

Intranasal dexmedetomidine versus oral chloral hydrate for diagnostic procedures sedation in infants and toddlers

A systematic review and meta-analysis

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Abstract

Background: Intranasal dexmedetomidine is a relatively new way to sedate young children undergoing nonpainful diagnostic procedures. We performed a meta-analysis to compare the efficacy and safety of intranasal dexmedetomidine in young children with those of oral chloral hydrate, which has been a commonly used method for decades.

Methods: We searched PubMed, Embase, and the Cochrane Library for all randomized controlled trials that compared intranasal dexmedetomidine with oral chloral hydrate in children undergoing diagnostic procedures. Data on success rate of sedation, onset time, recovery time, and adverse effects were extracted and respectively analyzed.

Results: Five studies with a total of 720 patients met the inclusion criteria. Intranasal dexmedetomidine provided significant higher success rate of sedation (relative risk [RR], 1.12; 95% confidence interval [CI], 1.02 to 1.24; $P = .02$; $I^2 = 74%$) than oral chloral hydrate. Furthermore, it experienced significantly shorter onset time (weight mean difference [WMD], -1.79 ; 95% CI, -3.23 to -0.34 ; $P = .02$; $I^2 = 69%$). Nevertheless, there were no statistically differences in recovery time (WMD, -10.53 ; 95% CI, -24.17 to 3.11 ; $P = .13$; $I^2 = 92%$) and the proportion of patients back to normal activities (RR, 1.11; 95% CI, 0.77–1.60; $P = .57$; $I^2 = 0%$). Intranasal dexmedetomidine was associated with a significantly lower incidence of nausea and vomiting (RR, 0.05; 95% CI, 0.01–0.22; $P < .0001$; $I^2 = 0%$) than oral chloral hydrate. Although adverse events such as bradycardia, hypotension and hypoxia were not synthesized due to lack of data, no clinical interventions except oxygen supplementation were required in any patients.

Conclusion: Our meta-analysis revealed that intranasal dexmedetomidine is possibly a more effective and acceptable sedation method for infants and toddlers undergoing diagnostic procedures than oral chloral hydrate. Additionally, it shows similar safety profile and could be a potential alternative to oral chloral hydrate.

Abbreviations: ABR = auditory brainstem response, CH = chloral hydrate, CI = confidence interval, CT = computed tomography, DEX = dexmedetomidine, MD = mean difference, MOAA/S = the modified Observer Assessment of Alertness and Sedation Scale, MRI = magnetic resonance imaging, OE = ophthalmic examination, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, RCTs = randomized controlled trials, RR = relative risk, TTE = transthoracic echocardiography, WMD = weight mean difference.

Keywords: adrenergic alpha-2 receptor agonists, adverse effects, child, noctec, procedural sedation, sedatives and hypnotics

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LL and JZ contributed equally to this work.

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1. Introduction

Diagnostic procedures for the uncooperative young children must be performed under either general anesthesia or procedural sedation. General anesthesia with intubation can be favorable for airway control but is time-consuming and associated with higher cost. Consequently, diagnostic procedures for children are frequently performed under procedural sedation, which can provide cooperation of children for clinicians. Children usually tend to receive relatively deep sedation to ensure sufficient immobility during the examinations. Thus, they may take a higher risk of the adverse effects of sedative agents. Because of this, it is probably necessary for us to completely evaluate the efficacy and safety of the commonly used sedative drugs for children.

Chloral hydrate has been a widely used sedative for infants and toddlers undergoing noninvasive diagnostic procedures over several decades. While procedural sedation using oral chloral hydrate is commonly considered to be safe, there have been concerns about its potential side effects, including inconsistent sedative effects, airway obstruction, nausea or vomiting, agitation and in particular severe neurologic injuries and carcinogenicity.^[1–4] Furthermore, it must be noted that chloral hydrate should not be recommended to sedate children older than 48 months because of increased failure rate of sedation.^[5] It is exactly in this young children group that chloral hydrate often result in unpleasant experiences and even resistance as a result of its bitter taste and gastrointestinal adverse effect. Additionally, due to limited availability of chloral hydrate in some countries,^[2] it is a great challenge to search for suitable alternative sedatives for pediatric patients.

