Original Article

Effect of different administration and dosage of dexmedetomidine in the reduction of emergence agitation in children: a meta-analysis of randomized controlled trials with sequential trial analysis

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Background: Beneficial effects of dexmedetomidine (DEX) against emergence agitation (EA) in children remain controversial. We performed a more comprehensive meta-analysis to evaluate the protective effect of different administration routes, timing, patterns, and doses of DEX on EA in children.

Methods: The randomized controlled trials about DEX preventing EA in children were searched in PubMed, Cochrane Library, Embase, and Web of Sciences up to October 7, 2020. The traditional meta-analysis and subgroup analysis were performed to study the influence of DEX on EA in children. The sequential trial analysis (TSA) further analyzed the pooled results to evaluate meta-analyses' robustness. Grading of recommendation, assessment, development, and evaluation (GRADE) was used to assess evidence quality.

Results: Sixty-seven studies with 5,688 pediatric patients were included. DEX significantly decreased EA in children compared to placebo [RR 0.29, 95% confidence intervals (CI): 0.25–0.34] and midazolam (RR 0.34, 95% CI: 0.25–0.45), with firm evidence from TSA. Notably, using DEX significantly reduced severe EA incidence (RR 0.23, 95% CI: 0.16–0.32), with firm evidence by TSA and high quality of GRADE. Pre-specified subgroup analyses revealed firm and high-quality evidence for a reduction of EA, only if the perineural route administers DEX (RR 0.24, 95% CI: 0.14–0.41), as premedication (RR 0.27, 95% CI: 0.20–0.36), as continuous dosage (RR 0.25, 95% CI: 0.18–0.33), at high dose (RR 0.24, 95% CI: 0.18–0.31). The pooled results also showed that DEX reduced the incidence of PONV compared to placebo (RR 0.43, 95% CI: 0.33–0.55). Evidence for DEX's influence on other secondary outcomes (emergence time, time in PACU, rescue analgesia, hypotension, and bradycardia) is insufficient to draw any conclusion.

Conclusions: Our findings confirm the beneficial effects of DEX on EA, severe EA, and PONV in children. There was firm and high-quality evidence for the efficacy of DEX in preventing EA in children when perineural routes administered DEX, as premedication, as continuous dosage, and at a high dose. The best dose, route, patterns, and timing of DEX and influence on other outcomes call for further studies.

Keywords: Dexmedetomidine (DEX); emergence agitation (EA); children; general anesthesia; meta-analysis; sequential trial analysis (TSA)

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Introduction

Emergence agitation (EA) is a state of perceptual disturbances and psychomotor agitation that occurs most commonly in preschool children during the early post-anesthetic period (1). The negative behavioral symptoms of EA include combative movements, excitability, thrashing, disorientation, and inconsolable crying. Although these events are often short-lived, they increase the risk of self-injury and delayed discharge from the PACU, require added nursing care, and increase medical costs (2). EA incidence varies from 10% to 80% in children, and 42% of pediatric anesthesiologists consider it a troublesome clinical situation (3,4).

Various drugs have been investigated to prevent EA in pediatric patients, including dexmedetomidine (DEX), midazolam, propofol, opioids, ketamine, and ketofol (2). Among these drugs, DEX, a highly selective α2-adrenoreceptor agonist, is the most prevalent drug used in pediatric anesthesia due to its sedative, analgesic, amnesic, anxiolytic, and sympatholytic properties with minimal respiratory depression (5). In recent years, DEX has been put at the forefront of pediatric clinical practice for its potential organ-protective effects and preservation of neurocognitive functions (6). The efficacy of DEX on EA prevention has been reported in many clinical trials, using different administration routes and different dosages. However, the sample size of all these trials was too small to supply a definite conclusion. Some of their results were inconsistent.

Several systematic reviews and meta-analyses assess using DEX to prevent EA in children (7-13). However, the results of the existing meta-analyses were prone to bias due to the limited sample size (7-12), high heterogeneity of included studies (11,13), or including non-randomized case-control studies (13). Moreover, none of these meta-analyses evaluated the evidence quality using either TSA or Grading of recommendation, assessment, development, and evaluation (GRADE) tools, which conclusions would not be dependable. Therefore, from the latest evidence, the present updated meta-analysis of RCTs was conducted to evaluate the effect of different administration and dosage of DEX in reducing EA in children. And the sequential trial analysis (TSA) was performed to determine whether the findings achieved the required information size (IS) to conclude.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tp-21-105).

Methods

Search strategy

Publications on randomized controlled clinical trials (RCTs) for EA in children were searched in biomedical databases including PubMed, Cochrane Library, EMBASE, Web of Sciences up to October 7, 2020. The keywords for searching were ("dexmedetomidine") and ("emergence agitation" or "delirium" or "excitement") and ("child" or "infant" or "pediatric"). There were no language restrictions. The references of related studies were manually searched to identify added eligible studies. The search strategy for each database is detailed in Table S1.

Selection criteria

Two independent reviewers (Xu Zhang and Yan Bai) removed duplicate references, screened the titles and abstracts of the remaining articles, and then examined the articles' full text to identify eligible RCTs. A third reviewer (Xiaogao Jin) was consulted for finalization if there were any differences in opinions between the reviewers. The trials selected for this meta-analysis met the following inclusion/exclusion criteria:

The inclusion criteria included (I) human randomized controlled trials; (II) the children with age ranged from 0 to 18 yrs old; (III) DEX as an intervention was compared with placebo and/or active comparator; (IV) the incidence of EA was addressed in the trial.

The exclusion criteria contained: (I) no validated EA evaluation method was mentioned; (II) the data was questionable or inconsistent; (III) articles published only as an abstract or letter; (IV) duplicated articles or data.

Data extraction

The details of the methodologies and publication data were extracted independently by the two reviewers (Xu Zhang and Min Shi). The following data were extracted, including primary author, publication year, types of surgery, study design, child characteristics, anesthesia used, intervention and control (type, dosage, time, route), the definition of EA, incidence of EA, and severe EA, several periods related to anesthesia recovery, and adverse events, including rescue analgesia, PONV, hypotension, bradycardia. The primary

outcomes of our review were the incidence of EA and the incidence of severe EA.

