Efficacy and safety of intranasal dexmedetomidine versus oral chloral hydrate as sedatives for pediatric patients: a systematic review and meta-analysis

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ABSTRACT

This study was designed to review published literature to determine the efficacy and safety of intranasal dexmedetomidine versus oral chloral hydrate (CH) for sedation in pediatric patients based on qualified studies. We searched the PubMed, Cochrane, and Embase databases for qualified studies published before March 2021. For each study, we analyzed the relative risk or weighted mean difference combined with a 95% CI. Fourteen studies including 3749 pediatric patients were included in this meta-analysis. Compared with oral CH, intranasal dexmedetomidine significantly increased the success rate of sedation and decreased the duration and latency of sedation, time of recovery from sedation, and total sedation time. Compared with oral CH, intranasal dexmedetomidine significantly decreased the incidence of adverse events, including vomiting, but increased the incidence of bradycardia. In conclusion, intranasal dexmedetomidine provides better sedation than oral CH for pediatric patients with good safety; however, the incidence of bradycardia is increased.

Significance of this study

What is already known about this subject?

⇒ Chloral hydrate (CH) is one of the most widely used sedatives in pediatric patients. Compared with other sedatives, dexmedetomidine exhibited the least inhibitory effect on respiration. Intranasal administration of dexmedetomidine can effectively avoid the first-pass effect of drugs in the liver.

What are the new findings?

⇒ Intranasal dexmedetomidine has better efficacy than oral CH as sedatives for pediatric patients with good safety, but the incidence of bradycardia is increased.

How might these results change the focus of research or clinical practice?

⇒ In terms of efficacy, compared with oral CH, intranasal dexmedetomidine attains a significantly higher success rate of sedation and shortens the duration and latency of sedation, time of recovery from sedation, and total sedation time. In terms of safety, compared with oral CH, intranasal dexmedetomidine significantly reduces the incidence of adverse events, including vomiting, but the incidence of bradycardia is higher.

INTRODUCTION

Procedural sedation decreases the perception of pain, helps patients tolerate unpleasant or painful procedures, and is usually used during pediatric diagnostic procedures such as auditory brainstem response, electroencephalography (EEG), CT, MRI, and echocardiography.[1–3] The dosage of sedatives can be adjusted according to the depth of sedation. Chloral hydrate (CH) is one of the most widely used sedatives for pediatric patients. Studies have confirmed its efficacy in programmed sedation in children. However, it has poor predictability and long duration of action, which may cause arrhythmias and serious adverse events (AEs) such as respiratory depression and permanent nerve damage.[4] Dexmedetomidine is a highly selective α2 adrenergic receptor agonist with sedative and mild analgesic effects. Dexmedetomidine nasal drops are easy to administer and are widely used in short operations and sedation of children. Dexmedetomidine nasal drops can be used in CT, MRI, EEG, and other examinations in children to provide safe and effective sedation. Compared with other sedatives, dexmedetomidine has the least inhibitory effect on respiration.[4–6] Dexmedetomidine is administered intramuscularly or intravenously according to the drug instructions, but a growing number of studies have demonstrated the safety and efficacy of intranasal administration of dexmedetomidine, which is less invasive than intramuscular or intravenous administration. Intranasal dexmedetomidine has a higher acceptance rate and can reduce the occurrence

of AEs compared with intravenous administration.[7] The nasal mucosa is rich in capillaries, and nasal drops can be absorbed directly into the blood and travel to the site of action, which can prevent drug degradation in the gastrointestinal fluid and the first-pass effect of the liver.[7] The blood concentration of the drug per unit dose is high, and the rate of AEs is low. Compared with intravenous administration, intranasal administration is convenient to operate, avoids intravenous puncture, and attenuates respiratory circulatory inhibition due to a rapid rise to peak drug concentration in the blood.[8–10]

Although studies have reported the effects of intranasal dexmedetomidine versus oral CH for sedation in children, the sample sizes have been small, and the conclusions of these studies are controversial. Based on a review of qualified case–control studies, the aim of the present study was to explore the efficacy and safety of intranasal dexmedetomidine versus oral CH as sedatives for pediatric patients.

MATERIALS AND METHODS

Search strategy

Clinical indexes of the efficacy and safety of intranasal dexmedetomidine versus oral CH as sedatives for pediatric patients were obtained from the included studies. All relevant studies published before March 2021 were reviewed in the databases (Cochrane, PubMed, and Embase). References in the eligible studies were also reviewed. The keywords included dexmedetomidine, DXM, chloral hydrate, CH, infant, child, pediatric, intranasal, and oral administration.

