Effect of dexmedetomidine on preventing perioperative respiratory adverse events in children: A systematic review and meta-analysis of randomized controlled trials

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Abstract. The most common critical incidents in pediatric anesthesia are perioperative respiratory adverse events (PRAEs). The present meta-analysis aimed to assess the preventive effect of dexmedetomidine on PRAEs in children. Dexmedetomidine is a highly selective α_2-adrenoceptor agonist that provides sedation, anxiolysis and analgesic effects without causing respiratory depression. Dexmedetomidine can diminish airway and circulatory responses during extubation in children. Original randomized controlled trial data were analyzed to study the putative effect of dexmedetomidine on PRAEs. By searched the Cochrane Library, EMBASE and PubMed, a total of ten randomized controlled trials (1,056 patients) was identified. PRAEs included cough, breath holding, laryngospasm, bronchospasm, desaturation (percutaneous oxygen saturation <95%), body movement and pulmonary rales. Compared with placebo, dexmedetomidine resulted in a significant reduction of incidence of cough, breath holding, laryngospasm and emergence agitation. The incidence of PRAEs was significantly reduced in dexmedetomidine compared with active comparators group. Moreover, dexmedetomidine decreased heart rate and increased post-anesthesia care unit stay duration by 11.18 min. The present analysis suggested that dexmedetomidine improved the airway function and decreased risks associated with general anesthesia in children. The present data demonstrated that dexmedetomidine may be a good choice to prevent PRAEs in children.

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Introduction

The most common critical incidents in pediatric anesthesia are perioperative respiratory adverse events (PRAEs) and account for a third of anaesthesia-associated cardiac arrests (1). The incidence of PRAEs is 15% in a general paediatric population, however, the rate of PRAEs is doubled in infants (aged ≤1 year) (2). Although pediatric anesthesia is improving, PRAEs remain the most common cause of severe perioperative morbidity and mortality (3). During general anesthesia in children, PRAEs are most likely to occur during recovery from anesthesia (4). Children have high oxygen demands and low oxygen reserves, making them more susceptible to PRAEs. Avoiding PRAEs during tracheal tube or laryngeal mask removal in pediatric anesthesia is a challenging task (1,5). Dexmedetomidine is a highly selective α_2-adrenoceptor agonist that is increasingly used due to its sedative, analgesic and anti-sympathetic effects (6,7). Dexmedetomidine has been reported to decrease airway and circulatory responses during extubation in children (8). To the best of our knowledge, however, there are insufficient data to demonstrate that dexmedetomidine can reduce the incidence of PRAEs in children undergoing anesthesia. Therefore, the present meta-analysis of randomized controlled trials was conducted to systematically review the preventive effects on the occurrence of PRAEs in pediatric anesthesia.

Materials and methods

Protocol registration. The present study was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines (9)and registered in the PROSPERO database (crd.york.ac.uk/prospero/; ID no. CRD42021268935).

Inclusion and Exclusion Criteria. Inclusion criteria were as follows: i) Prospective randomized controlled trials comparing dexmedetomidine with placebo or other drugs and published in English; ii) participants included in studies were children aged 0-18 years receiving general anesthesia; iii) primary outcome measures were the incidence of PRAEs, including breath holding or apnea, laryngospasm, bronchospasm, arterial oxygen desaturation, cough, fever and pulmonary rales and secondary outcome measures were the incidence of

emergence agitation (EA), recovery time, post-anesthesia care unit (PACU) stay duration and heart rate. Exclusion criteria were as follows: i) Studies on animals; ii) non-randomized clinical trials; iii) participants with other serious respiratory conditions that may influence the prognosis and incidence of PRAEs and iv) studies with insufficient data for analysis.