Risk of bias assessment

Two reviewers (Min Shi and Shaopeng Ming) independently evaluated the quality of included trials using the Cochrane Risk of Bias 2.0 tool for assessing the risk of bias in randomized trials. There are seven items to assess the risk of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias using the high, low, or unclear risk of bias. A consensus resolved all disagreements through discussion among authors, and the corresponding author made the final decision (Yubo Xie).

Statistical analysis

We performed all meta-analyses using Review Manager (version 5.4.1; Cochrane Collaboration, Copenhagen, Denmark) or STATA (version 14.0; Stata Corp, College Station, TX, USA). The pooled effect, risk ratio (RR) were calculated for dichotomous variables, and the mean difference (MD) was calculated for continuous variables. Assessment of heterogeneity was set up using the Chi-square test and I-squared (I^2) test. If the I^2>50% or the P value <0.10, significant heterogeneity of effect sizes was present, and a random-effects model was used instead of a fixed-effect model. All statistical outcomes were reported with 95% confidence intervals (CI). A two-sided P value <0.05 was assumed as statistically significant. Funnel plots were visually inspected, and Egger's linear regression test was performed to assess publication bias if at least ten trials were identified. If the outcomes showed significant publication bias, the trim and fill method was used for added analysis.

The TSA was performed to reduce the risks of random errors, increase the meta-analyses' robustness, and determine whether the current sample size was sufficient (14,15). We calculated the required IS and trial sequential monitoring boundaries (TSMB) that determined whether the evidence in our meta-analysis was reliable and conclusive. If the cumulative Z-curve entered the futility area or crossed TSMB, the anticipated intervention effect showed firm evidence. Otherwise, evidence was rated as absent (16). The risk of a type 1 error was set to 5% with a power of 80%. We set the effect measure as 'Relative Risk' and model as 'Random-effects (DL)' in TSA software for dichotomous outcomes. Relative risk reduction (RRR) was defined as 30%, the incidence in the control arm was calculated from the average incidence in the control group, heterogeneity correction was set as model variance-based; For continuous outcomes, we set the effect measure as "Mean Difference" and the model as "Random Effects (DL)" in TSA software. We calculated the IS from the low risk of bias studies. We used trial sequential analysis software (version 0.9.5.10 beta; http://www.ctu.dk/tsa) to perform this analysis.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence and strength of recommendations. The quality of all primary and secondary outcomes was independently assessed by two reviewers (Xu Zhang and Xiaogao Jin). On the risk of bias (of the included studies), inconsistency (for the I^2 statistic), indirectness (outcome data through direct or indirect comparisons of interest), imprecision (for the TSA), and publication bias (for the egg's test), the quality was classified as high, moderate, low, or very low. GRADEpro GDT software online (version 3.0; https://gdt.gradepro.org/app/) was used to evaluate the quality of evidence.

Results

Search results

We retrieved 1,032 literatures from PubMed (n=158), Cochrane Library (n=252), EMBASE (n=283) and Web of Sciences (n=339). After removing 577 duplicate records and excluding 337 citations by screening their titles and abstracts, 123 full-text articles were examined. We then excluded 55 articles because they were commentary articles, not RCT designs or studies without relevant outcomes. Also, one study (17) was excluded because the result of EA incidence was inconsistent between the text and the figure. Finally, 67 studies were included, which assessed the effectiveness of DEX in reducing the risk of incidence of EA in children. *Figure 1* displays our study screening and selection strategy.

Characteristics of the studies included

Five thousand six hundred eighty-eight children's data were pooled, including 1,616 EA events. The effectiveness of DEX against EA was assessed in 2,920 patients, while 2,768

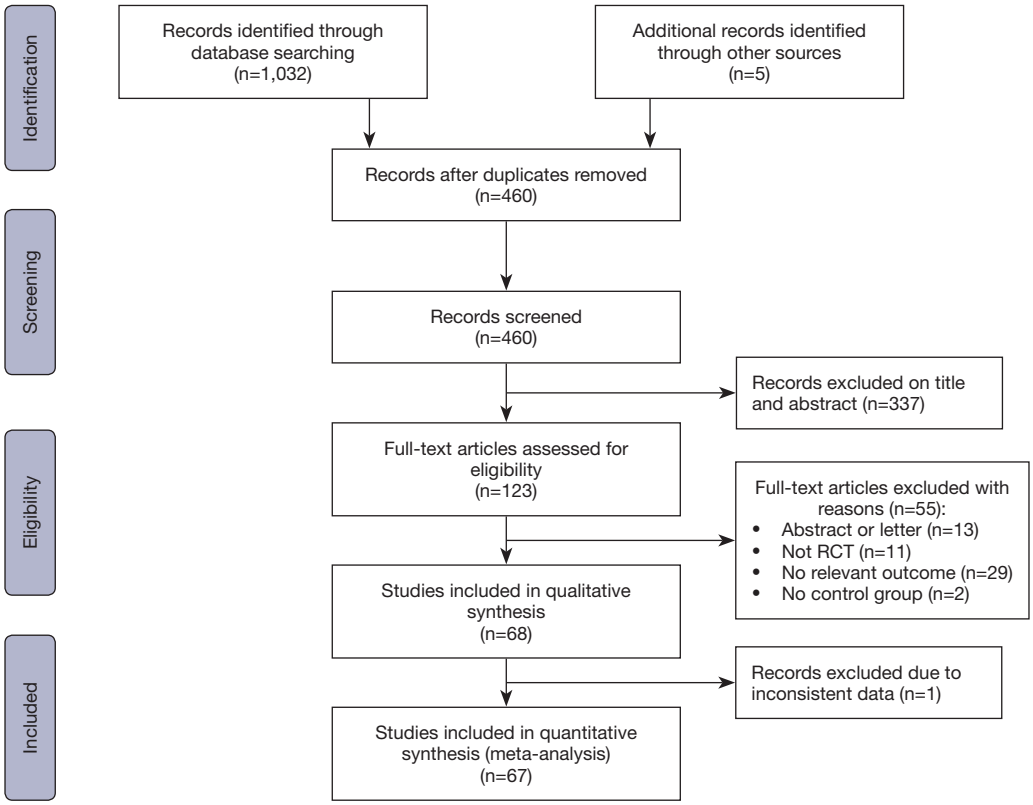

Figure 1 PRISMA flow chart depicting study selection criteria.

patients received various comparators, including placebo, midazolam, fentanyl, propofol, ketamine, ketofol, and clonidine. DEX was administered through different routes, including intravenous (bolus and continuous infusion), intranasal, perineural (caudal or nerve block), and oral. The detailed characteristics of the included studies are presented in *Table 1*.