All the above keywords were combined with 'AND' or 'OR'. The literature search was independently performed by two researchers. When there was a disagreement, a third investigator was asked to help reach a consensus.

The search terms included (P, participants) pediatric patients; (I, interventions) pediatric patients in the treatment group received dexmedetomidine, and pediatric patients in the control group received CH; (C/O, comparison/outcome) the comparison of the efficacy and safety outcome; and (S, study design) designed as a case–control study.

Study selection criteria

The inclusion criteria were as follows: (1) the study was designed as a case–control study; (2) the participants were pediatric patients; (3) the participants received intranasal dexmedetomidine or oral CH; and (4) the article was published in English or Chinese.

The exclusion criteria were as follows: (1) duplicate articles or similar results; (2) cohort studies, case analyses, theoretical studies or reviews, guidelines, reports, meta-analyses, or other forms of research or comments; and (3) lack of relevant data.

Two investigators independently reviewed each study to determine whether they met the inclusion and exclusion criteria. When there was a disagreement, a third investigator was asked to help reach a consensus.

Data extraction and quality assessment

The basic characteristics of the included articles and main clinical indices were extracted for analysis. The basic information included author names, publication years, detailed interventions, sample sizes, gender, age, and weight. The main clinical indexes included the success rate of sedation, duration and latency of sedation, time to recovery from duration, total sedation time, AEs, vomiting, crying or resisting, hypotension, bradycardia, and supplemental oxygen.

AEs referred to all unfavorable medical problems that occurred after patients received treatment, which may manifest as diseases with symptoms and signs or abnormal laboratory findings but may not necessarily be treatment related. Two investigators independently extracted the data, and a third investigator was involved when there was a disagreement.

Statistical analysis

STATA V.10.0 (Texas, USA) was used for all data analyses. The X^2 and I^2 tests were used to evaluate the heterogeneity of the included randomized controlled trials (RCTs), and the fixed-effects or random-effects model was selected based on the above results. When the included studies were highly heterogeneous (X^2 $p \leq 0.05$, I^2 $>50\%$), we chose the random-effects model for analysis. When the included RCTs had acceptable heterogeneity (X^2 $p > 0.05$, I^2 $\leq 50\%$), we chose the fixed-effects model for analysis. Means and SDs were used to describe continuous variables and then analyzed using weighted mean deviation (WMD). Categorical variables were expressed as percentages and were analyzed using relative risk (RR). The duration and latency of sedation, time to recovery from sedation, and total sedation time were analyzed using WMD, and other indicators were analyzed using RR.

RESULTS

Overview of the included studies

The search identified 519 articles, and 452 articles were excluded after reviewing the titles and abstracts. Sixty-seven articles were further analyzed, and 53 were excluded based on the inclusion and exclusion criteria. Finally, 14 studies[11–24] with a total of 3749 pediatric participants were included in the meta-analysis. The selection process is presented in figure 1, and the basic information of the included studies is summarized in online supplemental table 1.

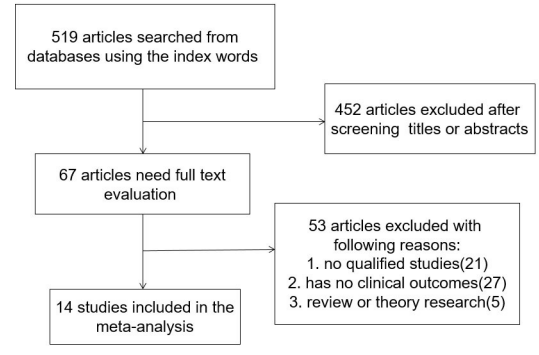

Figure 1 Literature search and selection strategy.

