Comparison of dexmedetomidine with chloral hydrate as sedatives for pediatric patients
A systematic review and meta-analysis

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Abstract

Background: Dexmedetomidine (Dex) and chloral hydrate (CH) are the most frequently used sedative agents in pediatric patients. We aimed to systematically review the literature comparing the efficacy and safety of Dex and CH for sedation in pediatric patients.

Methods: Seven electronic databases and 3 clinical trial registry platforms were searched for articles published prior to October 2019. Randomized controlled trials (RCTs) evaluating the efficacy and safety of Dex versus CH for sedation in children were examined by 2 reviewers. The extracted information included the success rate of sedation, sedation latency, sedation duration, sedation recovery time, and adverse events. Moreover, the extracted data included 5 subgroups: the effects of 1, 1.5, 2, 2.5, and 3 μg/kg doses of Dex were compared with the effect of CH on the success rate of sedation. We also formed separate subgroups for different types of adverse events (incidence of vomiting, hypotension, bradycardia, etc). The outcomes were analyzed by Review Manager 5.3 software and are expressed as relative risks (RR) or the mean difference (MD) with the 95% confidence interval (CI). Heterogeneity was assessed with I-squared (I²) statistics.

Results: A total of 15 RCTs involving 2128 children with Dex versus CH for sedation were included in the meta-analysis. The dose range of Dex ranged from 1 to 3 μg/kg. Compared with CH, the Dex group had a significantly higher success rate of sedation (RR = 1.14, 95% CI [1.05, 1.25], I² = 79%, P = .003). Additionally, subgroup analysis revealed that there was no significant difference in the success rate of sedation between the CH group and the 1, 1.5, 2, and 3 μg/kg Dex groups; only the 2 μg/kg Dex group had a significantly higher success rate than the CH group (RR = 1.15, 95% CI [1.03, 1.29], I² = 80%, P = .02). There was no significant difference in the number of subjects who required 2 doses or the duration of sedation between the CH and Dex groups. Furthermore, compared with the Dex group, the CH group had a significantly longer sedation latency (MD = −3.54, 95% CI [−5.94, −1.15], I² = 95%, P = .004), sedation recovery time (MD = −30.08, 95% CI [−46.77, −13.39], I² = 99%, P = .0004), and total time from sedative administration to discharge (MD = −12.73, 95% CI [−15.48, −9.97], I² = 0%, P < .05), as well as a higher number of adverse events in total (RR = 2.05, 95% CI [0.11, 6.01], I² = 89%, P = .002). Moreover, the subgroup analysis of adverse events revealed that CH was associated with higher risks of vomiting (RR = 0.07, 95% CI [0.03, 0.17], I² = 0%, P < .0001), crying or resisting (RR = 0.22, 95% CI [0.07, 0.71], I² = 60%, P = .01), and cough (RR = 0.15, 95% CI [0.05, 0.44], I² = 0%, P = .0006); there was no significant difference in the risk of hypotension, supplemental oxygen, or respiratory events between CH and Dex. However, Dex was associated with a higher risk of bradycardia (RR = 4.08, 95% CI [1.63, 10.21], I² = 0%, P = .003).

Conclusions: Dex is an appropriate effective alternative to CH for sedation in pediatrics. However, considering the possibility of bradycardia, Dex should be used with caution.

Abbreviations: ABR = auditory brainstem response testing, ASA = American Society of Anesthesiologists, CH = chloral hydrate, CI = confidence interval, CT = computed tomography, Dex = dexmedetomidin, EEG = electroencephalogram, MD = mean difference, MRI = magnetic resonance imaging, RCTs = randomized controlled trials, RR = relative risks, TTE = transthoracic echocardiogram.

Keywords: children, chloral hydrate, dexmedetomidine, efficacy, meta-analysis, safety, sedation
1. Introduction

Approximately 10,000 pediatric procedures occur under sedation in the UK each year.\(^1\) These sedations are mainly performed for painless procedures, such as transthoracic echocardiography and magnetic resonance imaging/computerized tomography (MRI/CT) scanning, during which the patient needs to remain still but should be easy to awaken. However, sedating children for diagnostic and therapeutic procedures continues to pose challenges.\(^2\) For these tests to be successfully performed, sedative agents are required for children, which prevent patient movement and mitigate emotional discomfort.