Search strategy. The databases, including Cochrane Library(cochranelibrary.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and EMBASE(https://www.embase.com/), were searched for studies up to May 2, 2022. The multi-search strategy was employed as follows: i) dexmedetomidine; ii) infants or toddlers or child or pediatric or pediatric or childhood; iii) 'respiratory complications' or 'adverse respiratory events' or 'perioperative respiratory adverse events' or 'airway complications' or 'respiratory depression'; iv) random or trial or placebo or 'randomized controlled trial' and v) i, ii, iii and iv. Relevant references were searched online and included or excluded according to the aforementioned criteria. The titles and abstracts of the studies were evaluated independently by two assessors (YL and JY). For trials that met the inclusion criteria, data extraction from the full text was performed. Full search strategy for all databases are shown in Tables SI and SII and Fig. S1.

Quality assessment and data extraction. A total of two reviewers extracted the data from the relevant studies independently. YL and JY assessed and scored the validity. This was checked by a third researcher (YZ) using the Jadad scoring system (Table SIII) (10) which primarily considers randomization (2 points), double blinding (2 points) and description of drop-outs (1 point). The following information was extracted: First author, published year, intervention, age, sample size, type of procedure and results.

Statistical analysis. Review Manager software 5.4 (Cochrane) was used to perform data analysis. For dichotomous data, number of participants experiencing the events in each group was recorded. Continuous data are reported as the mean ± SD. Incidence of PRAEs was assessed with the odds ratio (OR) and its 95% CI. The heterogeneity between studies was evaluated by I^2 statistic (ranging from 0 to 100%) and χ^2 test. I^2>50% was considered to have significant heterogeneity. A random effect model was used when I^2>50% and subgroup analysis was performed to determine the possible sources of heterogeneity. A fixed effects model (the Mantel-Haenszel method) was used when I^2≤50%. Publication bias was evaluated according to Egger's test using Stata 13.1 software (Stata). P<0.05 was considered to indicate a statistically significant difference.

Results

Included trials and characteristics. Fig. 1 shows study screening and selection strategy. Briefly, comprehensive search of Cochrane Library, EMBASE and PubMed was performed. This produced 246 records of which 82 duplicated records were removed manually. By screening the title, abstract and full-text of the remaining 164 citations, 99 records and 55 records were excluded based on the title/abstract and full text, respectively. Finally, 10 eligible studies with 1,056 patients were included in meta-analysis (11-20) and relevant data were extracted.

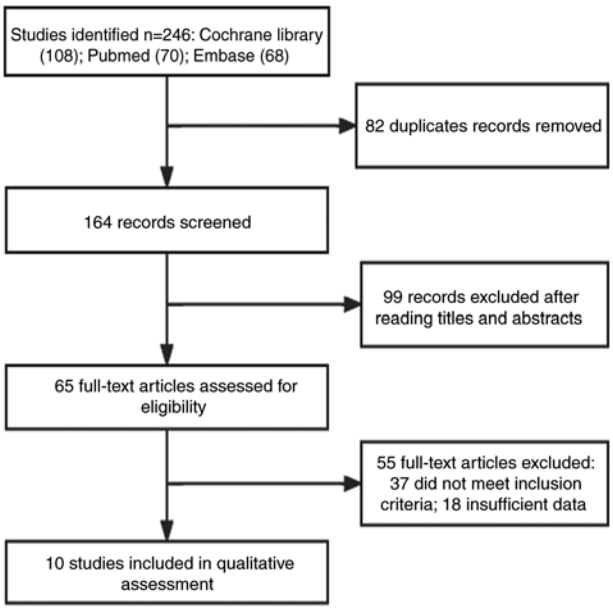

Figure 1. Flow diagram of search strategy for studies included in systematic review and meta-analysis.