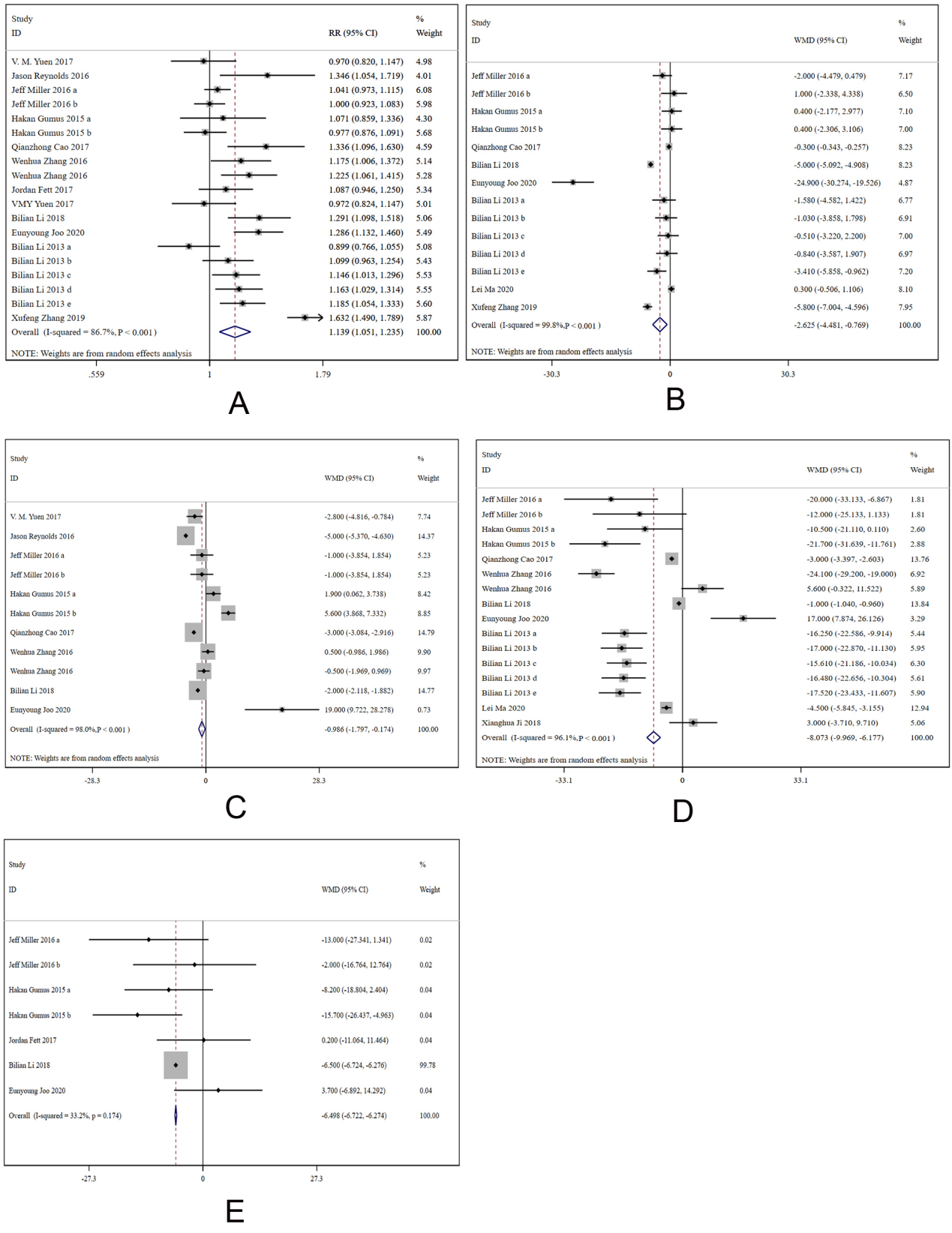

Figure 2 (A) Forest plot for the success rate of sedation; (B) forest plot for sedation duration; (C) forest plot for sedation latency; (D) forest plot for time to recovery from sedation; (E) forest plot for total sedation time. RR, relative risk; WMD, weighted mean difference.