Chloral hydrate (CH) is a central nervous system depressant; it is one of the oldest sedatives (discovered in 1832), and it is one of the most frequently used sedative agents in pediatric echocardiography, CT, MRI imaging, and so on.\(^3\,^4\) The NICE 2010 guidelines recommend that CH be considered for children under 13 kg who are unable to tolerate a painless procedure, as such procedures have a wide margin of safety.\(^5\) However, CH should be properly monitored and managed by appropriately trained personnel due to the risk of respiratory depression and hypoxia.\(^7\) and the use of CH often results in many undesirable side effects, including vomiting, inconsistent sedative effects, and longer periods of sleepiness.\(^8\)

In contrast, dexmedetomidine (Dex) appears to be an attractive alternative sedative agent; it is an a2 adrenal receptor agonist similar to clonidine but with a 6-fold greater specificity for the a2 receptor, and it is widely used for procedures requiring the sedation of pediatric patients due to its sedative and analgesic characteristics.\(^8\,^9\) Dex not only preserves respiratory measurements and creates a natural state of nonrapid eye movement sleep,\(^10\,^11\) but is colorless and odorless and is formulated in a strong concentration of 100 mg/mL (small volumes can be easily administered), which can reduce the secretion of respiratory glands in anesthetized patients, thereby reducing the stimulation of patients’ mucous membrane. Dex has been successfully administered via IV, intranasal inhalation, and intramuscular routes for pediatric radiologic imaging.\(^8\,^12\,^13\)

In addition to successful sedation, children’s safety is a priority goal in sedation. However, a previous meta-analysis only compared the efficacy of CH versus Dex with respect to on neurodiagnostic procedures and sedation.\(^14\,^15\) Recently, novel RCTs\(^16\,^17\) have been published, and the efficacy and safety of CH versus Dex when used as monosedatives for sedation in pediatrics has not yet been systematically reviewed. We included studies of all types of surgical or diagnostic procedures. Therefore, this review aims to systematically evaluate the efficacy and safety of CH versus Dex for sedation in pediatrics to provide evidence for health professionals who prescribe CH or Dex as well as for pharmaceutical research and development.

2. Methods

2.1. Search strategy

Our research used 3 English electronic databases (PubMed, Embase, Cochrane Library) and 4 Chinese electronic databases (China National Knowledge Infrastructure, Wan Fang Database, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals). Three clinical trial registry platforms were used to find additional studies, including Clinical Trials.gov, the World Health Organization Clinical Trials Registry Platform, and the Cochrane Central Registry of Controlled Trials. The search strategy was specific for each database and included a combination of the medical subject headings and free text terms (“Dex” or “DEX” or “Dexmedetomidine”) and (“CH” or “somnos” or “nycton” or “dormal”). We looked for additional studies in the reference lists of the selected articles and contacted the authors if there was unclear information. The databases were search for articles published prior to October 2019.

2.2. Inclusion criteria

The inclusion criteria were as follows: participants: pediatric patients (0–18 years) who required sedation before surgery or diagnostic procedures, American Society of Anesthesiologists (ASA) ASA I–III, no allergic history, intervention: studies evaluating the efficacy and safety of Dex versus CH when used as monosedatives for sedation in pediatrics, the intervention group only received Dex, and the route of administration was not limited, comparison: the control group received CH alone, and the route of administration was also not restricted, outcomes: the primary outcome was the success rate of sedation; the secondary outcome included the number of subjects who required 2 doses, sedation latency, sedation duration, sedation recovery time, total time from sedative administration to discharge, and different style of adverse events (incidence of nausea and vomiting, crying, hypotension, bradycardia, and so on) and type of study: randomized controlled trial (RCT). The exclusion criteria were as follows: patients in intensive care, adult subjects and per protocol use of additional sedative medication, unable to retrieve data; letters, reviews, and animal studies, noncomparative study design, repeated published studies.

2.3. Data extraction

Two authors independently extracted the data based on a previously designed data extraction table. The extracted data included the author, year of publication, country, experimental design, sample size, mean age, intervention measure, dose, type of procedure, and any outcome that met the inclusion criteria.

Two independent reviewers screened all the titles and abstracts to determine potential eligible articles. They independently applied the eligibility criteria to perform the final selection. When discrepancies occurred between both reviewers regarding the inclusion of the articles, they discussed and identified the reasons to either include or exclude the articles and then made the final decision. If they could not reach an agreement, the final decision was made by a third reviewer.

2.4. Risk of bias assessment

We used the Cochrane risk of bias tool for RCTs.

2.5. Statistical analysis

Meta-analysis was conducted with RevMan 5.3. The data were pooled and are expressed as relative risks (RR) or the mean difference (MD) with the 95% confidence interval (CI).

Heterogeneity assessment was measured by I-squared (\(I^2\)) statistics. A fixed effects model was initially used. If significant heterogeneity existed among the trials (\(I^2 > 50\%\)), potential sources of heterogeneity were considered, and where appropriate, a random effects model was used.
Moreover, these extracted data made it possible to conduct 5 pairwise comparisons of the doses of Dex. Thus, we formed 5 separate subgroups in our analysis, comparing 1, 1.5, 2, 2.5, and 3 μg/kg doses of Dex against CH. We also formed 5 separate subgroups based on the different kinds of adverse events (incidence of nausea and vomiting, crying, hypotension, bradycardia, supplemental oxygen, respiratory events, cough).

