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REVIEW ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Systematic review and meta-analysis found that intranasal dexmedetomidine was a safe and effective sedative drug during paediatric procedural sedation

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Abstract

Aim: This systematic review and meta-analysis evaluated the effectiveness of intranasal dexmedetomidine as a sole sedative during paediatric procedural sedation outside the operating room.

Methods: Relevant literature identified by PubMed, Scopus, ClinicalTrials.gov, ScienceDirect and Cochrane Library up to 31 December 2019 was systematically reviewed. Randomised controlled trials that compared intranasal dexmedetomidine with another sedative or placebo during paediatric procedural sedation were included. Trials that studied intranasal dexmedetomidine as a premedication before anaesthesia were excluded. The primary outcome was the success of the planned procedure.

Results: We analysed seven randomised controlled trials of 730 patients: four trials with 570 patients compared dexmedetomidine with chloral hydrate and three trials with 160 patients compared dexmedetomidine with midazolam. The incidence of successfully completing the procedure did not differ between dexmedetomidine and chloral hydrate, but dexmedetomidine had a higher success rate than midazolam. The incidence of hypotension, bradycardia or respiratory complications did not differ between the sedatives used. Nausea and vomiting were more common in children treated with chloral hydrate than in those treated with other sedatives.

Conclusion: Intranasal dexmedetomidine was a safe and effective sedative for minor paediatric procedures.

KEYWORDS

chloral hydrate, dexmedetomidine, intranasal sedation, midazolam, procedural sedation

1 | INTRODUCTION

Unavoidable medical procedures often cause discomfort and fear in children during hospitalisation.[1,2] The most fearful patients often require analgesics and sedative medication, because nonpharmacological care is frequently insufficient to ameliorate their pain and anxiety.[3] Sedative premedication is also commonly used in imaging studies, such as magnetic resonance imaging, computed tomography

Abbreviations: GRADE, Grading of Recommendations Assessment Development and Evaluations.

and transthoracic echocardiography to ensure good-quality images are obtained. Most sedative drugs can be administered intranasally and these have a more rapid and profound sedative effect than orally administered drugs.[4,5]

Short-acting midazolam is a benzodiazepine that is most commonly used as premedication for paediatric patients. It has anxiolytic and amnesic properties, but it does not provide analgesia. Intranasal or intravenous administration of midazolam has a more anxiolytic effect than oral administration.[6] Combining midazolam with other medication is recommended to achieve sufficient sedation, although it may increase the risk of adverse effects.[7]

Chloral hydrate has been used as a sedative premedication in the paediatric population because it has a relatively good sedative effect and safety profile. The most common adverse effects of chloral hydrate are a paradoxical reaction to sedation, vomiting and respiratory depression.[8] Concerns have been raised about the potential carcinogenic, neurotoxic and neuroapoptotic effects of chloral hydrate, especially when treating children who are younger than three years of age.[9,10]

Dexmedetomidine is a novel drug with anxiolytic, sedative and analgesic effects, and it has been shown to diminish the need for other pain medication during medical procedures.[11,12] It can be used in varying doses, from 0.5 to 4 μg/kg, depending on the level of sedation required, and it has been shown to provide more profound and longer sedation at higher doses and in younger patients.[13-15] Less frequent adverse respiratory events have been reported during dexmedetomidine premedication than for most other sedative drugs.[16] However, some evidence exists that dexmedetomidine suppresses respiratory responses to hypoxia and hypercapnia.[17] Although rapid intravenous administration of dexmedetomidine may initially cause elevated blood pressure, cardiovascular responses are mainly bradycardic and, to some extent, hypotensive.[18,19] Previous meta-analyses have revealed that intranasal dexmedetomidine was a more effective preoperative sedative drug than other traditional sedatives.[16,20,21] Intranasal dexmedetomidine is expected to be a feasible and effective alternative to chloral hydrate and midazolam and have a better safety profile, especially due to its potential neuroprotective properties.[22]

The purpose of this systematic review and meta-analysis was to investigate whether intranasal dexmedetomidine, administered as a sole sedative agent, was superior to other sedatives in facilitating the successful completion of minor paediatric procedures that did not require intravenous sedation. The safety and clinical pharmacokinetic profiles of dexmedetomidine were evaluated.