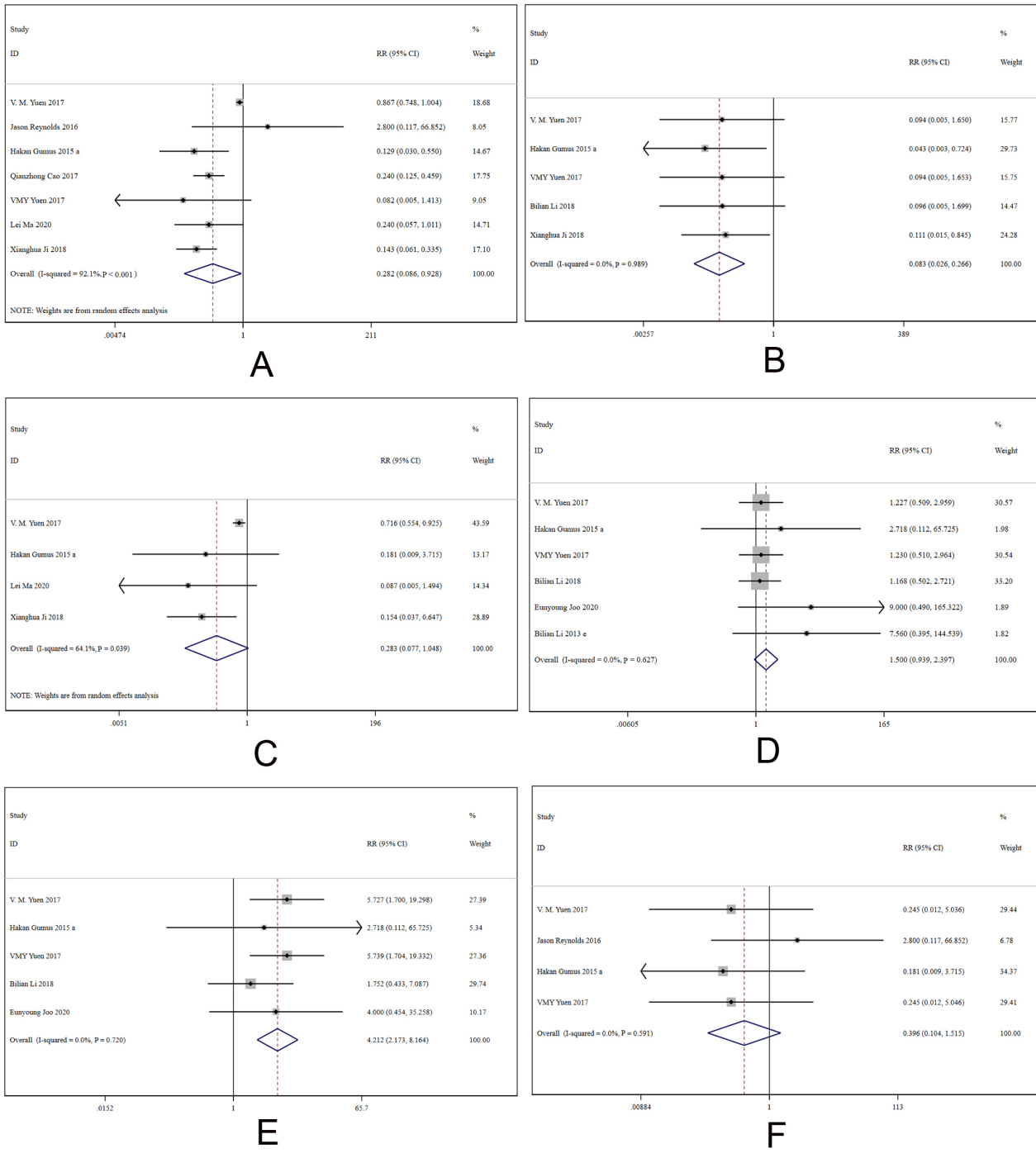

Figure 3 (A) Forest plot for adverse events; (B) forest plot for vomiting; (C) forest plot for crying or resisting; (D) forest plot for hypotension; (E) forest plot for bradycardia; (F) forest plot for supplemental oxygen. RR, relative risk.

Efficacy indexes

Compared with oral CH, intranasal dexmedetomidine significantly increased the success rate of sedation (RR, 1.139; 95% CI, 1.051 to 1.235). Compared with oral CH, intranasal dexmedetomidine significantly reduced the duration of sedation (WMD, −2.625; 95% CI, −4.481 to −0.769), latency (WMD, −0.986; 95% CI, −1.797 to −0.174), time to recovery from sedation (WMD, −8.073; 95% CI, −9.969 to −6.177), and total sedation time (WMD, −6.498; 95% CI, −6.722 to −6.274).

The above results are illustrated in figure 2.