3. Results

3.1. Study search and characteristics

A total of 160 articles were identified for the initial screening, and 15 eligible studies published between 2013 and 2019 were included in this meta-analysis (Fig. 1). A total of 2128 children were enrolled in this study. The CH group received a dose of 50 to 100 mg/kg, which was consistent with our current practice and consistent with the published dose range for pediatric sedation for nonpainful procedures.[19,20] The dose of Dex ranged from 1 to 3 mg/kg (Table 1).

3.2. Quality assessment (risk of bias tool)

According to the Cochrane risk of bias tool, 7 aspects, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, were evaluated. A total of 53.33% of the studies (8/15) used an adequate method for random sequence generation, such as using a random number table or a computer-generated random number table. Four studies mentioned allocation concealment. A total of 26.66% of studies (4/15) performed blinding of participants and personnel, such as using computer distribution in the center. A total of 86.67% of studies (13/15) reported complete outcomes. A total of 93.33% of studies (14/15) reported no selective reporting with checking protocols. Blinding of outcome assessment and other biases were vague in the majority of trials (Fig. 2).

3.3. Success rate of sedation

Among the 15 RCTs, 12 studies including 1938 children contributed to this analysis. Compared with the CH group,
| Study ID | Intervention | Sample size | Sex (male/female) | Age, mo | Weight size, kg | Examination type | ASA | Success rate of sedation | Number of subjects who required 2 mins | Sedation duration, min | Sedation latency, min | Sedation recovery time, min | Total time, min |
|----------|--------------|-------------|-------------------|--------|----------------|------------------|-----|------------------------|-------------------------------------|---------------------|------------------|------------------------|-----------------|
| Jason Reynolds[16] 2016 | Oral chloral hydrate 50mg/kg | 41 | 25/21 | 23.3 (8.5-27.2) | 123 (11.2-13.4) | ABR | NA | 27 (66.6%) | 3 (6.8%) | NA | 30 (70.6%) | NA |
| V.M. Yuen[16] 2017 | Intranasal dexmedetomidine 3 μg/kg | 108 | 68/40 | 24.0 (4.0-36.0) | 116.0 (6.0-13.7) | CT | ASA-II | 81 (76%) | NA | 22.4 (7.8%) | NA |
| Reynolds[13] 2016 | Oral chloral hydrate 15mg/kg | 50 | 24/26 | 13.6±7.6 | 8.9±2.0 | TTE | ASA-I | 48 (66%) | 2 (4%) | 10±8 | 14±9 | 77±33 | 96±34 |
| Hakan Gurum [25] 2014 | Oral chloral hydrate 50mg/kg | 36 | 18/18 | 47±21.9 | 14.1±4.2 | EEG | ASA-I | 28 (77.8%) | NA | 31.5±5.6 | 34.0±6.6 | 52.2±24.2 | 117.8±23.4 |
| Cap[24] 2017 | Intranasal dexmedetomidine 2 μg/kg | 70 | 43/27 | 14.5 (8.8-23.2) | 10 (8-12) | Ophthalmic | ASA-II | 45 (64.3%) | NA | 7.3 (5-10.3) | 16 (10-30) | 93 (74-117.5) | NA |
| Zhan [29] 2016 | Intranasal dexmedetomidine 2 μg/kg | 71 | 45/26 | 18 (10-29) | 30.5 (6-32) | Examination | ASA-I | 61 (85.3%) | NA | 7.6-9 | 13 (11-17.5) | 90 (70-105) | NA |
| Zhan [29] 2016 | Oral chloral hydrate 50mg/kg | 50 | 19/31 | 3.9±1.5 | 6.1±1.6 | MRI | I or II | 47 (64%) | NA | 15.3±2.1 | 61.8±12.2 | NA |
| U[24] 2013 | Intranasal dexmedetomidine 1 μg/kg | 107 | 70/37 | 23.0±18.7 | 11.02±4.9 | CT | ASA-I | NA | NA | NA | NA | NA |
| Chen[28] 2019 | Oral chloral hydrate 50mg/kg | 95 | 63/32 | 27.3±16.7 | 11.6±3.3 | MR | ASA-II | 88 (98.9%) | NA | 19.9±6.9 | 21.3±10.9 | 71.8±23.0 | 16 ± 2.66 |
| Zhang[28] 2014 | Intranasal dexmedetomidine 2.5 μg/kg | 92 | 62/30 | 25.3±17.0 | 10.9±3.0 | MR | ASA-I | 83 (89.7%) | NA | 16.2±3.4 | 20.8±6.1 | 50.9±16.7 | 88 ± 3.16 |
| Zhen [18] 2019 | Intranasal dexmedetomidine 2 μg/kg | 33 | 16/17 | 40.8±15.6 | 9±25 | MRI | ASA-II | 28 (84.8%) | NA | 25.7±10.3 | NA | 70 ± 4.38 |
| SH[23] 2016 | Intranasal dexmedetomidine 2 μg/kg | 33 | 17/16 | 43.2±13.2 | 31.9±9.8 | MRI | ASA-I | 31 (93.9%) | NA | 20.4±6.4 | NA | 85 ± 3.05 |
| SN[23] 2016 | Recital administration chloral hydrate 50mg/kg | 26 | / | 24.6±8.16 | 12.15±2.16 | MRI | ASA-II | 26 (96.1%) | NA | 14.0±5.2 | 20.0±5.09 | 65.2±7.72 | NA |
| L1[18] 2019 | Intranasal dexmedetomidine 2 μg/kg | 20 | 15/5 | 42 | 182 | Emergency | NA | NA | 8.9±3.4 | NA | 91.3±22.3 | NA |
| G[18] 2014 | Recital administration chloral hydrate 50–60mg/kg | 20 | 11/9 | 42.2±17.52 | 17.8±4.32 | MRI | ASA-I | 85% | NA | 30.5±2.10 | 27 | NA | NA |
| Zhang[28] 2014 | Intranasal dexmedetomidine 1.5 μg/kg | 20 | 10/10 | 41.5±18.48 | 17 | MRI | ASA-I | 31.4±9.87 | NA | 90% | NA | NA |
| L[18] 2019 | Intranasal dexmedetomidine 1 μg/kg | 35 | NA | 9–96 | NA | Tractional intubation after congenital heart surgery | NA | NA | NA | 19.9±5.8 | 210±3.5 | NA |