Risk of bias in included studies

We assessed the risk of bias for each RCT included in the study. Most identified studies were rated to have a low risk of bias. The Cochrane Risk of bias analysis is shown in *Figure 2*.

Meta-analysis of outcomes

Primary outcome 1: EA incidence

DEX vs. placebo

Fifty-five studies with 4,402 patients were included, which assessed the effects of DEX compared to placebo in reducing the risk of EA in children. There was evidence that DEX significantly decreased EA incidence compared to placebo (RR 0.29, 95% CI: 0.25–0.34, P<0.00001) (*Figure 3*). Moderate heterogeneity within the results (I^2=44%, P=0.0003) was shown, which is because of including three studies (42,70,75) according to the Galbraith plot analysis (*Figure 4*). Sensitivity analysis was performed by excluding data from these studies, the heterogeneity reduced to I^2=9% (P=0.29), and the summary estimate was essentially unchanged (RR 0.27, 95% CI: 0.24–0.31, P<0.00001) (*Figure 5*). Egger's tests showed there might be a publication bias (P=0.000). Therefore, trim and fill analysis were performed to identify the bias. It showed no trimming, revealing that the result was reliable (*Figure 6*). TSA's outcome proved that the cumulative Z-curve crossed the TSMB and reached the IS (calculated as 801) (*Figure 7*, *Table 2*). It suggested that the answer to such a clinical question was definitively clear, and the sample size of patients was enough. Further studies are unlikely to change the conclusions. However, we downgraded the GRADE evidence from high to moderate due to publication bias (Appendix 1).

DEX vs. active comparators

Twelve trials (18,19,27,28,35,58,60,65,68,71,78,82)

Table 1 Characteristics of included studies

First author	Year	Age	Surgery	Anesthesia	N	Intervention	Time	Route	Comparator	Assessment methods of EA
Abdelaziz (18)	2016	1–7 y	Elective strabismus surgery	Sevoflurane	98	DEX 1 μg/kg	Premedication	Intranasal	Midazolam/ normal saline	PAED scale ≥10
Abdel-Ghaffar (19)	2018	3–7 y	Bone marrow biopsy	Sevoflurane, propofol	90	DEX 2 μg/kg	Premedication	Inhalation	Midazolam/ ketamine	Three-point EA score ≥2
Abdel-Ghaffar (20)	2019	3–6 y	Tonsillectomy	Sevoflurane	90	DEX 0.5 or 1 μg/kg	Premedication	Oral	Normal saline	Watch a four-point agitation scale ≥3
Abdel-Ma'boud (21)	2014	4–6 y	Inguinal hernia repair	Sevoflurane + caudal block	60	DEX 1 μg/kg, followed by 0.1 μg/kg/h	After induction of anesthesia	Intravenous	Propofol/normal saline	Watch a four-point agitation scale ≥3
Abdel-Rahman (22)	2018	3–8 y	Strabismus surgery	Sevoflurane	90	DEX 0.25 or 0.5 μg/kg	Before the end of surgery	Intravenous	Normal saline	PAED scale ≥10
Ali (23)	2013	2–6 y	Adenotonsillectomy	Sevoflurane, N2O	120	DEX 0.3 μg/kg	Before the end of surgery	Intravenous	Propofol/normal saline	Aonos four-point scale ≥3
Ali (24)	2016	3–6 y	Orthopedic surgeries	Sevoflurane	90	DEX 0.3 μg/kg	Before the end of surgery	Intravenous	Ketofol/normal saline	Aonos four-point scale ≥3
Al-Zaben (25)	2016	1–6 y	Lower abdominal and perineal surgeries	Sevoflurane + caudal block	75	DEX 1 μg/kg	During or after caudal block	Caudal or intravenous	Normal saline	Watcha four-point agitation scale ≥3
Asaad (26)	2011	5–10 y	Inguinal hernia repair, hydrocele, or circumcision	Sevoflurane, N2O	90	DEX 0.15 μg/kg	After induction of anesthesia	Intravenous	Fentanyl/normal saline	Scale of behavior ≥3
Aydogan (27)	2013	12–18 y	Scoliosis surgery	Remifentanil, propofol	32	DEX 0.4 μg/kg/h	Postoperative	Intravenous	Midazolam	CAM-ICU positive
Bhadla (28)	2013	5–12 y	Ophthalmic day-care surgery	Sevoflurane	60	DEX 0.4 μg/kg	Premedication	Intravenous	Midazolam	Level of agitation =1
Bharti (29)	2014	1–8 y	Lower abdominal and perineal surgery	Sevoflurane, N2O+caudal block	78	DEX 0.5 or 1 or 1.5 μg/kg	During caudal block	Caudal	Normal saline	PAED scale ≥10
Bhat (30)	2018	1–8 y	Inguinal hernia	Sevoflurane, N2O, fentanyl + caudal block	90	DEX 0.5 or 1 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Aonos four-point scale ≥3
Bi (31)	2019	0.5–4 y	Tracheobronchial foreign body removal	Sevoflurane	40	DEX 1 μg/kg	Premedication	Intranasal	Normal saline	Five-point Agitation scale ≥4
Chen (32)	2013	3–7 y	Strabismus surgery	Sevoflurane, propofol	78	DEX 1 μg/kg, followed by 1 μg/kg/h	After induction of anesthesia	Intravenous	Ketamine/normal saline	PAED scale ≥10