Key Notes

- This systematic review and meta-analysis assessed the efficacy of intranasal dexmedetomidine as a sole sedative agent during paediatric procedures, using data from seven randomised control studies.
- Dexmedetomidine and chloral hydrate were equally successful when it came to completing the procedure without nausea or vomiting, but dexmedetomidine was superior to midazolam.
- The incidence of bradycardia, hypotension or adverse respiratory events did not differ between the sedatives used.

2 | METHODS

2.1 | Search strategy and selection criteria

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.[23] Two researchers (MT, OP) conducted independent searches of PubMed, Scopus, ClinicalTrials.gov, ScienceDirect and Cochrane Database of Systematic Reviews electronic databases for relevant studies published from their inception until 31 December 2019. The search term dexmedetomidine was used for the database search. The search was limited to the English language. Additional studies were searched for by examining the reference lists of all the identified papers (Figure 1). No ethical approval was necessary, as this study was a review of the previously published literature and a meta-analysis of previously published data.

2.2 | Inclusion and exclusion criteria

All randomised controlled trials that compared the efficacy of intranasal dexmedetomidine with another sedative administered through intranasal, buccal, oral or rectal routes during minor paediatric procedures with blind assessment of the outcomes were included. Animal studies and trials that studied the use of intranasal dexmedetomidine as premedication before surgery were excluded. Trials that included the routine use of intravenous sedatives were also excluded to rule out the effect of additional sedatives on the duration of sedation and adverse outcomes. In addition, one of the following outcomes was required in full-text papers: the success of the procedure, recovery time, time to discharge, emergence agitation, haemodynamic variables, respiratory depression or possible side effects (Figure 1).

2.3 | Data extraction and risk of bias assessment

A standardised record form was used to extract data from the included studies. Three authors (MT, TP, OP) independently evaluated the inclusion criteria, risk of bias and data extraction using the criteria of the Cochrane Handbook for Systematic Reviews of Interventions.[23] Three authors (MT, TP, MK) rates quality of evidence using the Grading of Recommendations, Assessment, Development