**ABR= auditory brainstem response testing, ASA=American Society of Anesthesiologists, CT=computerized tomography, EEG=electroencephalography, MRI=magnetic resonance imaging, TTE=trans/thoracic echocardiogram.**
the success rate of sedation was significantly higher in the Dex group when used for painless and painful sedation procedures (RR = 1.14, 95% CI [1.05, 1.25], I^2 = 79%, P = .003) (R1—Fig. 3).

There was no significant difference between the CH group and the Dex 1, 1.5, 2.5, and 3 μg/kg in the success rate of sedation (RR = 1.01, 95% CI [0.89, 1.15], I^2 = 68%, P = .88) (RR = 1.07, 95% CI [0.98, 1.16], I^2 = 36%, P = .11) (RR = 1.33, 95% CI [0.95, 1.87], I^2 = 81%, P = .10) (RR = 1.11, 95% CI [0.99, 1.25], I^2 = 69%, P = .08).

However, compared with the CH group, the success rate of sedation was significantly higher in the Dex 2 μg/kg group for the sedation procedure (RR = 1.15, 95% CI [1.03, 1.29], I^2 = 80%, P = .02) (R1—Fig. 4).

### 3.4. Number of subjects who required 2 doses

Among the 15 RCTs, 2 studies including 235 children contributed to this analysis. There was no significant difference between the CH and Dex groups in the number of subjects who required 2 doses before the procedure could be completed with or without interruptions (RR = 0.39, 95% CI [0.12, 1.25], I^2 = 0%, P = .11) (R1—Fig. 5).

### 3.5. Sedation latency

Among the 15 RCTs, 10 studies including 1782 children contributed to this analysis. The sedation latency of the CH group was longer than that of the Dex group (MD = -3.54, 95% CI [-5.94, -1.15], I^2 = 95%, P = .004) (R1—Fig. 6).

### 3.6. Sedation duration

Among the 15 RCTs, 8 studies including 1346 children contributed to this analysis. There was no significant difference in the duration of sedation between the CH and Dex groups (MD = -0.20, 95% CI [-0.72, 0.32], I^2 = 43%, P = .45) (R1—Fig. 7).

### 3.7. Sedation recovery time

Among the 15 RCTs, 9 studies including 1526 children contributed to this analysis. The sedation recovery time in the CH group was longer than that in the Dex group (MD = -30.08, 95% CI [-46.77, -13.39], I^2 = 99%, P = .0004) (Fig. 8). A sensitivity analysis for each comparison revealed no robust changes in the significance of this finding (R1—Fig. 8).

### 3.8. Total time from sedative administration to discharge

Among the 15 RCTs, 3 studies including 553 children contributed to this analysis. The total time from sedative administration to discharge in the CH group was longer than that in the Dex group (MD = -12.73, 95% CI [-15.48, -9.97], I^2 = 0%, P < .05) (R1—Fig. 9).

### 3.9. Adverse events

Among the 15 RCTs, 14 studies including 1978 children contributed to this analysis. The CH group had significantly more adverse events than the Dex group (RR = 0.25, 95% CI [0.11, 0.61], I^2 = 89%, P < .002) (R1—Fig. 10).

Compared with Dex, CH was associated with a higher risk of vomiting (RR = 0.07, 95% CI [0.03, 0.17], I^2 = 0%, P < .0001), crying or resisting (RR = 0.22, 95% CI [0.07, 0.71], I^2 = 60%, P = .01), and cough (RR = 0.15, 95% CI [0.05, 0.44], I^2 = 0%, P = .0006) (R1—Fig. 11).