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Age	Surgery	Anesthesia	N	Intervention	Time	Route	Comparator	Assessment methods of EA
Chen (33)	2018	3–7 y	Inguinal hernia repair surgery	Propofol, sevoflurane + nerve block	100	DEX 0.25 or 0.5 or 0.75 or 1 μg/kg	After induction of anesthesia	Intravenous	Normal saline	PAED scale ≥12
Cho (34)	2015	1–6 y	Ambulatory unilateral orchiopexy	Sevoflurane + caudal block	80	DEX 1 μg/kg	During caudal block	Caudal	Normal saline	Watcha four-point agitation scale ≥3
Cho (35)	2020	2–12 y	Tonsillectomy	Sevoflurane	66	DEX 0.3 μg/kg	Before the end of surgery	Intravenous	Midazolam	Aonos four-point scale ≥3
Di (36)	2014	8/12–3 y	Cleft lip and palate repair	Sevoflurane	60	DEX 0.5 μg/kg	Before the end of surgery	Intravenous	Normal saline	Five-point Agitation scale ≥4
El-Hamid (37)	2017	3–7 y	Tonsillectomy and/or adenoidectomy	Sevoflurane	86	DEX 1 μg/kg	After induction of anesthesia	Intranasal	Normal saline	Agitation scores ≥3
Erdil (38)	2009	2–7 y	Adenoidectomy and/or bilateral myringotomy	Sevoflurane, N2O	90	DEX 0.5 μg/kg	After induction of anesthesia	Intravenous	Fentanyl/normal saline	Five-point Agitation scale ≥4
Govil (39)	2017	2–8 y	Cochlear implant surgery	Sevoflurane, N2O, fentanyl	60	DEX 0.5 μg/kg, followed by 0.5 μg/kg/h	After induction of anesthesia	Intravenous	Normal saline	PAED scale >16
Guler (40)	2005	3–7 y	Adenotonsillectomy	Sevoflurane, N2O	60	DEX 0.5 μg/kg	Before the end of surgery.	Intravenous	Normal saline	Five-point Agitation scale ≥4
Gupta (41)	2013	8–12 y	Spinal corrective surgery	Sevoflurane, N2O, fentanyl	36	DEX 1 μg /kg, followed by 0.5 μg/kg/h	After induction of anesthesia	Intravenous	Normal saline	Agitation Cole score ≥4
Hauber (42)	2015	4–10 y	Tonsillectomy and/or adenoidectomy	Sevoflurane, N2O, propofol	382	DEX 0.5 μg/kg	Before the end of surgery	Intravenous	Normal saline	PAED scale ≥10
He (43)	2013	3–7 y	Minor surface surgery	Sevoflurane+ local block	87	DEX 0.5 or 1 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Agitation scale ≥4
Ibacache (44)	2004	1–10 y	Inguinal hernia repair, orchiopexy, or circumcision	Sevoflurane, N2O + caudal block	90	DEX 0.15 or 0.3 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Four-point behavior scale ≥3
Isik (45)	2006	1.5–10 y	Cranial MRI scanning	Sevoflurane, N2O	42	DEX 1 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Five-point Agitation scale ≥4
Kim (46)	2014	1–5 y	Strabismus surgery	Desflurane, propofol, fentanyl	94	DEX 0.2 μg/kg/h	After induction of anesthesia	Intravenous	Normal saline	PAED scale ≥11

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Age	Surgery	Anesthesia	N	Intervention	Time	Route	Comparator	Assessment methods of EA
Kim (47).	2014	1–5 y	Ambulatory hernioplasty or orchiopexy	Sevoflurane + caudal block	40	DEX 1 μg/kg, followed by 0.1 μg /kg/h	After induction of anesthesia	Intravenous	Normal saline	Watcha four-point agitation scale ≥3
Li (48)	2017	3–8 y	Tonsillectomy	Midazolam, propofol, sufentanyl, Remifentanil	80	DEX 1 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Five-point Agitation scale ≥3
Li (49)	2018	4–6 y	Tonsillectomy	Desflurane, propofol, fentanyl	80	DEX 0.2 μg/kg/h	After induction of anesthesia	Intravenous	Normal saline	Four-point EA score ≥3
Xu (50)	2012	3–7 y	Vitreoretinal surgery	Sevoflurane, remifentanil, propofol	60	DEX 0.5 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Four-point EA score ≥3
Lin (51)	2016	1–8 y	Cataract surgeries	Sevoflurane	90	DEX 1 or 2 μg/kg	Premedication	intranasal	Normal saline	PAED scale ≥10
Lin (52)	2017	3–7 y	Odontotherapy	Propofol, sufentanyl, sevoflurane	80	DEX 1 μg /kg, followed by 0.1-0.4 μg /kg/h	After induction of anesthesia	Intravenous	Normal saline	Aonos four-point scale ≥3
Liu (53)	2015	2–12 y	Achilles-tendon lengthening procedure	Sevoflurane, sufentanyl +caudal block	80	DEX 0.5 μg/kg	5 min before surgery	Intravenous	Normal saline	Aonos four-point scale ≥3
Lundblad (54)	2015	1.5–8 y	Outpatient inguinal hernia repair	Sevoflurane, propofol, fentanyl + nerve block	43	DEX 0.3 μg/kg	During nerve block	IINB	Placebo	PAED scale ≥11
Makkar (55)	2016	2–8 y	Infra-umbilical surgery	Sevoflurane, desflurane + caudal block	100	DEX 0.3 μg/kg	Before the end of surgery	Intravenous	Propofol/normal saline	PAED scale ≥10
Meng (56)	2012	5–14 y	Tonsillectomy	Propofol, sufentanyl, sevoflurane	120	DEX 0.5 μg/kg, followed by 0.2 μg /kg/h or DEX 1 μg /kg, followed by 0.4 μg /kg/h	After induction of anesthesia	Intravenous	Normal saline	Four-point EA score ≥3
Mohamed (57)	2015	18–38 months	Congenital hernia surgery	Sevoflurane+ local block	48	DEX 2 μg/kg	During caudal block	Caudal	Placebo	Aonos four-point scale ≥3
Mountain (58)	2011	1–6 y	Dental restoration and/or extractions	Sevoflurane, N2O, fentanyl	41	DEX 4 μg/kg	Premedication	Oral	Midazolam	PAED scale ≥10
Mukherjee (59)	2015	3–7 y	Elective day care surgery	Sevoflurane	80	DEX 1 μg/kg	Premedication	Intranasal	Clonidine	Aonos four-point scale ≥3