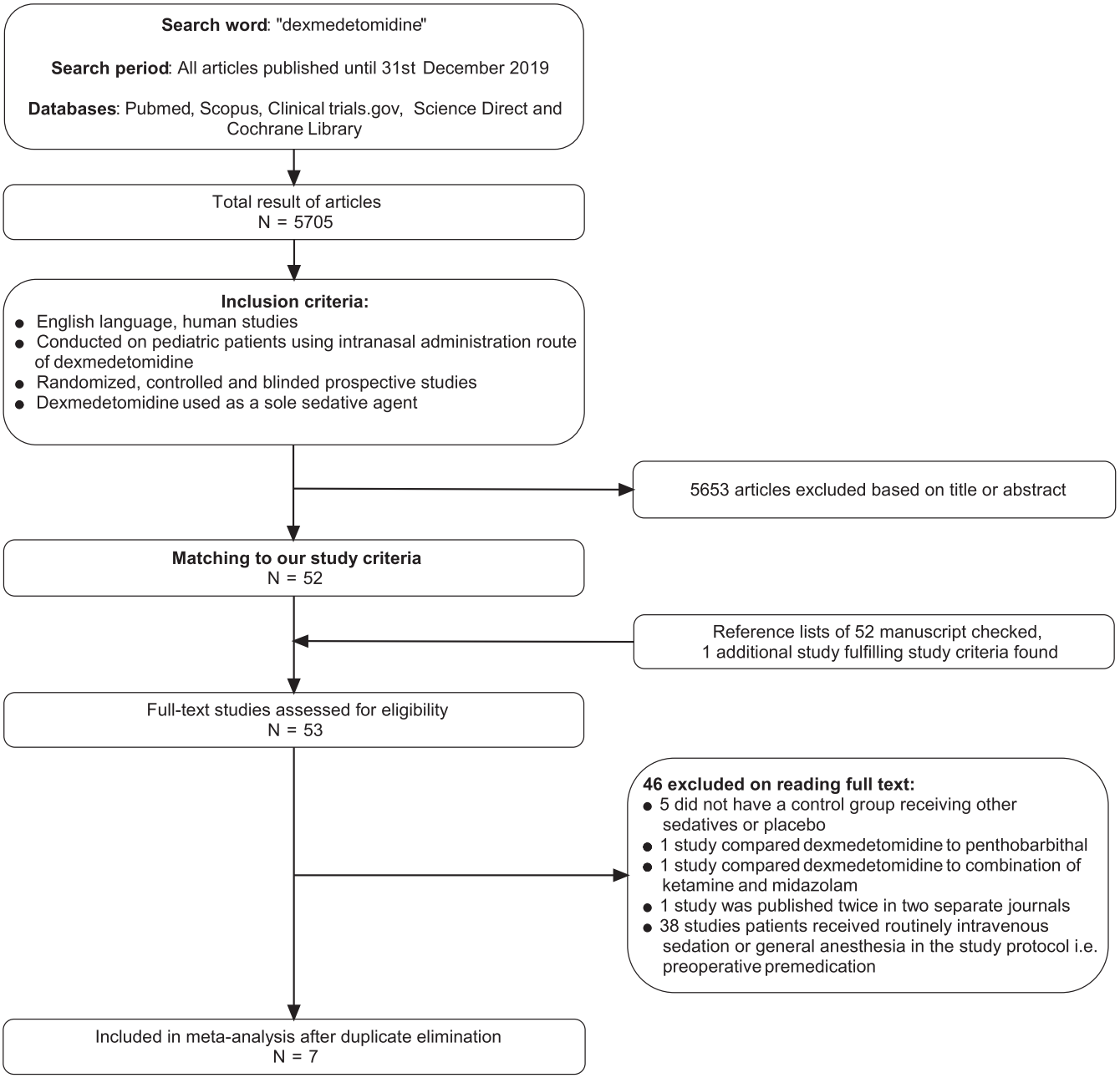

FIGURE 1 Flowchart of the systematic review and meta-analysis

and Evaluations (GRADE).[24] The Cochrane Collaboration tool[25] was used to assess the risk of bias in the studies included in the meta-analysis. Possible disagreements were discussed, and consensus was reached. Original data were collected from the included studies without any modifications. If the relevant data were not reported in the papers, the principal investigators were contacted for the missing data.

The primary outcome was the success of the procedure. This was any successful procedure reported by a study, because the procedure had been completed without any additional sedatives or the clinicians had achieved the desired level of sedation after administering the study drug. The secondary outcomes were the onset time and duration of sedation, time to discharge and occurrence of adverse events, such as nausea or vomiting, haemodynamic events and peripheral oxygen desaturation. Adverse haemodynamic and respiratory events were defined as a change in heart rate, blood pressure or oxygen saturation that required any intervention.[26] The primary and secondary outcomes were determined before the data extraction.

2.4 | Statistical analysis

Given the high chance of the primary outcome, which was the success of the planned procedure, the relative risk (RR) and its 95% confidence interval (CI) were calculated for the combined effect.

Statistical heterogeneity was evaluated with Cochran's Q test and Higgins' I^2 quantity test.[27] For the primary outcome, the findings were as follows: Cochran's Q test (P = .259) and Higgins' I^2 (25.4%) in the midazolam control group and Cochran's Q test (P = .0185) and Higgins' I^2 (66.5%) in the chloral hydrate control group. The critical level of significance was 0.10 in Cochran's Q test and ≥50% in Higgins' I^2 test. As funnel plots showed no noticeable asymmetry, publication bias was considered unlikely.