There was no significant differences in the risks of hypotension (RR = 1.34, 95% CI [0.59, 3.03], I^2 = 0%, P = .48), supplemental oxygen (RR = 0.47, 95% CI [0.08, 2.78], I^2 = 0%, P = .41), or respiratory events (RR = 0.29, 95% CI [0.06, 1.51], I^2 = 0%, P = .14) between the CH and Dex groups (Fig. 11).

Compared with CH, Dex was associated with a higher risk of bradycardia (RR = 4.08, 95% CI [1.63, 10.21], I^2 = 0%, P = .003) in 8 studies including a total of 925 patients (R1—Figure 11).
Figure 3. The success rate of sedation between the chloral hydrate group and dexmedetomidine group.

| Study or Subgroup | dexmedetomidine group | choral hydrate group | Risk Ratio | M-H Random 95% CI | M-H Random 95% CI |
|-------------------|-----------------------|----------------------|-----------|--------------------|--------------------|
|                   | Events | Total | Weight |                      |                    |
| Cao 2017          | 61     | 71   | 45     | 70 1.7% | 1.34 [1.10, 1.63]  |
| Chen 2019         | 59     | 66   | 15     | 34 3.8%  | 2.03 [1.38, 2.98]  |
| Hakim Gurus, MD 2014 | 74   | 84   | 28     | 36 8.0%  | 1.13 [0.94, 1.37]  |
| Huang 2016        | 174    | 183  | 58     | 60 12.0% | 0.98 [0.93, 1.04]  |
| Jason Reynolds 2016 | 39   | 44   | 27     | 41 6.5%  | 1.35 [1.01, 1.82]  |
| Jeff Miller 2016  | 98     | 100  | 48     | 50 11.9% | 1.02 [0.96, 1.09]  |
| Li 2013           | 419    | 494  | 83     | 107 10.7%| 1.06 [0.98, 1.15]  |
| Li 2019           | 34     | 40   | 16     | 20 6.2%  | 1.06 [0.92, 1.22]  |
| Q. 2014           | 20     | 20   | 17     | 20 7.7%  | 1.17 [0.96, 1.43]  |
| V. M. Yuen 2017   | 64     | 88   | 83     | 108 8.8% | 0.97 [0.82, 1.15]  |
| Zeng 2016         | 25     | 26   | 20     | 26 7.1%  | 1.25 [1.00, 1.56]  |
| Zhang 2016        | 98     | 100  | 40     | 50 9.5%  | 1.20 [1.04, 1.39]  |
| Total (95% CI)    | 1316   | 1622 | 100.0% | 1.14 [1.05, 1.25] |
| Total events      | 1163   | 478  |        |                      |                    |

Heterogeneity: $I^2 = 52.72$, $d.f. = 11$ ($p < 0.00001$), $I^2 = 79$
Test for overall effect: $Z = 2.96$ ($p = 0.003$)

Figure 4. The proportion of successful sedation at varying doses of dexmedetomidine between chloral hydrate group.
4. Discussion

CH and Dex are used as sedative agents in current clinical diagnostic and therapeutic procedures, including nonpainful examinations, such as magnetic resonance imaging scans and transthoracic echocardiography, and painful procedures, such as dentistry and venous cannulation.

However, CH has been in short supply in the USA since 2013, when its production was discontinued for business reasons. Compounding pharmacies can prepare the drug, but concerns about costs and quality control limit access to this option, leading to a search for alternative sedative regimens.[31] Additionally, the efficacy of CH is limited in children with neurological disorders,[32] and it has repeatedly been shown to have higher failure rates in older children and those weighing >15kg, thus limiting its broad application.[33,34]

Dex is an a2 adrenergic agonist that has sedative and anxiolytic properties and
is known for its analgesic potential owing to its reduction in sympathetic tone. It is colorless, odorless, and does not result in respiratory depression and can provide good sedative and antisympathetic effects through nasal drip and oral administration.[35,36]

The present study was a meta-analysis to evaluate the efficacy and safety of Dex versus CH for sedation in pediatrics. Based on the existing evidence from 15 RCTs, the analysis revealed that the success rate of sedation was significantly higher in the Dex groups than in the CH group. Additionally, comparing the effect of different doses of Dex (1, 1.5, 2, 2.5, and 3 mg/kg) with the effect of CH, only the 2.0 mg/kg dose of Dex had a significantly higher success rate of sedation than CH, which was consistent with the results of Lewis and Bailey.[37] This effect is due to Dex being able to induce sedation by decreasing the release of noradrenaline at the locus coeruleus[38]; the sedation state was similar to that of natural non-REM sleep,[39] with neither paradoxical reactions nor euphoria occurring, thus making children quieter, more communicative and more cooperative when examined at parent–child separation after Dex administration. These are unique properties among the sedative medications in common use (Figs. 12–17).