Table I summarizes the characteristics of the included studies. A total of 21 participants in three trials dropped out. Participants in three trials (11-13) were children aged 0-5 years-old, while patients in the other seven trials (14-20) were 2-13 years-old. Participants in three trials underwent foreign body removal and four trials performed tonsillectomy. A total of three studies involved minor surface, eye or vitreoretinal surgery. In 10 trials, sevoflurane with or without propofol was used for induction and maintenance of anesthesia. In five trials, intubation was performed and in four trials, laryngeal mask airway (LMA) was used. Patients in one trial had airways managed using face mask ventilation without airway instrumentation. Propofol (3 mg/kg), fentanyl (2 μg/kg) and cisatracurium (0.2 mg/kg) were intravenously injected after 3 min preoxygenation with a mask (100% oxygen; 6 l/min) before suitable LMA or endotracheal tube (ETT) was placed. In two trials (8,15), dexmedetomidine were administered intranasally 40-60 min before induction of anesthesia. In eight trials, a loading dose of dexmedetomidine was given and continuously pumped until the end of surgery.

Risk of bias assessment. The risk of bias graph indicated good methodology (Fig. 2A) as most included studies had a low risk of bias. Only two studies were rated as high risk of bias as they did not state the method of sample size determination (Fig. 2B).

Pooled results of the included studies. Firstly, the impact of dexmedetomidine on PRAEs was analyzed. A total of five trials (655 patients) was included for analysis of the impact of dexmedetomidine on coughing. Incidence of coughing was significantly decreased in the dexmedetomidine compared with the placebo group and heterogeneity was not observed (OR 0.19; 95% CI 0.09-0.37; I^2 =0%; P<0.05; Fig. 3A).

Table I. Characteristics of included studies.

First author, year	n	Patient age (years)	Procedure	Anesthesia method	Intervention and groups	Jadad score	(Refs.)
Bi *et al* 2019	40	0-4	FB removal	Sevoflurane, LMA	DEX (n=20): DEX, 1 μg/kg intranasal; P (n=20): Normal saline 25 min before anesthesia induction.	5	(11)
Cai *et al* 2013	80	0-4	FB removal	Spontaneous ventilation	SV (n=40): DEX (4 μg/kg) i.v. and topical lidocaine (3-5 mg/kg); MJV (n=40): Fentanyl (2 μg/kg) i.v., propofol (3-5 mg/kg) i.v., succinylcholine (1 mg/kg) i.v.	3	(12)
Chen *et al* 2014	77	0-5	FB removal	Sevoflurane, LMA	DEX (n=39): DEX4 μg/kg i.v. then 1-2 μg/kg/h; R (n=38): R 0.05 μg/kg/min i.v. pumping	4	(13)
Di *et al* 2017	75	3-7	Tonsillectomy	Sevoflurane, intubation	DEX1 (n=25): DEX 1 μg/kg i.v.; DEX2 (n=25): DEX 2 μg/kg i.v.; P (n=25): Saline i.v. over 10 min before anesthesia induction.	4	(14)
Hauber *et al* 2015	393	4-10	Tonsillectomy	Propofol, intubation	DEX (n=195): DEX 0.5 μg/ml i.v.; P (n=198): Equivalent volume saline i.v. 5 min before the completion of surgery	4	(15)
He *et al* 2013	87	3-7	Minor surface surgery	Sevoflurane, LMA	DEX1 (n=29): DEX 0.5 μg/kg i.v.; DEX2 (n=32): DEX 1 μg/kg i.v.; P (n=26): Saline infusion for 10 min	4	(16)
Koceroglu *et al* 2019	60	2-9	Tonsillectomy	Sevoflurane, intubation	DEX (n=30): DEX 1 μg/kg i.v.; T (n=30): T 1.5 mg/kg i.v. for 10 min prior to the end of surgery	3	(17)
Qiao *et al* 2017	124	2-5	Eye surgery	Propofol, LMA	DEX (n=42): DEX 2.5 μg/kg intranasal; DK (n=41): Intranasal DEX 2 μg/kg and oral ketamine 3 mg/kg; K (n=41): Oral ketamine 6 mg/kg	5	(18)
Xu *et al* 2012	60	3-7	Vitreoretinal surgery	Sevoflurane, intubation	DEX (n=30): DEX 0.5 μg/kg i.v.; P (n=30): Normal saline i.v. over 10 min	4	(19)

Table I. Continued.