Event rates of secondary outcomes were infrequent, and no heterogeneity was detected. Thus, only the fixed effects model was used to calculate the combined effect. For dichotomous outcomes, the combined odds ratio (OR) and its 95% CI were calculated. For continuous outcomes, the mean difference and its 95% CI were calculated. If only the median, range and size of the trial were reported in a paper, the mean was estimated according to the formula presented by Wan et al[28] and the standard deviation (SD) was estimated according to the formula in the Cochrane Handbook.[23] For dichotomous outcomes, in which the event number was zero in both of the comparison groups, continuity correction was used in the analysis.[29] Publication bias could not be reliably evaluated, due to the small number of included trials. The meta-analysis was performed using Comprehensive Meta-Analysis software (Biostat) and StatsDirect v3 (StatsDirect Ltd.).

3 | RESULTS

The initial search was conducted on 3 February 2020 and it identified 5,705 studies using the search term dexmedetomidine. After we excluded unsuitable studies, seven studies were included in the meta-analysis (Figure 1). All the studies included in the final analysis were from the PubMed database: four studies compared intranasal dexmedetomidine with chloral hydrate[30-33] and the other three studies compared it with midazolam[34-36] (Table 1). The overall risk of bias was assessed to be low and the detailed assessment is shown in Table S1.

The patients' ages varied from 3 months to 8 years in six studies[30-35] and from 4 to 14 years in one study[36] (Table 1). One of the studies included patients with congenital heart defects.[31] Of the four studies that studied dexmedetomidine versus chloral hydrate, the indication for sedation was imaging, namely (transthoracic echocardiography and computed tomography) in two,[31,33] auditory brainstem response testing in one[32] and an ophthalmic examination in one.[30] The chloral hydrate dosage was 50 mg/kg in two studies,[32,33] 70 mg/kg in one[31] and 80 mg/kg in another.[30] The indications for sedation in the three studies that compared dexmedetomidine with midazolam[34-36] were dental treatment, computed tomography imaging including intravenous cannulation and laceration repair. The midazolam doses used in these three studies were 0.2 mg/kg intranasally, 0.4 mg/kg intranasally and 0.5 mg/kg orally. The dexmedetomidine dose ranged from 1 to 3 μg/kg in all seven studies included in this analysis.[30-36] Intranasal medication was administrated by a mucosal atomisation device in four studies[30,32,33,35] and as drops from a syringe in three studies.[31,34,36]

3.1 | Primary outcome

All the studies that compared intranasal dexmedetomidine with chloral hydrate defined success as completing the procedure with

TABLE 1 Brief description of the randomised control trials included in the meta-analysis

Author, year (ref) Country	Indication	Age	Drug: dose	Patients number
Cao et al, 2017[30]	Ophthalmic examination	3 mo-3 y	dex:2 μg/kg	71
China			CH: 80 mg/kg	70
Miller et al, 2016[31]	Transthoracic echocardiography	3 mo-3 y	dex: 2 μg/kg	50
			dex: 3 μg/kg	50
USA			CH: 70 mg/kg	50
Reynolds et al, 2016[32]	Auditory brainstem response testing	6 mo-8 y	dex: 3 μg/kg	44
USA			CH: 50 mg/kg	41
Yuen et al, 2017[33]	Computed tomography imaging	7 mo-5.8 y	dex: 3 μg/kg	87
Hong Kong/China			CH: 50 mg/kg	107
Ghai et al, 2016[34]	Computed tomography imaging	1 y-6 y	dex: 2.5 μg/kg	30
India			oral mid: 0.5 mg/kg	29
Neville et al, 2016[35]	Laceration repair	1 y-5.4 y	dex: 2 μg/kg	20
USA			i.n. mid: 0.4 mg/kg	18
Surendar et al, 2014[36]	Dental treatment	4 y-12 y	dex: 1 μg/kg	21
			dex: 1.5 μg/kg	21
India			i.n. mid: 0.2 mg/kg	21