Our study showed that compared with CH, Dex required a shorter time to achieve adequate sedation and a shorter time to return to normal behavior postdischarge. Also, Dex also has a shorter half-life (2 hours) than CH,[40] which may lead to a shorter time for adequate sedation and faster recovery than CH.[41] Moreover, there was no significant difference in the duration of sedation between the CH and Dex groups. Similarly, the total time from sedative administration to discharge in the CH group was longer than that in the Dex group.

The study evaluated the overall adverse effects between the 2 groups. There were no significant differences in the incidence of hypotension, supplemental oxygen, or respiratory events between the 2 groups. Dex has a reputation of causing hypotension, which is sometimes preceded paradoxically by hypertension. However, the hypotensive effect of Dex can be mitigated by preventing rapid infusion and by not using bolus dosing. High peak plasma levels are responsible for the complex hemodynamic effects of Dex.[42] In all the included studies, the loading dose of Dex was slowly administered via oral or intranasal inhalation. Alternatively, intranasal administration of Dex avoids high peak plasma levels but still results in adequate plasma levels after uptake, as shown by Irola et al.[43] Moreover, the usefulness of intranasal administration for procedural sedation has been demonstrated by Zhang et al.[44] and Nooh et al.[45] Notably, careful dosing, preferably by titration, is the key to procedural sedation. Within the confines of carefully protocolized studies and small, non-intravenous doses, Dex and CH would appear to have similar safety profiles with respect to supplemental oxygen and respiratory events.

However, CH was associated with a higher risk of vomiting, crying or resisting, and cough, consistent with the results of Napoli et al.[4,46,47]; these differences are probably related to the bitter and irritating nature of oral CH. Intranasal Dex was associated with a significantly lower incidence of postoperative nausea and vomiting and nasal irritation than CH. Notably, Dex had a higher risk of bradycardia, consistent with the results of Petroz et al.[48] It has been suggested that this drug should be used with caution in patients with low HR and low blood pressure.[49,50]

Interestingly, we also found that the incidence of adverse events was lower in Dex groups with doses of 1.5, 2, and 2.5 mg/kg than in the CH group. Through analysis of the included studies and a comprehensive consideration of its effectiveness and safety, we could deduce that a dose of 2 mg/kg is the optimum choice for Dex
because higher doses do not necessarily increase the rate of successful sedation but may cause severe bradycardia.

In addition, we used subgroup analysis to investigate the differential effects of the types of administration of Dex and CH on the primary outcomes (the success rate of sedation) and secondary outcomes (sedation latency, sedation duration, sedation recovery time, total time from sedative administration to discharge, and adverse events). The results reveal that there were differences in the success rate of sedation and sedation latency between the intranasal, oral, and intravenous infusion administration methods of Dex compared with the CH group. However, there were no differences in the sedation duration, sedation recovery time, total time from sedative administration to discharge, and adverse events between the intranasal, oral, and
intravenous infusion administration methods of Dex compared with the CH group. In addition, a quality assessment of the studies included in the present meta-analysis was performed. Most of the trials were of high quality, indicating a reliable evidence level of the results. Heterogeneity was identified in the following outcomes: the success rate of sedation ($I^2 = 76\%$), sedation latency ($I^2 = 97\%$), sedation recovery time ($I^2 = 99\%$), and adverse events ($I^2 = 87\%$). Removing the study by Chen [16]
and Huang et al.\textsuperscript{[30]} decreased the heterogeneity of the success rate of sedation ($P<0.0001$, $I^2=47\%$) but revealed no robust changes in significance. Therefore, the pooled results of this meta-analysis are reliable. Moreover, no significant change in heterogeneity emerged when sensitivity analysis was performed on recovery time and sedation latency. It was assumed that the high level of heterogeneity originated from the inconsistency in sedation details and different sample sources; no details about these indexes were available.

We also recognize the limitations of this study. First, only 25\% of the studies (4/16) were performed with blinded participants and personnel. Blinding of the outcome assessment, allocation concealment, and other biases were ambiguous in the majority of trials. Due to only 9 studies being blinded, we performed a sensitivity analysis of the primary outcome (the success rate of sedation), and the results indicated no differences in the success rate of sedation between CH and Dex. Furthermore, before sensitivity analysis, some studies had high levels of heterogeneity, which may have been caused by the quality of the studies, the dose of the treatment and control groups, the sample size, the age of the child, and the type of examination. Third, this study only included the Chinese and English literature, and there might be varying degrees of language bias. Although this systematic review and meta-analysis used mainstream databases, there might still be cases of missed detection. In addition, the high heterogeneity among the studies limits the credibility of the study. This study only reported the efficacy and safety of Dex versus CH for sedation in pediatrics; future studies should investigate the economics of these medications, alternative sedation in pediatrics, and the use of Dex across the entire age spectrum.

Therefore, the above evidence suggests that Dex is an appropriate and effective alternative to CH for sedation in pediatrics.