First author, year	n	Patient age (years)	Procedure	Anesthesia method	Intervention and groups	Jadad score	(Refs.)
Zhuang *et al* 2011	60	2-13	Tonsillectomy	Sevoflurane, intubation	DEX (n=30): DEX 1.0 μg/kg i.v.; M (n=30): M 100 μg/kg i.v.	4	(20)

FB, foreign body; LMA, Laryngeal Mask Airway; DEX, Dexmedetomidine; P, Placebo; SV, Spontaneous ventilation; MJV, Manual Jet Ventilation; R, Remifentanil; T, Tramadol; DK, Dexmedetomidine Ketamine; M, Morphine.

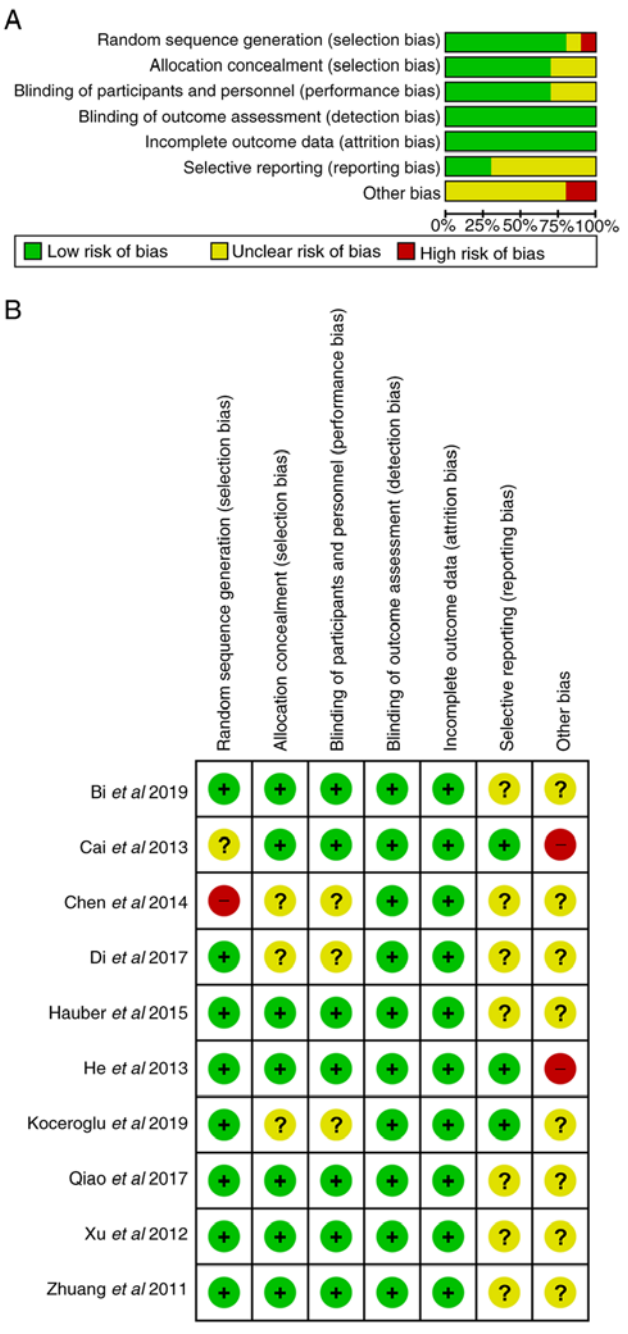

Figure 2. Risk of bias. (A) Risk of bias summary. (B) Risk of bias item for each study.

