trials that used midazolam and chloral hydrate as comparators because they are widely used in clinical practice.⁴⁴ In fact, chloral hydrate is recommended by the National Institute for Health and Care Excellence 2010 guideline for moderate sedation for painless procedures in children.⁴⁵ Although chloral hydrate is no longer approved by the US Food and Drug Administration, it may still be used in other countries. IND provided adequate sedation in 79.7% of children, greater than that of chloral hydrate (75.7%) and oral (24.1%) and intranasal midazolam (43.4%). This is consistent with a recent

systematic review in which IND was superior to oral benzodiazepines in children undergoing anesthetic premedication,¹⁶ another systematic review in which authors found inconsistent evidence of procedural anxiety for intranasal midazolam,¹¹ and with a trial of 300 children undergoing ABR testing in which IND sedated significantly more children than chloral hydrate (91% vs 78.5%, respectively).⁴² IND may be a safer alternative to chloral hydrate given the latter’s propensity to cause respiratory depression⁴⁶ and other major adverse effects such as bradycardia, hypotension, and oxygen desaturation.⁴⁷ In response to evidence that general anesthetics and sedatives in young children may have adverse neurodevelopmental consequences, in 2016, the US Food and Drug Administration issued a Drug Safety Communications mandating label changes for all anesthetic gases as well as the IV agents propofol, ketamine, barbiturates, and benzodiazepines.⁴⁸ Dexmedetomidine has been shown to be neuroprotective in animal studies,⁴⁹ but little long-term data in humans exist. Although IND was reported to produce adequate sedation in more children than intranasal ketamine (79.7% vs 57.8%), IND was deemed neutral versus intranasal ketamine in all trials that compared the 2 agents.^{35,36,40} Each trial was small and may not have been sufficiently powered to detect differences in sedation. IND, however, may be more suitable than intranasal ketamine for uncooperative children because fewer intranasal sprays are required. At 100 µg/mL, an IND dose of 4 µg/kg in a child weighing 25 kg would only require two 0.5 mL sprays. Interestingly, in a single study of children undergoing IV insertion, IND was deemed unfavorable compared to a combination of IND and oral ketamine, with the latter producing adequate sedation in 80.4% of children.³⁷ The sedative effects of

dexmedetomidine may have complemented the well-known analgesic effects of intranasal ketamine,^{50,51} and future studies should explore the sedative potential of this novel therapeutic combination.

The most effective noninvasive approach to providing dexmedetomidine appeared to be the intranasal route. Although informed by only 1 trial, oral dexmedetomidine was unsuccessful in all cases.⁴¹ Oral absorption of dexmedetomidine is possible,⁵² but its bioavailability is reduced by first-pass metabolism.⁵³ What remains unclear is whether IND administration using a MAD is more efficacious than nasal drops. Li et al²⁷ found no difference among children undergoing TTE, a relatively painless procedure. In contrast, Xie et al³⁸ found lower pain scores during IV insertion using a MAD. Nasal drops may result in excess volume entering the oropharynx and more difficult administration in uncooperative patients. Conversely, the MAD takes advantage of the nasal cavity’s large mucosal surface area and rich vascular supply,^{13,54,55} resulting in a median bioavailability of 65%.⁵³

Insight into the analgesic potential of IND was limited to 2 trials in which authors reported lower FLACC scores with IND versus intranasal midazolam for dental procedures⁴⁰ and IND using a MAD versus drops for IV insertion.³⁸ Reduced opioid requirements have been reported with IND in children postadenotonsillectomy⁵⁶ and adults post-hip arthroplasty.⁵⁷ IV dexmedetomidine has also been shown to reduce opioid requirements in children undergoing scoliosis repair⁵⁸ and cardiac surgery.⁵⁹ However, the proportion of participants deemed as being adequately sedated for painful versus nonpainful procedures (61.2% vs 84.1%) suggests that sedation using IND may be improved by the addition of a more potent analgesic, perhaps one with sedative properties.

Currently, IND as monotherapy is not indicated for severely painful procedures, and its analgesic potential appears to be realized in conjunction with local anesthetics.⁶⁰ Future studies should explore the analgesic potential of IND for acutely painful procedures using rigorous methodology and optimal dosing.