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Age	Surgery	Anesthesia	N	Intervention	Time	Route	Comparator	Assessment methods of EA
Ozcengiz (60)	2011	3–9 y	Esophageal dilatation procedures	Sevoflurane, N2O	100	DEX 2.5 μg/kg	Premedication	Oral	Midazolam/ melatonin/ normal saline	Four-point EA score ≥3
Park (61)	2017	3–12 y	Orthopedic surgery	Sevoflurane, propofol, remifentanil + epidural block	57	DEX 1 μg/kg	Before the end of surgery	Epidural	Fentanyl	PAED scale ≥12
Patel (62)	2010	2–10 y	Tonsillectomy and/or adenoidectomy	Sevoflurane, N2O	122	DEX 2 μg/kg, followed by 0.7 μg/kg/h	After induction of anesthesia	Intravenous	Fentanyl	Five-point Cole scale ≥4
Peng (63)	2015	3–24 months	Cleft palate repair surgery	Sevoflurane, propofol, fentanyl, remifentanyl	40	DEX 0.8 μg/kg/h	After induction of anesthesia	Intravenous	Normal saline	Five-point Agitation scale ≥4
Pestieau (64)	2011	0.5–6 y	Bilateral myringotomy	Sevoflurane, N2O	101	DEX 1 or 2 μg/kg	After induction of anesthesia	Intranasal	Fentanyl/normal saline	Watcha four-point agitation scale ≥2
Prabhu (65)	2017	1–10 y	Elective surgeries of <2 h of the expected duration	Sevoflurane, N2O, fentanyl	90	DEX 4 μg/kg	Premedication	Oral	Midazolam	Aonos four-point scale ≥3
Prasad (66)	2017	3–10 y	Oropharyngeal and urological procedures	Thiopentone, fentanyl, sevoflurane	75	DEX 0.3 μg/kg	Before the end of surgery	Intravenous	Ketofol/normal saline	PAED scale ≥10
Saadawy (67)	2009	1–6 y	Unilateral inguinal hernia/orchidopexy	Sevoflurane, N2O, propofol	60	DEX 1 μg/kg	During caudal block	Caudal	Placebo	Four-point behavior scale ≥3
Sajid (68)	2019	1–6 y	Elective herniotomy	Thiopentone sodium, isoflurane, N2O, fentanyl+caudal block	80	DEX 4 μg/kg	Premedication	Oral	Midazolam	PAED scale ≥10
Sato (69)	2010	1–9 y	Ambulatory surgery	Sevoflurane	81	DEX 0.3 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Aonos four-point scale ≥3
Sharma (70)	2019	5–10 y	Adenotonsillectomy	Isoflurane, N2O, propofol, fentanyl	60	DEX 1 μg/kg	Before induction of anesthesia	Intravenous	Normal saline	PAED scale ≥12
Sheta (71)	2014	3–6 y	Complete dental rehabilitation	Sevoflurane, N2O, fentanyl	72	DEX 1 μg/kg	Premedication	Intranasal	Midazolam	Four-point EA score ≥3
Shi (72)	2019	2–7 y	Tonsillectomy and/or adenoidectomy	Sevoflurane, remifentanil, propofol, fentanyl	90	DEX 0.5 μg/kg	After induction of anesthesia	Intravenous	Normal saline	PAED scale ≥10

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Age	Surgery	Anesthesia	N	Intervention	Time	Route	Comparator	Assessment methods of EA
Shukry (73)	2005	1–10 y	Elective outpatient surgical procedures	Sevoflurane	46	DEX 0.2 μg /kg/h	After induction of anesthesia	Intravenous	Normal saline	Watcha four-point agitation scale ≥3
Soliman (74)	2015	4–14 y	Adenotonsillectomy	Sevoflurane, propofol, fentanyl	150	DEX 0.5 μg/kg, followed by 0.1–0.3 μg /kg/h	After induction of anesthesia	Intravenous	Placebo	PAED scale ≥16
Song (75)	2016	2–6 y	Elective strabismus surgery	Sevoflurane, N2, desflurane	103	DEX 0.25 or 0.5 or 1 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Four-point agitation scale ≥3
Sun (76)	2017	1–5 y	Laparoscopic Hernia Repair	Sevoflurane, midazolam, fentanyl, propofol	97	DEX 0.25 or 0.5 or 1 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Five-point Agitation scale ≥3
Tsiotou (77)	2018	3–14 y	Tonsillectomy and/or adenoidectomy	Propofol, fentanyl, remifentanil	60	DEX 1 μg/kg	After induction of anesthesia	Intravenous	Normal saline	Watcha four-point agitation scale ≥3
Wang (78)	2020	3–6 y	Full-mouth dental rehabilitation	Sevoflurane, propofol, sufentanyl, remifentanil	60	DEX 2 μg/kg	Premedication	Intranasal	Midazolam	PAED scale ≥10
Xiao (79)	2015	3–11 y	Abdominal surgery	Sevoflurane	140	DEX 0.4 or 0.7 or 1 μg/kg	Before induction of anesthesia	Intravenous	Normal saline	PAED scale ≥10
Yao (80)	2015	3–7 y	Unilateral strabismus surgery	Sevoflurane, N2O, propofol	89	DEX 1 or 2 μg/kg	Premedication	Intranasal	Normal saline	PAED scale ≥10
Yao (81)	2018	2–5 y	Unilateral inguinal hernia repair	Sevoflurane, propofol + caudal block	90	DEX 1 μg/kg	During caudal block	Caudal or Intravenous	Normal saline	PAED scale ≥12
Yao (82)	2020	2–6 y	Unilateral strabismus surgery	Sevoflurane, N2O, propofol, sufentanil	153	DEX 2 μg/kg	Premedication	Intranasal	Midazolam/ normal saline	PAED scale ≥10
Ye (83)	2019	2–7 y	Vitreoretinal surgery	Propofol, remifentanyl, fentanyl	40	DEX 1 μg/kg	During retrobulbar block	Retrobulbar block	Placebo	PAED scale ≥12
Zhang (84)	2020	0–16 y	Elective interventional cardiac catheterization	Midazolam, fentanyl, propofol, sevoflurane	134	DEX 1.5 μg/kg	Premedication	Intranasal	Normal saline	Aonos four-point scale ≥3