Abbreviations: CH, chloral hydrate; dex, dexmedetomidine; i.n., intranasally; mid, midazolam.

the given medication. In the studies that compared dexmedetomidine with midazolam, procedural success was achieving a predetermined desired level of sedation,[34] a successful procedure[36] or a calm patient at the beginning of the procedure.[35] The incidence rate for successfully completed procedures did not differ between the use of intranasal dexmedetomidine and chloral hydrate, with a combined relative risk (RR) of 1.08 and a 95% confidence interval (95% CI) of 0.98-1.19. The success rate was higher in children treated with intranasal dexmedetomidine than in those treated with midazolam (combined RR 1.52, 95% CI 1.19-1.94) (Figure 2). The overall success rate in children treated with intranasal dexmedetomidine was 83%. The quality of evidence for the primary outcome was moderate, according to GRADE. This was because of the indirectness caused by the different dosages in the study protocols and imprecision due to the small sample size in the midazolam studies (Table 2).

3.2 | Secondary outcomes

The pooled estimate of the onset time of sedation was 16.9 ± 2.6 minutes, and the duration of sedation was 81.5 ± 4.8 minutes in the patients who received dexmedetomidine. The onset time was marginally shorter in patients receiving dexmedetomidine than chloral hydrate. However, the duration of sedation and time to discharge did not differ significantly between patients receiving dexmedetomidine and those receiving chloral hydrate. A meta-analysis of the onset time and duration of sedation between dexmedetomidine with midazolam could not be performed, as they were only reported in one paper. The time to discharge did not differ between the three sedatives used. Using GRADE, the quality of evidence for the time variables was assessed to be low, except for the duration of sedation, which was moderate (Table 2).

Although none of the studies provided a comprehensive description of bradycardia or hypotension, none of the bradycardic or hypotensive events required treatment. All the studies reported respiratory complications as events of decreased peripheral oxygen saturation. Oxygen saturation below 92%, the need for oxygen therapy or the need for repositioning the patient occurred in two out of 302 (0.7%) patients who received intranasal dexmedetomidine and 2/268 (0.7%) patients who received chloral hydrate. None of the patients in the studies that compared dexmedetomidine with midazolam experienced desaturation events (Table 2).

Nausea and vomiting were reported in 23/177 patients who received chloral hydrate and occurred in most cases within 10 minutes of drug administration. In contrast, only one of the 394 patients who received dexmedetomidine experienced nausea or vomiting (Table 2). The risk of nausea and vomiting was 25-fold higher (95% CI 3.2-201) among patients who received chloral hydrate than among those who received dexmedetomidine. Using GRADE, the quality of evidence for the adverse outcomes was assessed to be poor for hypotension and moderate for bradycardia, desaturations and nausea and vomiting (Table 2).