**Author contributions**

Xianghong Lian conducted the data analysis and wrote the manuscript. Ting Luo, Hongbo Yuan, and Yuan Chen retrieved and screened the literature, as well as extracted data. Yunzhu Lin designed the study and resolved the problems in the research process. All the authors contributed to data analysis, drafted and revised the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

**References**

[1] Sury MR, Arumainathan R, Belhaj AM, et al. The state of UK paediatric anaesthesia: a survey of National Health Service activity. Paediatric Anaesth 2015;25:1085–92.
[2] Hijazi OM, Ahmed AE, Anazi JA. chloral hydrate versus midazolam as sedative agents for diagnostic procedures in children. Saudi Med J 2014;35:123–31.
[3] Kao SC, Adamson SD, Tatman LH, et al. A survey of post-discharge side effects of conscious sedation using chloral hydrate in pediatric CT and MR imaging. Pediatr Radiol 1999;29:28–90.
[4] Greenberg SB, Faerber EN, Aspinall CL. High dose chloral hydrate sedation for children undergoing CT. J Comput Assist Tomogr 1991;15:467–9.
[5] Coskun S, Yuksel H, Onag A. Chloralhydrate in children undergoing echocardiography. Indian J Pediatr 2001;68:319–22.
[6] National Institute for Health and Care Excellence. Sedation in under 19s: Using Sedation for Diagnostic and Therapeutic Procedures. UK; 2010:17–18.
[7] Mace SE, Brown LA, Francis L, et al. Clinical policy: critical issues in the sedation of pediatric patients in the emergency department. J Emerg Nurs 2008;34:13–107.
[8] Li BL, Ni J, Huang JX, et al. Intranasal dexmedetomidine for sedation in children undergoing transhoracic echocardiography study-a prospective observational study. Paediatr Anaesth 2015;25:891–6.
[9] Yuen VM, Li BL, Cheuk DK, et al. A randomised controlled trial of oral chloral hydrate vs. intranasal dexmedetomidine before computerised tomography in children. Anaesthesia 2017;72:1191–5.
[10] Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother 2007;41:245–52.

[11] Hoy SM, Keating GM. Dexmedetomidine: a review of its use for sedation in mechanically ventilated patients in an intensive care setting and for procedural sedation. Drugs 2011;71:1481–501.

[12] Meikitarian Filho E, Robson F, de Carvalho WB, et al. Intranasal dexmedetomidine for sedation for pediatric computed tomography imaging. J Pediatr 2015;166:1313.e1–5.e1.

[13] Reynolds J, Rogers A, Medellin E, et al. A prospective, randomized, double-blind trial of intranasal dexmedetomidine and oral chloral hydrate for sedated auditory brainstem response (ABR) testing. Paediatr Anaesth 2016;26:286–93.

[14] Fong CY, Tay CG, Ong LC, et al. CH as a sedating agent for neurodiagnostic procedures in children. Cochrane Database Syst Rev 2017;11:CD011786.

[15] Chen Z, Lin M, Huang ZY, et al. Efficacy of chloral hydrate oral solution for sedation in pediatrics: a systematic review and meta-analysis. Drug Des Devel Ther 2019;13:2643–53.

[16] Chen R-Q, sedative effects and nursing care of dexmedetomidine nasal drops in children with motor retardation during MRI. Chin J Mod Med 2019;13:129–31.

[17] Zeng Y, Li Z-Y, Gao G-Y, et al. Clinical observation on sedation of chloral hydrate and dexmedetomidine in pediatric MRI. J Pract Med 2019;36:99–102.

[18] Li J. Sedative effect of dexmedetomidine in MRI of children with psychomotor retardation. China Med Innov 2019;16:61.

[19] Sharon EM, Lance AB, Lisa A, et al. Clinical policy: critical issues in the neurodiagnostic procedures in children. Cochrane Database Syst Rev 2019;36:CD0072.

[20] British National Formulary for Children (BNFc) 2010/11. British Royal College of Paediatrics and Child Health, Neonatal and Paediatric Pharmacist Groups; 2010. Available at: www.bnf.org.

[21] Miller J, Xue B, Hossain M, et al. Comparison of dexmedetomidine and chloral hydrate for sedation for pediatric computed tomography. Paediatr Anaesth 2016;26:266–72.

[22] Gums H, Bayram AK, Poyrazoglu HG, et al. Comparison of effects of different dexmedetomidine and chloral hydrate doses used in sedation on electroencephalography in pediatric patients. J Child Neurol 2015;30:983–8.

[23] Gao Q-Z, Lin Y-Q, Xie Z-B, et al. Comparison of sedation by intranasal dexmedetomidine and oral chloral hydrate for pediatric ophthalmic examination. Paediatr Anaesth 2017;27:639–36.

[24] Zhang W-H, Wang Z-X, Song X-R, et al. Comparison of rescue techniques for failed chloral hydrate sedation for magnetic resonance imaging scans-additional chloral hydrate vs intranasal dexmedetomidine. Paediatr Anaesth 2016;26:273–9.