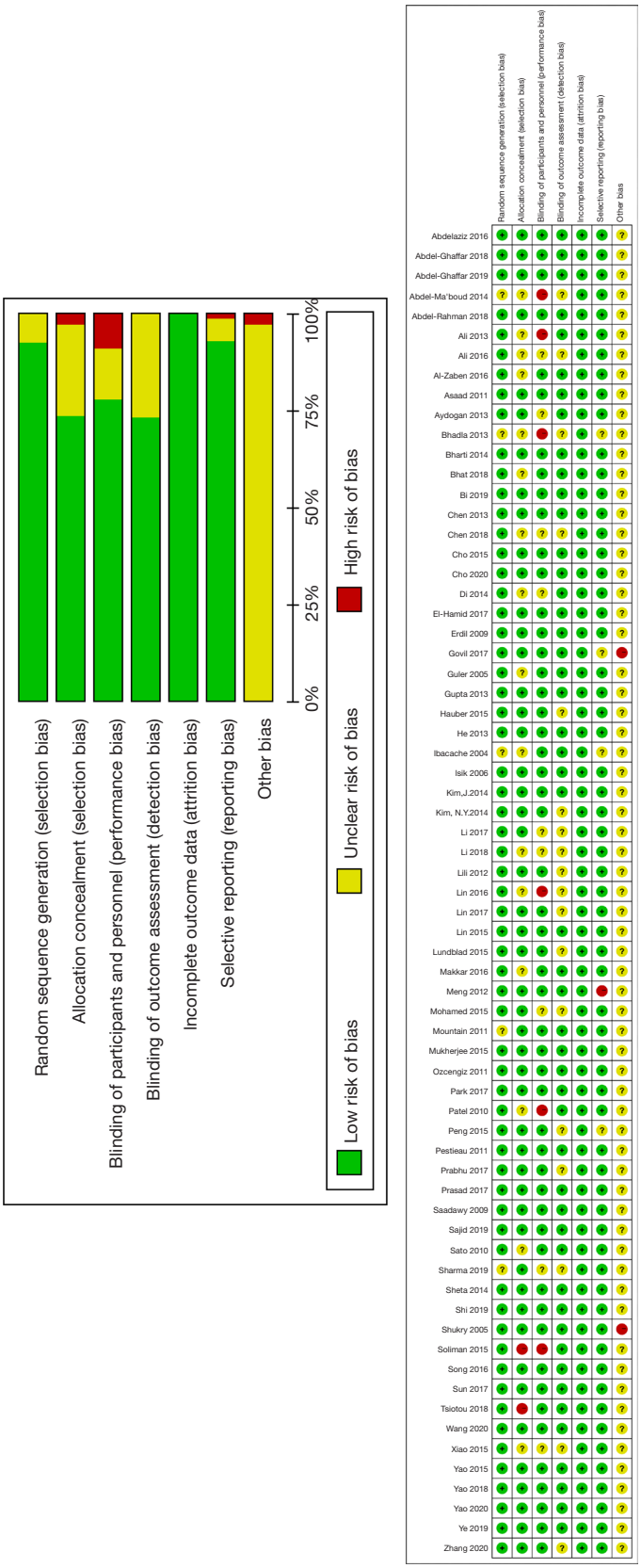

Figure 2 Summary of risk of bias assessment.