Dexmedetomidine is a highly selective alpha-2 adrenergic agonist with sedative, anxiolytic, and analgesic properties. Sedation with dexmedetomidine is reported to associated with minimal respiratory depression and acceptable cardiovascular effects, such as hypertension, hypotension, and bradycardia.^[6] There exists a substantial body of evidence with regards to intravenous administration of dexmedetomidine as a sedative both in the theatre and intensive care unit.^[7,8] However, intravenous cannulation for infants not only is technically difficult but also may cause long-term psychological problems. Therefore, the intranasal route is increasingly advocated to dexmedetomidine administration before getting IV access in pediatric patients, especially in the infants. Many studies have demonstrated the efficacy and safety of dexmedetomidine in pediatric patients,^[9–11] but most of the pediatric patients enrolled in these studies cover a wide range of age and few of randomized controlled trials (RCTs) directly compare intranasal dexmedetomidine with oral chloral hydrate.

We therefore did a comprehensive meta-analysis of RCTs to examine whether intranasal dexmedetomidine would be more effective and safer for sedation in infants and toddlers when compared with oral chloral hydrate.

2. Methods

We used a systematic review and meta-analysis to identify publications that compared the efficacy and safety of intranasal dexmedetomidine with oral chloral hydrate in infants and toddlers. This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.

Ethical approval was not necessary because this was a review of RCTs.

2.1. Literature search

Two reviewers independently (Linji Li and Deshui Yu) searched PubMed, EMBASE, and the Cochrane library from the inception of the databases to December 22, 2018. The search terms we used were as follows: “Dexmedetomidine or dexmedetomidin* or Precedex or dexdor” and “chloral hydrate or hydrate, chloral or noctec.” No limitation was imposed. Reference lists of identified articles were searched for relevant studies and manually scanned to include additional eligible studies.

2.2. Inclusion and exclusion criteria

We included studies that complied with the following criteria:

- (1) Children (almost <4 years old) receiving noninvasive diagnostic procedures under procedural sedation.
- (2) The intervention group was intranasal administration of dexmedetomidine.
- (3) The control group was oral chloral hydrate.
- (4) Only RCTs were included.
- (5) Only studies with a full text available were included.

We excluded studies where dexmedetomidine or chloral hydrate was combined with other sedative drugs for procedural sedation.

2.3. Data extraction and outcomes

The data extraction was independently performed by two reviewers (Linji Li and Deshui Yu), and the following items of information were extracted: the name of the first author, year of publication, baseline characteristics of patients, type of examination, sample size, intervention of the intranasal dexmedetomidine group and oral chloral hydrate group, the onset time, success rate of sedation, recovery time, and adverse effects. The primary outcome was success rate of sedation; secondary outcomes were the onset time and adverse effects.

2.4. Assessment of methodological quality

Two reviewers (Linji Li and Xuechao Hao) blindly assessed the methodological qualities using the Cochrane risk of bias tool for assessing the risk of bias. In case of any unresolved disagreements between the two reviewers, a third reviewer (Tao Zhu) was consulted to reach a final decision.

2.5. Statistical analysis

For binary outcomes, a relative risk (RR) with 95% confidence intervals (CIs) was estimated. For continuous outcomes, mean difference (MD) with 95% CI was calculated and the generic inverse variance method was used to determine weighted mean differences (WMDs). Heterogeneity between the included studies was assessed by I^2 statistic. Random effects models were used when an I^2 statistic >50% was detected, which is considered to be statistically heterogeneous. Funnel plots were not used to evaluate publication bias because only 5 RCTs were included in our meta-analysis. All the outcome data were analyzed using RevMan software version 5.3 (Cochrane Collaboration, 2014).