A total of three trials (187 patients) was included for analysis of the impact of dexmedetomidine on breath holding (Fig. 3B). The risk of breath holding was significantly decreased in the dexmedetomidine group when compared with placebo group and heterogeneity was not observed (OR 0.37; 95% CI 0.17-0.8; I^2=13%; P<0.05). A total of three trials (493 patients) was included for analysis of the impact of dexmedetomidine on laryngospasm. Risk of laryngospasm was significantly reduced in the dexmedetomidine compared with the placebo group and heterogeneity was not observed (OR 0.14; 95% CI 0.04-0.48; I^2=0%; P<0.05; Fig. 3C). A total of two trials (453 patients) was included for analysis of the impact of dexmedetomidine on desaturation (Fig. 3D). Compared with placebo group, no significant change in incidence of desaturation was observed after treatment with dexmedetomidine (OR 0.47; 95% CI 0.15-1.45; I^2=7%; P>0.05).

The effect of dexmedetomidine on EA was analyzed. A total of four trials (584 patients) was included for analysis of the impact of dexmedetomidine on EA (Fig. 4A). Compared with saline, children in the dexmedetomidine group experienced a significant decrease of EA (OR 0.24; 95% CI 0.17-0.35; I^2=12%; P<0.05).

Dexmedetomidine vs. active comparators. There were four studies that used an active comparator as the control group, including fentanyl, ketamine, remifentanil and tramadol. These trials (300 patients) were included for analyzing of the impact of dexmedetomidine on PRAEs (Fig. 4B). The incidence of PRAEs was significantly reduced in the dexmedetomidine group compared with the active comparators group, however, no significant heterogeneity was observed (OR 0.41; 95% CI 0.22-0.76; I^2=11%; P<0.05).

Dexmedetomidine vs. morphine. Only one study (60 patients) compared the effects of dexmedetomidine and morphine on PRAEs (17). The study recorded end-tidal carbon dioxide, Children's Hospital of Eastern Ontario Pain Scale score and supplementary morphine administration. The results showed that respiratory depression of dexmedetomidine was less than that of morphine, but the analgesic effect was poor.

Safety outcomes. PACU stay duration in four trials (621 patients) was evaluated. Compared with control group, dexmedetomidine increased PACU stay duration by 11.18 min