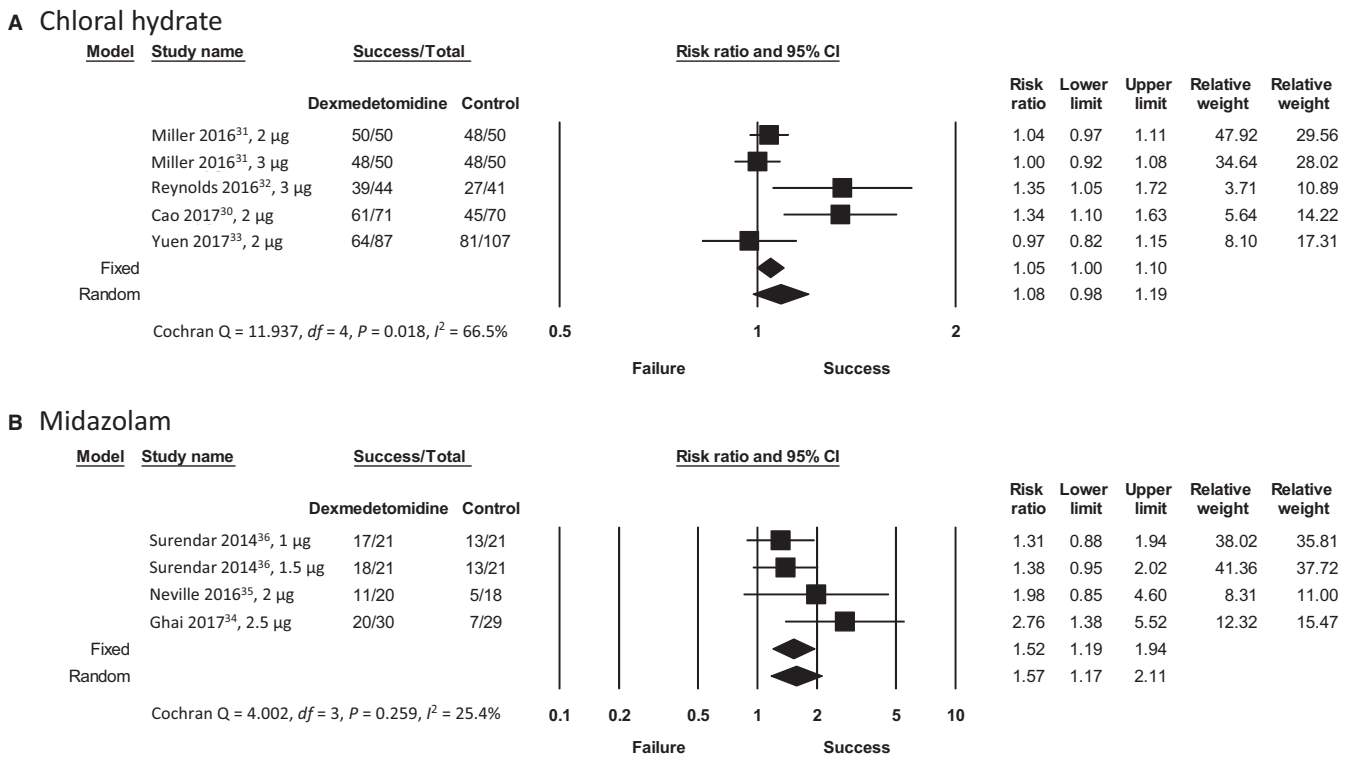

FIGURE 2 Success of the procedures

TABLE 2 Summary of findings

Primary outcome			Meta-analysis	No. of participants (studies)	Certainty of the evidence (GRADE) Comments
	Dexmedetomidine	*Midazolam*			
Success	66/92	25/68	RR (95% CI) 1.52 (1.19 to 1.94)	160 (3 RCTs)	Moderate
	Dexmedetomidine	*Chloral hydrate*			
Success	262/302	201/268	RR (95% CI) 1.08 (0.98 to 1.19)	570 (4 RCTs)	Moderate
Secondary outcomes			**Meta-analysis**	**No. of participants (studies)**	**Certainty of the evidence (GRADE) Comments**
	Dexmedetomidine	*Chloral hydrate*	Effect size (95% CI)	570 (4 RCTs)	Low
Time to onset of sedation (minutes)	*Pooled mean* 16.9 ± 2.6	*Pooled mean* 19.5 ± 3.7	−0.2 (−0.4 to −0.07)		
Duration of sedation (minutes)	81.5 ± 4.8	92.8 ± 5.1	−0.5 (−1.0 to − 0.05)	291 (2 RCTs)	Moderate
Time to discharge (minutes)	60.2 ± 5.2	71.0 ± 5.1	−0.2 (−0.4 to 0.1)	291 (2 RCTs)	Low
Drop in heart rate	*Pooled n/N* 0/302	*Pooled n/N* 0/268	OR (95% CI) 1.03 (0.2 to 5.1)	570 (4 RCTs)	Moderate
Drop in blood pressure	0/202	0/218	1.04 (0.1 to 10.1)	420 (3 RCTs)	Low
Drop in oxygen saturation	2/302	2/268	1.04 (0.2 to 5.1)	570 (4 RCTs)	Moderate
Nausea and vomiting	0/158	23/177	0.04 (0.0 to 0.3)	335 (2 RCTs)	Moderate
Secondary outcomes			**Meta-analysis**	**No. of participants (studies)**	**Certainty of the evidence (GRADE) Comments**
	Dexmedetomidine	*Midazolam*			
Time to discharge (minutes)	*Pooled mean* 24.4 ± 0.5	*Pooled mean* 28.1 ± 0.6	Effect size (95% CI) 0.05 (−0.5 to 0.6)	97 (2 RCTs)	Low
Drop in heart rate	*Pooled n/N* 0/72	*Pooled n/N* 0/50	OR (95% CI) 0.99 (0.1 to 9.7)	122 (2 RCTs)	Moderate
Drop in blood pressure	0/72	0/50	0.99 (0.1 to 9.7)	122 (2 RCTs)	Low
Drop in oxygen saturation	0/72	0/50	0.99 (0.1 to 9.7)	122 (2 RCTs)	Moderate
Nausea and vomiting	1/92	1/68	0.97 (0.2 to 5.7)	160 (3 RCTs)	Moderate

Note: Intranasal dexmedetomidine compared with midazolam and chloral hydrate during paediatric procedural sedation.

Patient population: Paediatric patients,

Intervention: Procedural sedation,

Setting: Meta-analysis of randomised controlled trials,

Study drug: Intranasal dexmedetomidine,

Comparison: Midazolam, chloral hydrate.

High certainty: We are very confident that the true effect lies close to the estimate of the effect.