3. Results

3.1. Identification of studies and characteristics of the studies

A total of 206 studies were initially identified through the database search. After removing duplicate papers, 166 studies were obtained for further assessing. Then, we excluded 157 studies after screening the titles and abstracts. Finally, 5 RCTs^[12–16] that satisfied all the inclusion criteria were identified and included in this meta-analysis after review of the remaining 9 full manuscripts. In total, 720 patients were included in 5 RCTs. Of these, 402 patients (55.8%) were sedated with intranasal dexmedetomidine compared with those of oral chloral hydrate (Fig. 1). We also summarized the basic characteristics of the included RCTs, such as publication year, nationality, interventions of all groups, doses of drugs, patient number, and age (Table 1).

3.2. Quality of the included studies

All of the 5 included studies^[12–16] described in detail the random sequence generation and the allocation concealment. The risk of

blinding in outcome assessment was unclear in only 1 study.^[12] With regard to incomplete outcome data, intention-to-treat analysis was not performed in 1 study which reported loss follow-up^[12] and 1 study was of unclear risk^[15] (Fig. 2).

3.3. Results of meta-analysis

All of the 5 trials^[12–16] with 720 patients compared success rate of sedation. We found that patients who were sedated with intranasal dexmedetomidine had significantly higher success rate of sedation when compared with those sedated with oral chloral hydrate (RR, 1.12; 95% CI, 1.02–1.24; $P = .02$; $I^2 = 74\%$) (Fig. 3A). The onset time of sedation was also reported in all of the 5 trials.^[12–16] We found the onset time of intranasal dexmedetomidine was significantly shorter when compared with those of oral chloral hydrate (WMD, -1.79 ; 95% CI, -3.23 to -0.34 ; $P = .02$; $I^2 = 69\%$) (Fig. 3B). A trend of shorter recovery time could be observed in the intranasal dexmedetomidine group. However, unfortunately, the trend did not reach the significance level (WMD, -10.53 ; 95% CI, -24.17 to 3.11 ; $P = .13$; $I^2 = 92\%$)^[12,13,16] (Fig. 4A). Two trials including 279 patients reported the situation of patients to return to normal activities