[25] Zhou H-D, Hao B-J, Chen M, et al. Observation on sedative effect of intranasal administration of dexmedetomidine and oral chloral hydrate on MRI in children. Chin Med Innov 2016;13:40–3.

[26] Li B-L, Song X-R, Li Y-Q, et al. Efficacy and safety of intranasal administration of dexmedetomidine and oral chloral hydrate in CT examination of children. J Clin Anesthesiol 2013;29:859–62.

[27] Shi B-Z, Shi X-Z, Yang M-H, et al. Observation on the effect of dexmedetomidine nasal spray for emergency debridement and suture in children. China Contemp Med 2016;23:103–5.

[28] Qi S, Li L-Y, Liang F. Observation on the sedative effect of dexmedetomidine nasal spray in children’s MRI examination. China Mater Child Health Care 2014;29:3832–3.

[29] Zhang L-L, Liu Y-Y, Wang Y-J, et al. Application of dexmedetomidine and chloral hydrate in sedation of children with tracheal intubation removed after congenital heart disease. Jilin Med Sci 2014;33:7828.

[30] Huang Y-H, Tong Y, Xue B, et al. Comparison of sedative effects of dexmedetomidine and chloral hydrate on cardiac color Doppler ultrasound examination. Chin J Extracorp Circ 2016;14:26–9, e34.

[31] Mason KP. Challenges in paediatric procedural sedation: political, economic, and clinical aspects. Br J Anaesth 2014;113(suppl):ii48–62.

[32] Rummm PD, Takao RT, Fox DJ, et al. Efficacy of sedation of children with chloral hydrate. South Med J 1990;83:1040–3.

[33] West SK, Griffiths B, Shariff Y, et al. Utilisation of an outpatient sedation unit in paediatric ophthalmology: safety and effectiveness of chloral hydrate in 1509 sedation episodes. Br J Ophthalmo 2013;97:1437–42.

[34] Lee YJ, Kim do K, Kwak YH, et al. Analysis of the appropriate age and weight for pediatric patient sedation for magnetic resonance imaging. Am J Emerg Med 2012;30:1189–95.

[35] Su F, Nicolson SC, Gastosguay MR, et al. Population pharmacokinetics of dexmedetomidine in infants after open heart surgery. Anesth Analg 2010;110:1383–92.

[36] Potts AL, Anderson BJ, Holford NH, et al. Dexmedetomidine hemodynamics in children after cardiac surgery. Paediatr Anaesth 2010;20:425–33.

[37] Lewis J, Bailey CR. Intranasal dexmedetomidine for sedation in children; a review. J Perioper Pract 2019;30:170–3.

[38] Schemin M, Schwinn DA. The locus coeruleus. Site of hypnotic actions of alpha 2-adrenoceptor agonists? Anesthesiology 1992;76:873–5.

[39] Mason KP, O’Mahony E, Zurakowski D, et al. Effects of dexmedetomidine sedation on the EEG in children. Paediatric Anaesth 2009;19:1175–83.

[40] Vilo S, Rauttainen P, Kaisti K, et al. Pharmacoekinetik of intravenous Dex in children under 11 yr of age. Br J Anaesth 2008;100:697–700.

[41] Mason KP, Lerman J. Review article: dexmedetomidine in children: current knowledge and future applications. Anest Analg 2011;113:1129–42.

[42] Ebert TJ, Hall JE, Barney JA, et al. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382–94.

[43] Irolla T, Vilo S, Manner T, et al. Bioavailabilty of dexmedetomidine after intranasal administration. Eur J Clin Pharmacol 2011;67:825–31.

[44] Zhang X, Bai X, Zhang Q, et al. The safety and efficacy of intranasal dexmedetomidine during electrochemotherapy for facial vascular malformation: a double-blind, randomized clinical trial. J Oral Maxillofac Surg 2013;71:1835–42.

[45] Nooh N, Sheta SA, Abdulah WA, et al. Intranasal atomized dexmedetomidine for sedation during third molar extraction. Int J Oral Maxillofac Surg 2013;42:857–62.

[46] Napoli KL, Inglis CG, Martin GR. Safety and efficacy of chloral hydrate sedation in children undergoing echocardiography: J Pediatr 1996;129:287–91.

[47] Gauillard J, Cheref S, Vacherontrestrmann MN, et al. Chloral hydrate: a hypnotic best forgotten? Encephale 2002;28:200–4.

[48] Petroz GC, Sikich N, James M, et al. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. Anesthesiology 2006;105:1098–110.

[49] Sichrovsky TC, Mittal S, Steinberg JS. Dexmedetomidine sedation leading to refractory cardiogenic shock. Anesth Analg 2008;106:1784–6.

[50] Tobias JD, Gupta P, Naguib A, et al. Dexmedetomidine: applications for the pediatric patient with congenital heart disease. Pediatr Cardiol 2011;32:1075–87.