Moderate certainty: We have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different to the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different to the estimate of the effect.

4 | DISCUSSION

According to the present meta-analysis, intranasal dexmedetomidine appeared to provide safe and effective premedication for minor paediatric procedures when used as a sole sedative agent. It seems applicable to both nonpainful and painful procedures, with a success rate of 83%. The success rate for completed procedures was similar for dexmedetomidine and chloral hydrate, but the use of dexmedetomidine was associated with a significantly lower incidence of nausea and vomiting. Dexmedetomidine was superior to midazolam in facilitating the successful completion of procedures.

Six of the seven studies included in the present analysis used 2-3 μg/kg of dexmedetomidine. This led to an insignificantly shorter onset time of sedation in the dexmedetomidine group than in the chloral hydrate group, but without any difference in the time to discharge between the groups. Greater doses of sedative drugs produce a deeper level of sedation, which may lead to improved procedural success, but with an increased likelihood of adverse events. Although the onset time or duration of sedation could not be compared between patients receiving dexmedetomidine and those receiving midazolam, one study reported a slower onset of sedation using intranasal dexmedetomidine than using oral benzodiazepines.[21]

Intranasal dexmedetomidine administered by an atomisation device was shown to be more effective than administration as drops by a syringe.[37] In this meta-analysis dexmedetomidine showed superior sedative properties when compared to midazolam, even though only one of the three studies used an atomising device to administer the drugs.

The overall number of adverse events among children receiving procedural sedation was low. There was a trend towards a higher incidence of vomiting in the chloral hydrate group, whereas dexmedetomidine did not cause any vomiting. The increased risk of vomiting after the administration of chloral hydrate is a known side effect, due to the bitter taste of the medicine. In contrast, intranasal dexmedetomidine is odourless and tasteless[15] and neither nausea nor vomiting has been reported in any published research on this drug.