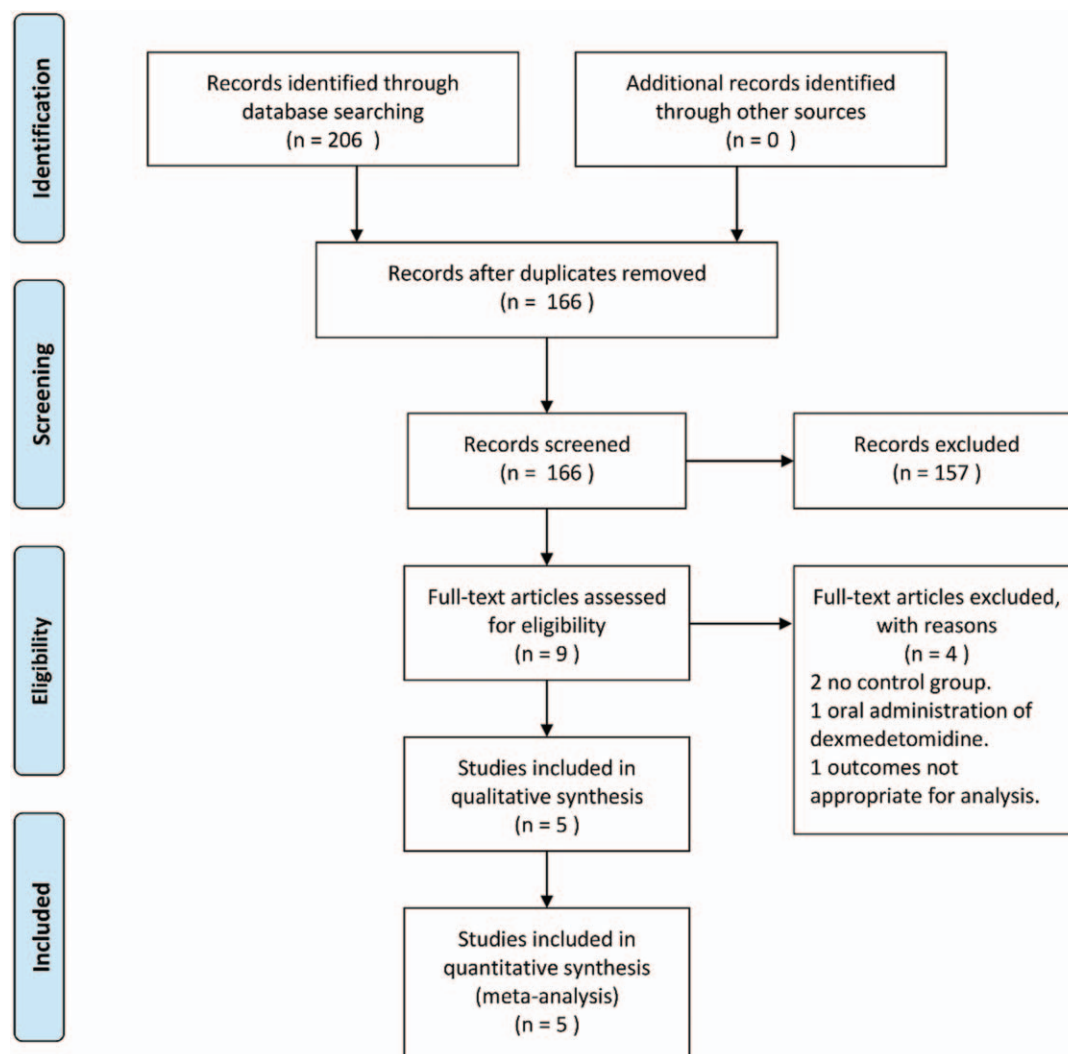


Figure 1. The flow diagram of the literature search strategy.

Table 1
Characteristics of the included studies evaluating intranasal dexmedetomidine vs oral chloral hydrate in diagnostic examination.

Author	Year	Nation	Intervention	Dose	No. patients (male/female)	Age (month)	Examination	Assessment methods of sedative effect	Observers determining
Sedative effectiveness									
Cao et al ^[12]	2017	China	Intranasal DEX	2 μg/kg	71 (45/26)	18 (10–25)	OE	MOAA/S	Not mentioned
Miller et al ^[13]	2016	USA	Oral CH	80 mg/kg	70 (43/27)	14.5 (8.8–23.2)	TTE	Modified Ramsay scale	Anesthesiologist
			Intranasal DEX	2 μg/kg	50 (33/17)	13.7 ± 8.6			
Reynolds et al ^[14]	2016	USA	Intranasal DEX	3 μg/kg	50 (27/23)	15.4 ± 8.5	ABR	A state that allowed the audiologist to place ABR electrodes	Audiologist
			Oral CH	70 mg/kg	50 (26/24)	13.6 ± 7.6			
			Intranasal DEX	3 μg/kg	44 (23/21)	23.3 (19.5–27.2)			
Yuen et al ^[15]	2017	Hong Kong,	Oral CH	50 mg/kg	41 (27/14)	25.6 (22.0–29.0)	CT	University of Michigan Sedation Scale	Research nurse
		China	Intranasal DEX	3 μg/kg	88 (63/25)	32.5 (19.8–39.0)			
Zhang et al ^[16]	2016	China	Oral CH	50 mg/kg	108 (67/41)	24.0 (14.0–36.0)	MRI	MOAA/S	Blinded observer
			Intranasal DEX	1 μg/kg	48 (30/28)	3.3 ± 1.6			
			Intranasal DEX	2 μg/kg	46 (22/24)	3.3 ± 1.5			
			Oral CH	25 mg/kg	40 (19/21)	3.8 ± 1.5			