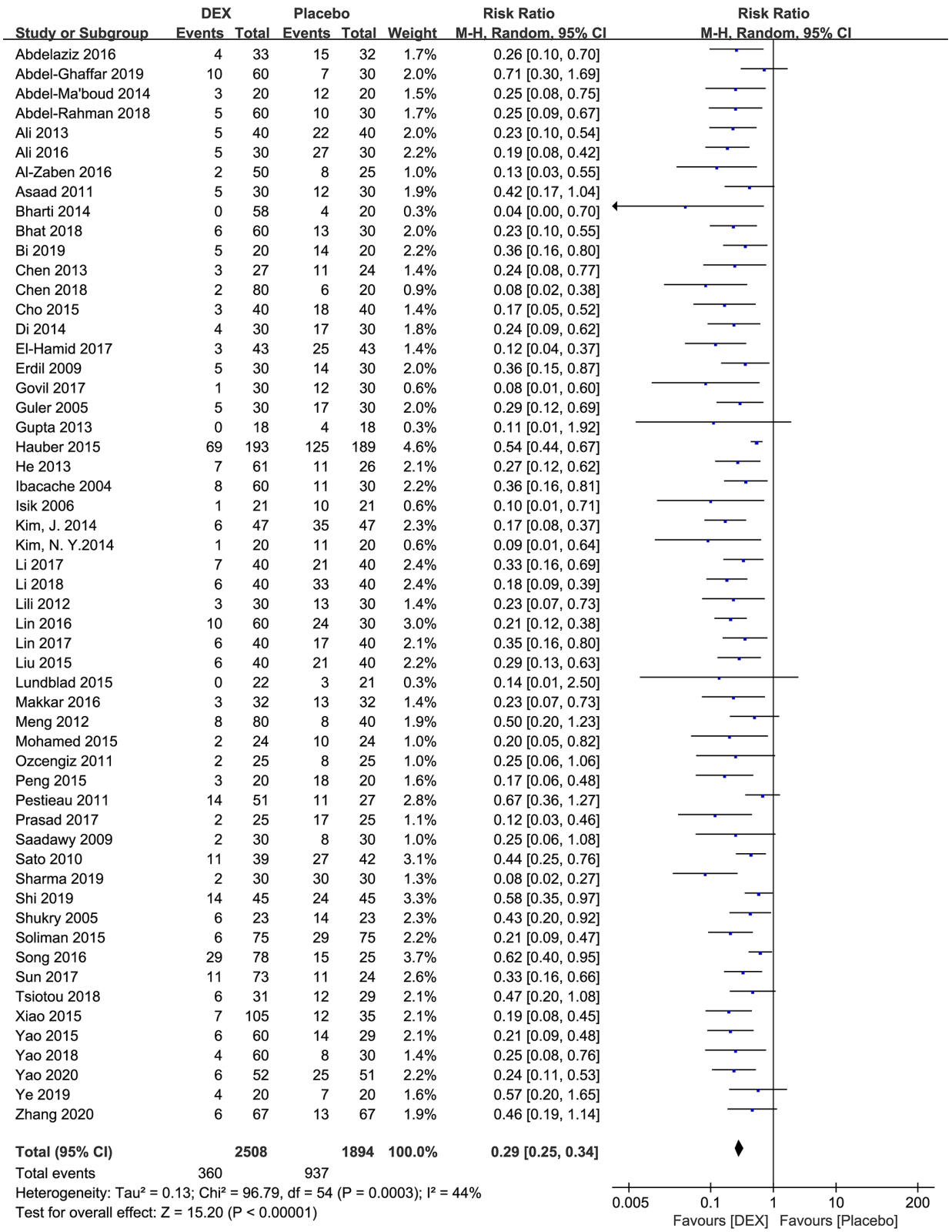

Figure 3 Forest plot for EA incidence: DEX *vs.* placebo. EA, emergence agitation; DEX, dexmedetomidine.

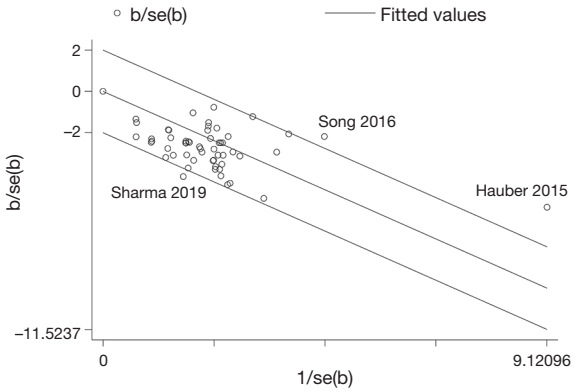

Figure 4 Galbraith plot analysis indicated three studies were the potential source of heterogeneity.

compared the effects of DEX and midazolam on preventing EA. Three hundred ninety-three patients received DEX, and 386 patients received midazolam. The pooled results showed that EA incidence was lower in the DEX group than in the midazolam group (RR 0.34, 95% CI: 0.25–0.45, P<0.00001, I^2=24%) (*Figure 8A*). Egger's tests did not suggest publication bias (P=0.886). Although cumulative Z-curves did not reach the IS, TSA's results showed the curves crossed both the conventional boundary and TSMB (*Figure 8B*, *Table 2*). It suggested that the level of evidence about the DEX's superiority over midazolam in reducing EA incidence was sufficient. And the GRADE-rated evaluation showed the high quality of evidence (Appendix 1).

Five studies (26,38,61,62,64) compared DEX and fentanyl, three studies (21,23,55) compared DEX and propofol, two studies compared DEX and ketamine (19,32) or ketofol (24,66), respectively, showed no significant differences between them in EA incidence (P>0.05) (*Figure 9*). TSA results showed that Z-curves did not cross any of the boundaries (*Table 2*), and further evidence with large sample size is needed. Only one article (59) compared DEX and clonidine and reported that intranasal DEX was more effective than clonidine in decreasing EA incidence and severity, so we could not perform a meta-analysis for trials in the group of clonidine.

Primary outcome 2: severe EA incidence

Eleven studies (18,23,32,39,46,51,53,55,72,74,75) with 927 patients evaluated severe EA incidence of DEX compared to placebo. A score of 4 was defined to severe EA in the two studies (46,75) that used a 4-point EA scale, while a score of ≥15 was used to define severe EA in the nine studies (18,23,32,39,51,53,55,72,74) that used the PAED scale. The pooled results revealed that DEX significantly reduced severe EA incidence (RR 0.23, 95% CI: 0.16–0.32, P<0.00001) (*Figure 10A*). No heterogeneity was found for severe EA incidence in the eleven studies (I^2=0%, P=0.97). Egg's test (P=0.171) showed that publication bias was not found in the analysis. The TSA proved the Z-curves crossed the conventional boundary, TSMB, and reached IS (calculated as 657). TSA of pooled meta-analysis had firm evidence for the anticipated intervention effect (*Figure 10B*, *Table 2*). GRADE evidence for severe EA incidence within all included studies was strong (Appendix 1).

Subgroup analysis

To further investigate the effects of DEX on EA incidence, we conducted subgroup analyses from four perspectives base on priori hypothesis: different administration routes (intravenous, intranasal, oral, and perineural), different administration time (premedication, after induction of anesthesia, before the end of surgery), different administration patterns (bolus dosage, continuous dosage) and different dose [low dose (<0.5 μg/kg), moderate dose (≥0.5, <1 μg/kg), and high dose (≥1 μg/kg)]. The subgroup analysis results are shown in *Table 3*.

Different administration routes

Our study suggested that DEX effectively decreased the incidence of EA when administered through intravenous (RR 0.29, 95% CI: 0.24–0.35, P<0.00001, I^2=47%), intranasal (RR 0.29, 95% CI: 0.20–0.43, P<0.00001, I^2=45%) and perineural route (RR 0.24; 95% CI: 0.14–0.41, P<0.00001, I^2=0%). However, there was no significant difference when DEX administered orally (RR 0.50; 95% CI: 0.18–1.34, P=0.17, I^2=35%) (Figure S1, *Table 3*). TSA revealed firm evidence for the intravenous, intranasal, and perineural subgroup (*Table 2*). GRADE for intravenous, intranasal, and oral subgroups showed the moderate quality of evidence due to publication bias, inconsistency, imprecision, respectively. It should be noted the results for EA incidence were more robust with high GRADE evidence when DEX was administered through the perineural route (Appendix 1).