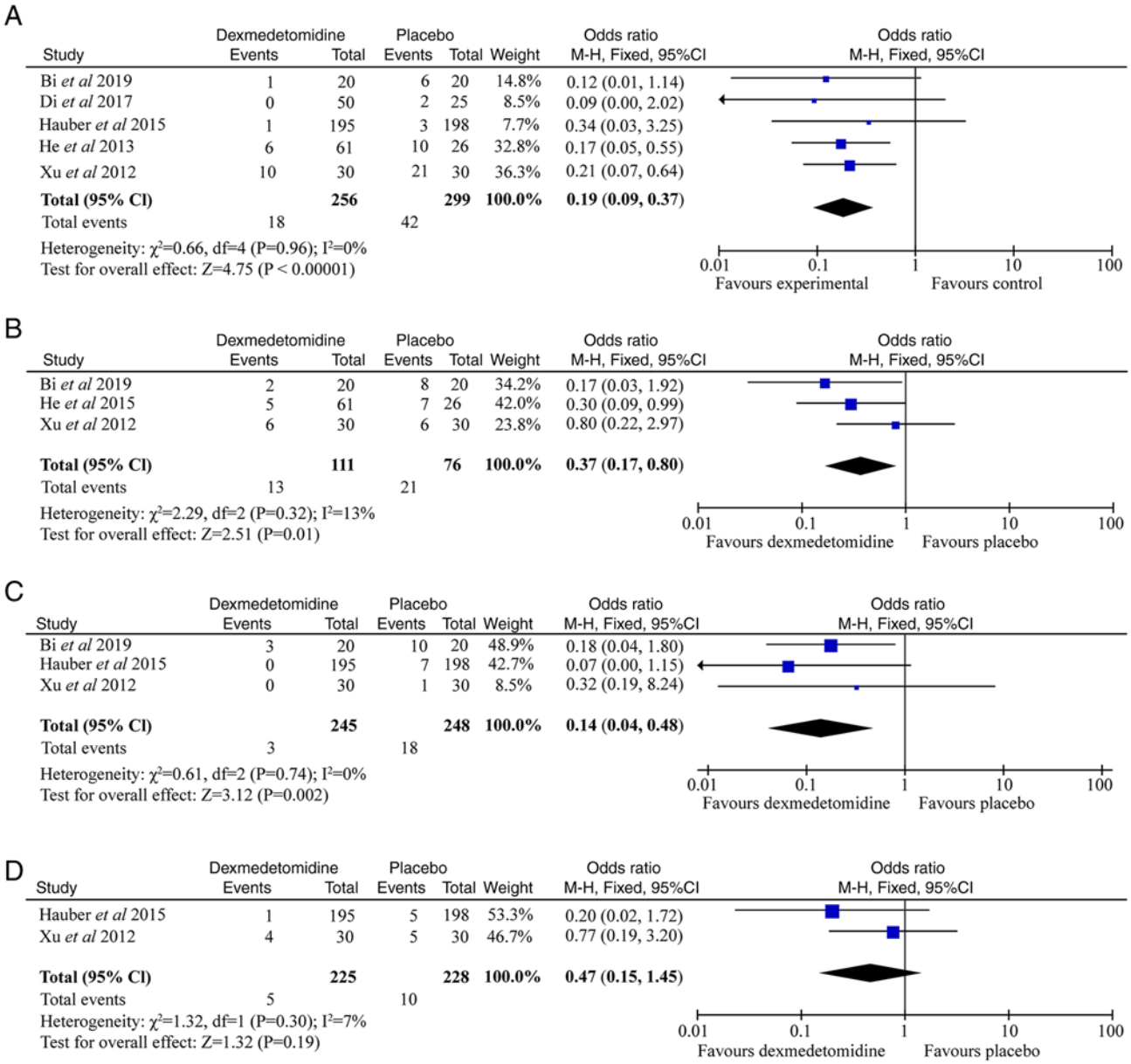

Figure 3. Effect of dexmedetomidine and placebo for children regarding the overall PRAEs. Forest plot showing the effect of dexmedetomidine on the overall (A) coughing, (B) breath holding and (C) laryngospasm and (D) desaturation.

(OR 6.56; 95% CI 4.97-8.16; I^2=99%; P<0.05; Fig. 4C). A total of four trials (596 patients) was included for analyzing the impact of dexmedetomidine on heart rate (Fig. 4D). The heart rate of the dexmedetomidine group was lower than that in the control group (OR 11.07; 95% CI 8.66-13.47; I^2=48%; P<0.05). However, none of the patients required treatment for bradycardia.

Testing for publication bias. Funnel plots of the outcome of coughing, breath holding, laryngospasm, desaturation and heart rate treatment with dexmedetomidine and placebo in the included studies demonstrated symmetry, indicating there was no serious publication bias (Fig. S2A-D, H). Three funnel plots of the outcome of EA, the overall PRAEs and PACU stay duration treatment with dexmedetomidine and placebo or active comparators in the included studies demonstrated there was significant publication bias (Fig. S2E, F, G). However, the number of trials included was <10, thus this conclusion may not be entirely accurate.

Discussion

The present meta-analysis demonstrated the protective effect of dexmedetomidine on PRAEs. Treatment with dexmedetomidine decreased the incidence of PRAEs, including coughing, breath holding and laryngospasm. Dexmedetomidine most potently decreased the incidence of EA and exhibited a significant effect on heart rate and PACU stay duration.