Data are expressed as mean ± standard deviation or mean (95% confidence interval); ABR = auditory brainstem response, CH = chloral hydrate, CT = computed tomography, DEX = dexmedetomidine, MOAA/S = the modified Observer Assessment of Alertness and Sedation Scale, MRI = magnetic resonance imaging, OE = ophthalmic examination, TTE = transthoracic echocardiography.

after drug administration.^{12,15} It was observed that there were no significant differences between intranasal dexmedetomidine and oral chloral hydrate at this point (RR, 1.11; 95% CI, 0.77–1.60; $P = .57$; $I^2 = 0\%$) (Fig. 4B). The incidence of nausea and vomiting was extracted from 3 trials including 485

patients.^[12,15,16] We found the intranasal dexmedetomidine group experienced a significantly lower incidence of nausea and vomiting when compared with oral chloral hydrate group (RR, 0.05; 95% CI, 0.01–0.22; $P < .0001$; $I^2 = 0\%$) (Fig. 4C). Although all of the 5 trials had their own criteria for adverse events such as bradycardia, hypotension and hypoxia, no clinical interventions except oxygen supplementation were required in any patients.

4. Discussion

This systematic review and meta-analysis suggested that intranasal dexmedetomidine administration could result in higher success rate of sedation and reduce the onset time for procedural sedation in infants and toddlers compared with oral chloral hydrate. Furthermore, a significantly lower incidence of nausea and vomiting was also observed in the intranasal dexmedetomidine group. However, in our study, there were no significant differences in the recovery time and post-sedative behavior between intranasal dexmedetomidine and oral chloral hydrate. Although we failed to acquire the pooled data about hemodynamic and respiratory parameters of the patients because of insufficient data, no children included in the study needed pharmacologic treatment due to severe bradycardia or hypotension and no interventions beyond oxygen supply were required among few of them due to hypoxemia.

Dexmedetomidine, a highly selective α₂-adrenoceptor agonist, can induce a unconscious state similar to natural non-rapid eye movement sleep by activating central pre- and postsynaptic α₂-receptors in the locus coeruleus. Contrary to sedation with the majority of other drugs, patients sedated with dexmedetomidine are easily rousable and cooperative and are associated with acceptable adverse effects such as minimal respiratory depression, bradycardia and hypotension.^[6,17] Therefore, dexmedetomidine has the potential to be a suitable sedative for procedural sedation in children undergoing diagnostic procedures. The intranasal route is the most common extravascular route of dexmedetomidine administration, the bioavailability of which varies from ~40%^[18] to 80%.^[19]