The onset and duration of sedation are important considerations in a busy acute care setting. We found wide ranges in onset and duration of IND (7–31 and 41–91.5 minutes, respectively), and data did not support a dose effect. This may reflect heterogeneity in dosing or definitions of sedation but are consistent with previous reports. Among healthy adult men, Iriola et al⁵³ reported a median (range) peak plasma concentration at 38 (15–60) minutes and onset of sedation of 30 to 45 minutes. In children, Yuen et al⁶¹ reported a median (95% confidence interval [CI]) onset and duration of sedation of 25 (25–30) and 85 (55–100) minutes, respectively. These results suggest that IND should be administered at least 30 minutes before an anxiety-provoking procedure.⁵³ The American Academy of Pediatrics has published guidelines outlining monitoring requirements for children undergoing procedural sedation. Regardless of agent or route of administration, all children should receive comprehensive monitoring for the duration of sedation. This should include, but is not limited to, pulse oximetry and capnography.⁶²

Acceptance of intranasal administration was only assessed in 4 trials and not objectively. However, there is good reason to believe that intolerance of nasal sprays is unlikely to preclude IND administration because the drug is tasteless, odorless, and painless^{53,54} and reportedly “not noxious to the nasal mucosa,”^{53,63} a notable difference from intranasal midazolam in which discomfort is commonly reported.^{12,13}

Adverse effects identified in our review such as bradycardia,

hypotension, and desaturation were reported across the dosing range and are likely to inform bedside monitoring requirements. For the adverse cardiovascular effects we identified, no resuscitative maneuvers were reported, suggesting they were self-resolving. This is consistent with 2 pediatric systematic reviews in which authors reported no respiratory compromise with either IND¹⁶ or IV dexmedetomidine.¹⁵ In addition, authors of several pediatric studies found that IV dexmedetomidine was associated with bradycardia without hemodynamic instability.^{15,54,58,64,65} Nevertheless, it is difficult to know to what degree these occurrences compromised patient care. The most prudent approach would be to limit the use of IND to children without cardiac conduction anomalies, bradycardia, hypotension, or concomitant use of sympatholytic agents. Future studies should be used to define adverse events and corresponding interventions on the basis of published guidelines.⁶⁶

Our review included a large number of small studies with some methodologic shortcomings, the most notable of which was subjective determination of adequacy of sedation. The lack of a consistent and objective determination of this parameter may have led to biased outcome reporting for this and other related outcomes such as onset and duration of sedation. Because of heterogeneity in dosing and indications, it was difficult to appreciate differences in adequate sedation among trials that used validated sedation instruments versus trials that did not. However, on the basis of the classification system outlined by the American College of Emergency Physicians’ clinical policy, we believe that across trials, adequate sedation most closely paralleled dissociative sedation, with the caveat that few trials determined the degree of analgesia and no trials assessed amnesia.⁶⁷ We found large heterogeneity across studies, which may

be because of different comparators. The funnel plot revealed some asymmetry, suggesting the potential for publication or small study bias. As such, we downgraded our certainty of the evidence for some outcomes.

CONCLUSIONS

Our findings suggest that IND is well tolerated and may provide more effective sedation than midazolam and chloral hydrate for distressing procedures in children. However, the quality of evidence was low, and larger, more methodologically rigorous trials are needed. The available limited data for painful procedures (mostly IV insertion) suggest that although IND may provide reasonable sedation, it may not provide adequate analgesia as monotherapy. As such, more study is urgently required to understand the role of IND, perhaps in combination with a more widely studied analgesic sedative for painful procedures. Transient cardiovascular adverse effects, without reports of resuscitative intervention, were identified, and more rigorously designed trials with standardized and objective reporting of adverse effects are needed to inform the safe use of IND in children.

ABBREVIATIONS

ABR: auditory brainstem response
CI: confidence interval
CT: computed tomography
FLACC: Faces, Legs, Activity, Cry, and Consolability
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
IND: intranasal dexmedetomidine
IQR: interquartile range
IV: intravenous
MAD: mucosal atomizer device
TTE: transthoracic echocardiography
VEP: visually evoked potential

and reviewed and revised the manuscript; Mr Vandermeer conducted the initial analyses and reviewed and revised the manuscript; Drs Joubert, Trottier, Shah, Sabhaney, and Bhatt critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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