PRAEs remain a major risk in pediatric anesthesia (4). There was a broad range of PRAE rates in the included trials, this may be because young age is associated with higher risk PRAEs (2). The rate of PRAEs is also associated with the type of surgery (21). For example, the incidence of PRAEs is higher in foreign body removal compared with other types of surgery,

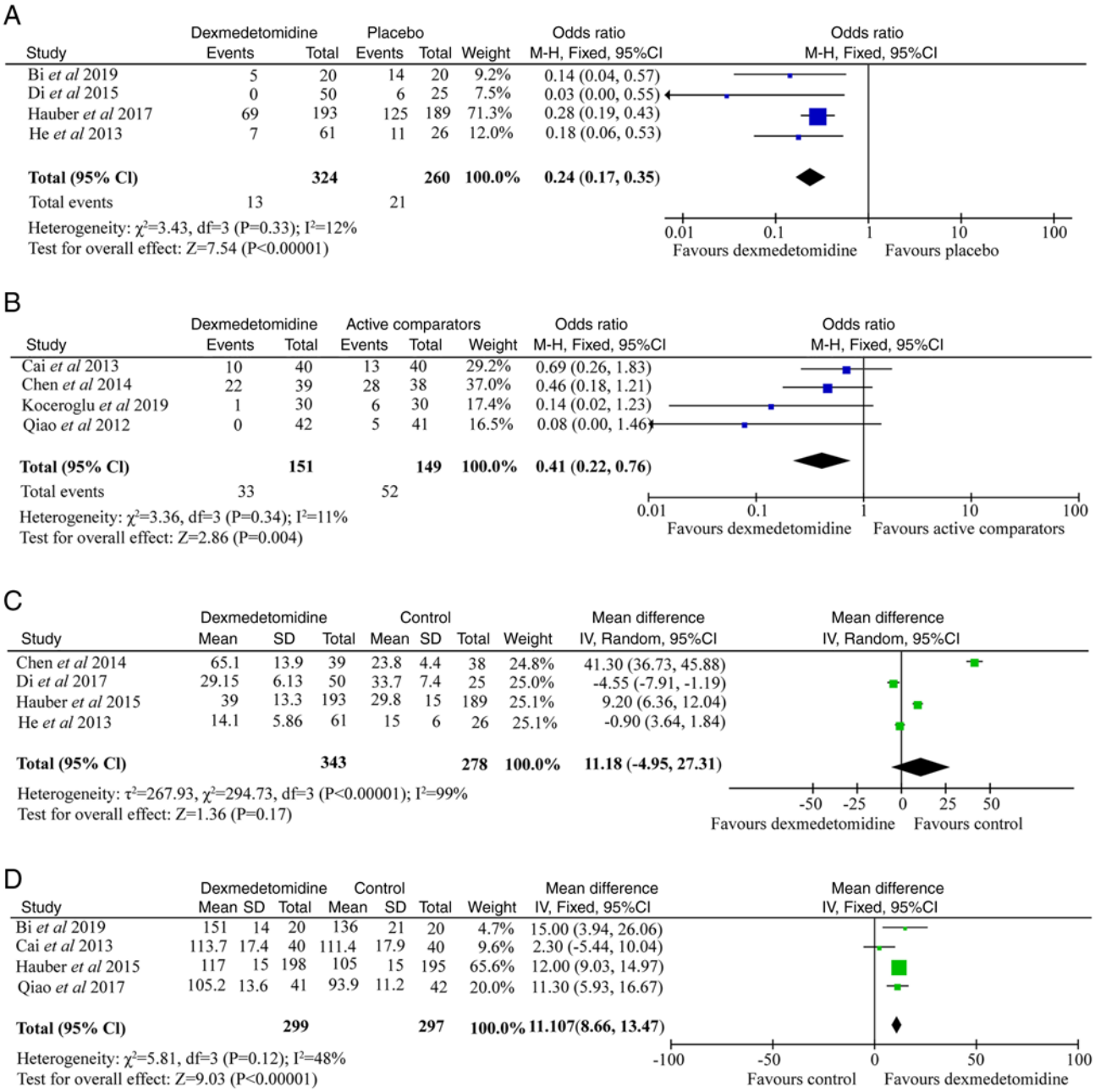

Figure 4. Pooled analysis showing the emergence agitation, the overall PRAEs, PACU stay duration and heart rate. Forest plot showing effect of dexmedetomidine vs. (A) placebo on the overall EA, (B) active comparators on the overall PRAEs and control on (C) overall PACU stay duration and (D) heart rate. EA, emergence agitation; PRAEs, perioperative respiratory adverse events; PACU, post-anesthesia care unit.