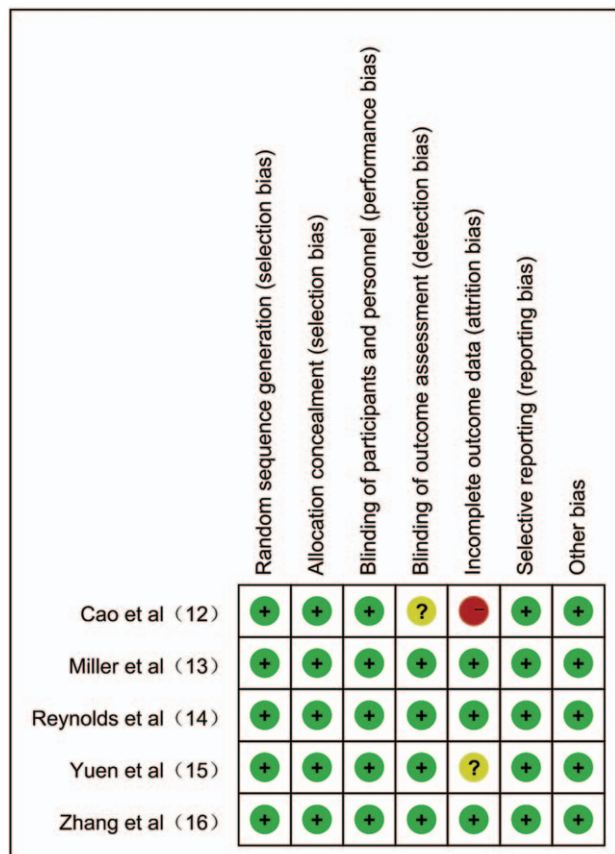


Figure 2. Risk-of-bias summary for all the included randomized-controlled trials.

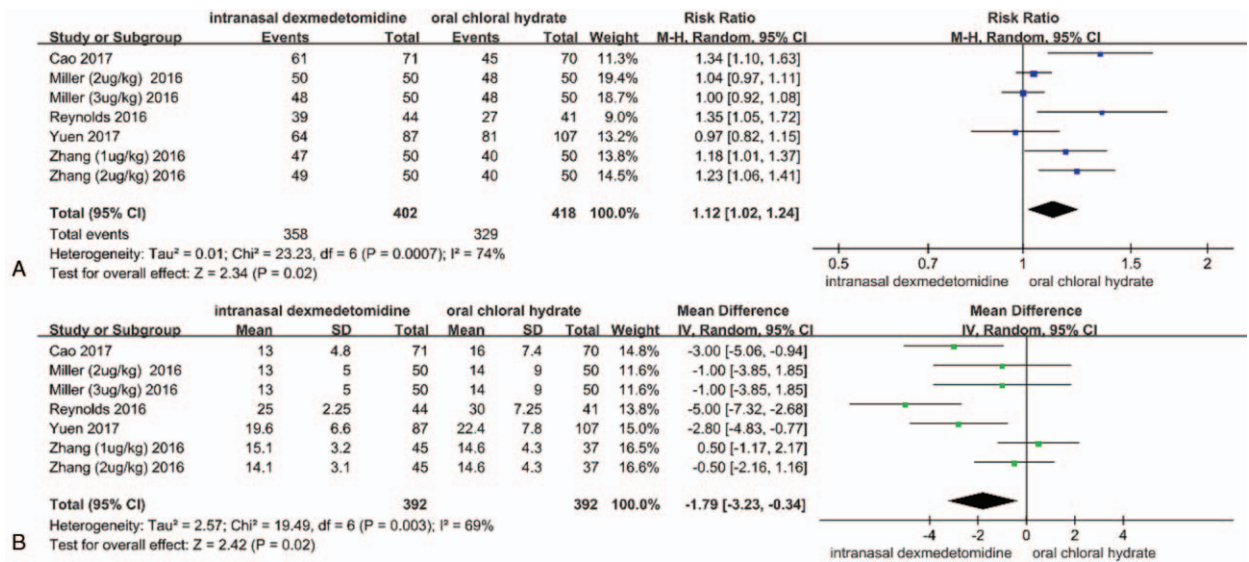


Figure 3. The effects of intranasal DEX vs oral CH: (A) impact on success rate of sedation; (B) impact on onset time of sedation; CH=chloral hydrate, DEX=dexmedetomidine.