The adverse cardiovascular and respiratory events in this meta-analysis were defined as a change in a patient's condition that required intervention, as suggested in the consensus-based recommendation for reporting sedation-related adverse events.[26] None of the patients required treatment for bradycardia or hypotension, although mild bradycardia and hypotension have been reported to be associated with the administration of intranasal dexmedetomidine.[16,20] Bradycardia caused by intranasal administration has been reported to be mild, even at higher doses, and it did not usually require treatment.[14] However, a case report of a formerly healthy paediatric patient who developed symptomatic bradycardia lasting two hours after intranasal dexmedetomidine sedation has been published.[38] The occurrence of adverse respiratory events did not differ between the sedatives used. All the reported events were mild, mainly involving slight desaturation requiring position change or the administration of supplemental oxygen. These results were in line with previous paper that also reported that dexmedetomidine appeared to suppress the respiratory responses to hypoxia and hypercapnia.[17] Thus, respiratory monitoring is necessary when using intranasal dexmedetomidine sedation.

4.1 | Relationship to other reviews

The findings of this meta-analysis were similar to those of a meta-analysis by Lin et al, which was published in 2020 and compared dexmedetomidine with other sedatives during nonpainful paediatric procedures.[39] However, our aim was to evaluate the safety and efficacy of dexmedetomidine administered solely by the intranasal route, as it does not require much co-operation and is less invasive than the intravenous route. Lin et al also included studies where dexmedetomidine was administered orally or intravenously, thereby adding heterogeneity as intravenous, intranasal and oral routes have different pharmacokinetic, safety and efficacy profiles.[40-42] Previously published meta-analyses on the use of intranasal dexmedetomidine as a premedication before surgery also revealed similar results on the superiority of intranasal dexmedetomidine premedication in comparison with benzodiazepines.[16,20,21]

Sedating children outside the operating room during therapeutic and diagnostic interventions is continuously increasing. Traditional sedative drugs are often insufficient to provide sedation and anxiolysis in paediatric procedures when used as a sole sedative agent.[7] Combining multiple sedatives often increases the sedative effects, but tends to also increase the adverse effects.[43] One of the advantages of intranasal dexmedetomide appears to be that supplementing other sedatives is only rarely needed to successfully perform the planned procedure.

Children have an increased risk of complications. In particular, respiratory complications, such as desaturation, apnoea and laryngospasm during procedural sedation, and severe cardiovascular complications related to sedation have been reported.[43] Procedural sedation outside the operating room has been reported to be equally safe when provided by different paediatric specialists.[44] However, to ensure patient safety, procedural sedation outside the operation room must conform to the established guidelines for paediatric care and must only be performed by experienced specialists with adequate skills.[45] Further studies on paediatric procedural sedation with relevant patient outcomes, such as patient comfort and pain scale, together with standardised reporting of adverse events are needed.

4.2 | Strengths and limitations

The data collection in our meta-analysis was systematic and thorough. The cardiovascular and respiratory side effects of procedural sedation were carefully analysed. The findings reinforced the

perception that dexmedetomidine had minimal impacts on the respiratory drive, heart rate and blood pressure.

A major limitation of this meta-analysis was the overall heterogeneity of the data in terms of drug dosing and the indications for sedation in the individual studies. In addition, the determination of our primary outcome, successful completion of the procedure, was heterogeneous in studies comparing intranasal dexmedetomidine with midazolam, which included both nonpainful and painful interventions like laceration repair. Finally, many studies in our meta-analysis presented their outcomes using median values, suggesting a skewed distribution in their outcomes. We used mean values by converting the median values in all our analyses, which may have diminished the effect of the treatments.

5 | CONCLUSION

This meta-analysis found that intranasal dexmedetomidine was a safe and effective sedative drug during paediatric procedural sedation outside the operating room. It had similar procedural success rates to chloral hydrate but seemed to be superior to midazolam. Clinically relevant adverse events associated with intranasal dexmedetomidine were rare.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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