Safety

Compared with oral CH, intranasal dexmedetomidine significantly reduced the incidence of AEs (RR, 0.282; 95% CI, 0.086 to 0.928), including vomiting (RR, 0.083; 95% CI, 0.026 to 0.266). Compared with oral CH, intranasal dexmedetomidine significantly increased the incidence of bradycardia (RR, 4.212; 95% CI, 2.173 to 8.164). There

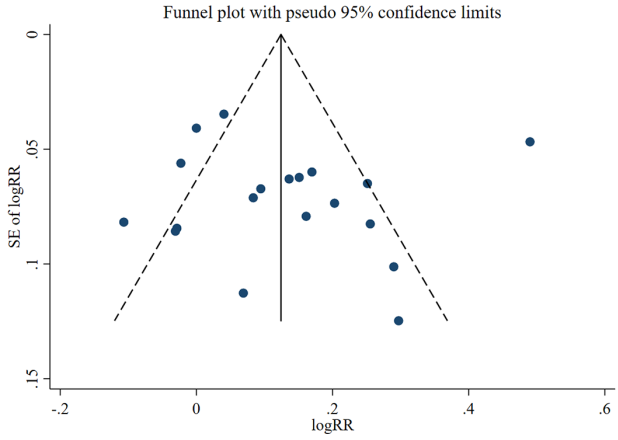

Figure 4 Funnel plot of the included studies. RR, relative risk.

was no significant difference in the incidence of crying or resisting (RR, 0.283; 95% CI, 0.077 to 1.048), hypotension (RR, 1.500; 95% CI, 0.939 to 2.397), and supplemental oxygen (RR, 0.396; 95% CI, 0.104 to 1.515).

The above results are illustrated in figure 3.

Quality and bias assessment

Multiple complementary methods (funnel plot, Begg and Mazumdar rank test, and Egger's test) were used to assess the quality of the study and the risk of bias. The funnel chart is based on the log RR funnel chart of the sedation success rate of all these studies (figure 4) and shows obvious symmetry, indicating low publication bias. In addition, the Begg and Mazumdar rank (Z=0.63, p=0.529) and Egger's tests (p=0.725) were not significant for the risk of bias in the included studies.

DISCUSSION

Children are usually unable to cooperate during prolonged outpatient examinations and treatment, and often require sedation. Currently, commonly used clinical drugs, including CH, midazolam, propofol, and ketamine, which, in addition to their sedative role, are likely to cause respiratory depression and restlessness during the awakening period as well as other AEs. CH has already been widely used for sedation in children and can be administered orally or rectally. It is absorbed in the gastrointestinal tract and can reach peak plasma concentrations within 30–60 min. However, its long-active metabolite trichloroethanol has a half-life of 12–24 hours and is hepatotoxic, so its safety is not good. However, CH can cause respiratory depression in children with delayed sedation, nausea, and vomiting; therefore, its use is limited. In addition, CH, as a γ-aminobutyric acid receptor agonist and an N-methyl-D-aspartate receptor antagonist, may affect brain development, or neuronal apoptosis-induced neurotoxicity.[25–27]

Dexmedetomidine exhibits a characteristic of rapid onset. In adults, dexmedetomidine was administered intranasally at a single dose of 84 μg. Plasma concentrations of dexmedetomidine peaked 38 min after administration, with a half-life of 114 min. Metabolic parameters in children are similar to those in adults. Dexmedetomidine reduces respiratory depression and arousal and has unique advantages as a preoperative medication for children. This drug can be used alone or in combination with other drugs for sedation during pediatric general anesthesia and mechanical ventilation in pediatric intensive care units, reduce the dosage of other sedative hypnotic drugs and opioids, and lower the incidence of AEs due to anesthesia. Because of its mild respiratory depression and certain analgesic effects, it can be safely used for sedation for extubation, postoperative analgesia, and prevention of restlessness in the recovery period. Meanwhile, dexmedetomidine has an anti-sympathetic effect that can reduce the stress response of the body. It acts on α2 adrenergic receptors in the locus ceruleus of the brainstem and induces natural non-rapid eye movement sleep, resulting in sedative and anti-anxiety effects. Intranasal administration of dexmedetomidine resulted in greater bioavailability and fewer AEs. Intranasal dexmedetomidine can be readministered in the event of sedation failure (the dose range is 1–4 g/kg, usually 1 g/kg). The mean onset time was 30–40 min, and the mean recovery time was approximately 90 min. The main AEs of dexmedetomidine are hypotension and bradycardia, but they are mild and do not require treatment.[28 29]

In terms of efficacy, compared with oral CH, intranasal dexmedetomidine has a significantly higher success rate of sedation and shortens the duration and latency of sedation, time to recovery from sedation, and total sedation time. In terms of security, compared with oral CH, intranasal dexmedetomidine significantly lowered the incidence of AEs, including vomiting, but the incidence of bradycardia was higher.

In conclusion, this meta-analysis shows that intranasal dexmedetomidine has better efficacy than oral CH as sedatives for pediatric patients with good safety, but it increases the incidence of bradycardia.

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