With respect to the efficacy of sedation, previous studies have shown conflicting results between intranasal dexmedetomidine and oral chloral hydrate. For instance, according to Yuen et al,^[15] there were no differences in the proportion of children achieved satisfactory sedation level between 3 μg/kg intranasal dexmedetomidine and 50mg/kg oral chloral hydrate. Nevertheless, Reynolds et al^[14] reported that 3 μg/kg intranasal dexmedetomidine was associated with a higher incidence of testing completion and shorter onset time to desired sedation level compared to 50mg/kg oral chloral hydrate. In our meta-analysis,

we found the sedative effects of intranasal dexmedetomidine in children are superior to oral chloral hydrate, with higher success rate of sedation and shorter onset time. In two other recent studies, Kim et al^[20] and Jun et al^[21] also demonstrated the advantages of intranasal dexmedetomidine compared to other sedation methods. Moreover, they reported the possible sources of the heterogeneity, which mainly came from different administration route and doses of drug. In our meta-analysis, allocation concealment and double blinding were relatively well performed in the including trials. Besides, we only included trials

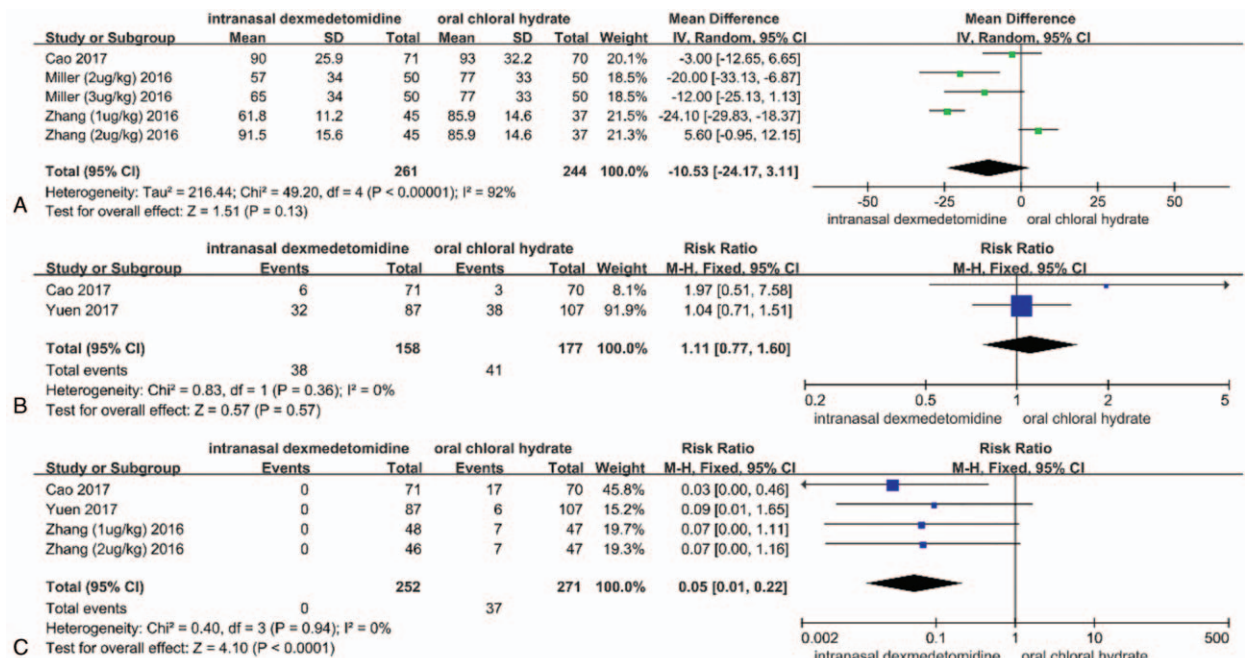


Figure 4. The effects of intranasal DEX vs oral CH: (A) impact on recovery time; (B) impact on post-sedative behavior; (C) impact on the incidence of nausea and vomiting; CH=chloral hydrate, DEX=dexmedetomidine.

comparing intranasal dexmedetomidine and oral chloral hydrate in infants and toddlers, because chloral hydrate is not recommended for children older than 4 years due to increased rates of sedation failure.^[15] Thus, trials covering a wide range of age might exaggerate the sedation effects of intranasal dexmedetomidine. Although measures have been taken to control heterogeneity, the rate of heterogeneity in our meta-analysis was still not greatly reduced. From our perspective, the heterogeneity might be highly related to different doses of drug. According to Zhang et al,^[22] even in children younger than 3 years old, the ED₅₀ increases with advancing age. In addition, other sources of heterogeneity were possibly derived from different type of examinations, various assessment methods of sedative effect, even different observers who determined sedative effectiveness, all of which were presented in Table 1. All these factors could possibly have influence on the evidence grade of our meta-analysis. Consequently, further RCTs limited to a common sedation goal state for very similar procedures would be needed to identify the optimal doses for children of different ages.