such as tonsillectomy (22). The definition of PRAEs, such as, breath holding or apnea, laryngospasm, bronchospasm, arterial oxygen desaturation, cough, fever and pulmonary rales, was chosen based on preliminary assessment of the published literature (2). Coughing may be a precursor of laryngeal spasm (12). Studies have shown that anesthesia for patients with a respiratory infection increases the risk of complications, including laryngeal spasm, bronchospasm, atelectasis and arterial oxygen desaturation (21,23). These changes are typically transient and well-tolerated by most adult patients, but may be deleterious in children (2).

It is widely accepted that decreased PRAEs are associated with airway management or anesthesia (2,24). Numerous studies have shown that the use of LMAs has a lower incidence of PRAEs compared with ETT in children (2,25). However, a few studies (4,26) report the association between dexmedetomidine and airways. Dexmedetomidine possesses sedative, analgesic and anxiolytic effects without causing respiratory depression (6). These properties render dexmedetomidine a potential useful drug for airway protection (27). The present data demonstrated that dexmedetomidine significantly attenuated the incidence of PRAEs and improved the airway function. Compared with the active comparators group, dexmedetomidine significantly decreased the incidence of PRAEs and there was no respiratory depression in children.

However, compared with opioids, dexmedetomidine has a weak analgesic effect (28). Dexmedetomidine cannot replace the analgesic effect of opioids in general anesthesia

and can only be used as an auxiliary drug for general anesthesia (29).

EA is a common complication after inhaled anesthesia in children (30). Although EA is typically self-limited, it can lead to patient injury and increase hospital length of stay and utilization of PACU resources (27). Many anesthetics and anesthesia adjuncts (dexmedetomidine, opioids, midazolam, propofol and clonidine) attenuate the incidence of EA (10). Consistent with a previous study (31), the present meta-analysis supported the use of dexmedetomidine as an effective drug to prevent EA.

Hypotension and bradycardia are the most common hemodynamic adverse effects because of the direct effect of dexmedetomidine on the α_2 adrenoceptor (8). Koceroglu *et al* (17) found that bradycardia may be more common with the use of dexmedetomidine. The heart rate effects of dexmedetomidine are associated with rate of infusion and dose (29). The heart rate-lowering effect of dexmedetomidine is dose-dependent: The higher the dose of dexmedetomidine, the lower the heart rate (32). At the same time, high dose of dexmedetomidine may prolong the post-operative recovery time (5). Consistently, the present analysis showed that dexmedetomidine decreased heart rate and increased PACU stay duration by 11.18 min. However, none of the patients required treatment for bradycardia.

There are limitations in the present meta-analysis. First, the small sample size limited the presented study. Second, routes of administration and dose of dexmedetomidine may be biased by small study effect. Finally, airway management was not analyzed in subgroups. As a result, more well-designed high-quality studies are required to draw definitive conclusions.

In conclusion, comprehensive literature search found a few reports of PRAEs in children and the present data demonstrated that dexmedetomidine reduced the incidence of PRAEs and improved airways. More importantly, dexmedetomidine has fewer side effects compared with opioid analgesics. These results may affect the choice of anesthetic in children. The present analysis demonstrated dexmedetomidine had a beneficial effect on children receiving general anesthesia in regard to preventing PRAEs. Further studies should identify the effect of age, type of surgery and patient characteristics on PRAE occurrence.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JZ and HY confirm the authenticity of all the raw data. HY made substantial contributions to conception and design. JY, YL and YZ designed the meta-analysis. JZ and YB analyzed data. JZ wrote the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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