Only 3 trials^[12,13,16] included in this meta-analysis reported recovery time. We found that there was not a statistically significant difference in awaking time between the two groups. It was reported that the average recovery time of intranasal dexmedetomidine is approximately from 90 min to 2 h,^[2,6] which is, to some extent, comparable to our including trials. However, a heterogeneity as high as about 90% was also detected in our meta-analysis. It could be interpreted as a high inter-individual variability of pharmacokinetics and pharmacodynamics of drugs.^[17]

Two trials^[12,15] included in our meta-analysis investigated the situation of resumption of normal activity after sedation. To our surprise, there were no significant differences between these two groups at this point. Generally, it is commonly believed that dexmedetomidine has a shorter half-life compared with chloral hydrate. According to Yuen et al,^[23] we may attribute this result to inadequate sample size and higher sensitivity of young children to drugs. Further studies are needed to provide more evidence about this topic.

The occurrence of gastrointestinal adverse effects, such as vomiting, poor appetite and altered bowel habit, were almost all associated with oral chloral hydrate. On the contrary, it could hardly be observed in the intranasal dexmedetomidine group. Thus, intranasal dexmedetomidine may be better accepted by young children compared to oral chloral hydrate.

In our meta-analysis, children in the intranasal dexmedetomidine group did show lower blood pressure and heart rate during the examinations. Although we could not acquire the pooled data of the incidence of bradycardia and hypotension because of differences in the criteria, it is noteworthy that there were no severe cardiovascular adverse events that require intervention in either group. Severe bradycardia and transient hypertension, followed by hypotension are usually associated with a rapid intravenous infusion with dexmedetomidine. Nevertheless, intranasal administration shows a delayed onset time with lower peak concentration, which may result in lower risk of adverse events,^[24] either by atomizer or by drops.^[25] To the best of our knowledge, few studies reported severe hemodynamic adverse events such as cardiac arrest after intranasal administration of dexmedetomidine in the young children group. Most of the bradycardia and hypotension caused by intranasal dexmedetomidine in children require no clinical intervention. Generally speaking, the incidence of decreases in oxygen saturation was rare in patients with either dexmedetomidine or chloral hydrate. No airway interventions except oxygen

supplementation were required, even in children with unrepaired tetralogy of Fallot whose oxygen saturation declined to 82%.^[13]

5. Limitations

Some potential limitations should be considered. First, the heterogeneity among our included studies, which mainly originated from doses of sedatives and type of diagnostic procedures, were still significant. Consequently, random effects models were used for our meta-analysis. Second, we failed to acquire the pooled data of hemodynamic and respiratory adverse effects due to the diversity of the measured data. Finally, only five RCTs with a total of 720 patients were included, which might be a relatively small sample size to detect the difference of the efficacy and safety between intranasal dexmedetomidine and oral chloral hydrate. Thus, further larger RCTs are needed to verify the clinical meaning of intranasal dexmedetomidine.

6. Conclusion

In conclusion, we believe that intranasal dexmedetomidine is possibly a more effective and acceptable sedation method for infants and toddlers undergoing diagnostic procedures than oral chloral hydrate. Although a trend of lower blood pressure and heart rate were observed, intranasal dexmedetomidine has the potential to be a safe alternative to oral chloral hydrate as a method of sedation for young children.

Author contributions

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