Different administration timing

Added subgroup analyses were performed for different administration timing. The pooled results showed that using DEX decreases EA incidence regardless of the

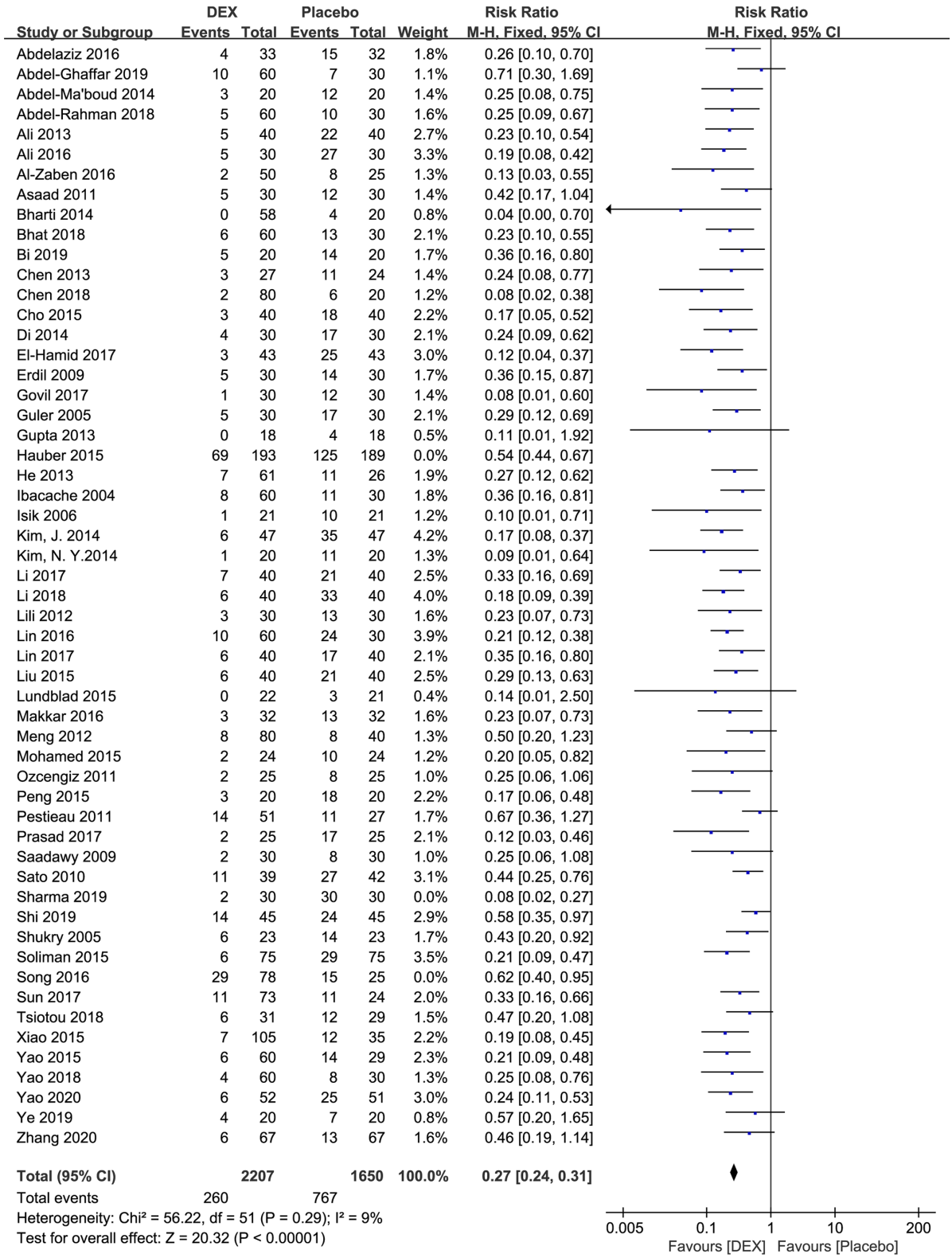

Figure 5 Forest plot for EA incidence after sensitivity analysis. EA, emergence agitation.

timing when administered preoperatively (RR 0.27, 95% CI: 0.20–0.36, P<0.00001, I^2=20%), after induction of anesthesia (RR 0.30, 95% CI: 0.25–0.37, P<0.00001, I^2=35%), and before the end of surgery (RR 0.26, 95% CI: 0.16–0.43, P<0.00001, I^2=66%) (Figure S2, *Table 3*). TSA showed Z-curves crossed TSMB and reached the IS for premedication and 'after induction of anesthesia' subgroup; needed IS was not reached in 'before the end of surgery' subgroup Z-curve crossed TSMB. Therefore, TSA revealed firm evidence for each subgroup (*Table 2*). The GRADE-rated evaluation showed the moderate and low quality of evidence for after-induction and before-the-end-of-surgery administration, respectively. However, the GRADE evidence for premedication was of high quality (Appendix 1).

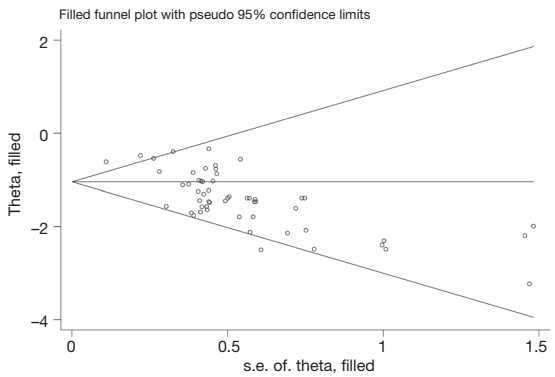

Figure 6 Filled funnel plots for publication bias test of EA incidence. EA, emergence agitation.

Different administration patterns

Further subgroup analysis was performed according to the DEX administration patterns. Compared with placebo, DEX administered as bolus dosage (RR 0.30, 95% CI: 0.25–0.36, P<0.00001, I^2=46%) or as continuous dosage (RR 0.25, 95% CI: 0.18–0.33, P<0.00001, I^2=0%) significantly reduced EA incidence (Figure S3, *Table 3*). TSA showed Z-curves reached the IS and crossed TSMB for both patterns (*Table 2*). GRADE evidence for bolus dosage subgroup showed low due to inconsistency and publication bias (Egger's tests P=0.000). However, GRADE for the continuous dosage subgroup had high-quality evidence, showing that the beneficial effects of continuous DEX on EA incidence were more reliable (Appendix 1).

Different administration dose

To further investigate the effect of DEX on EA incidence, we perform additional subgroup analysis according to the different DEX dose for intravenous administration.

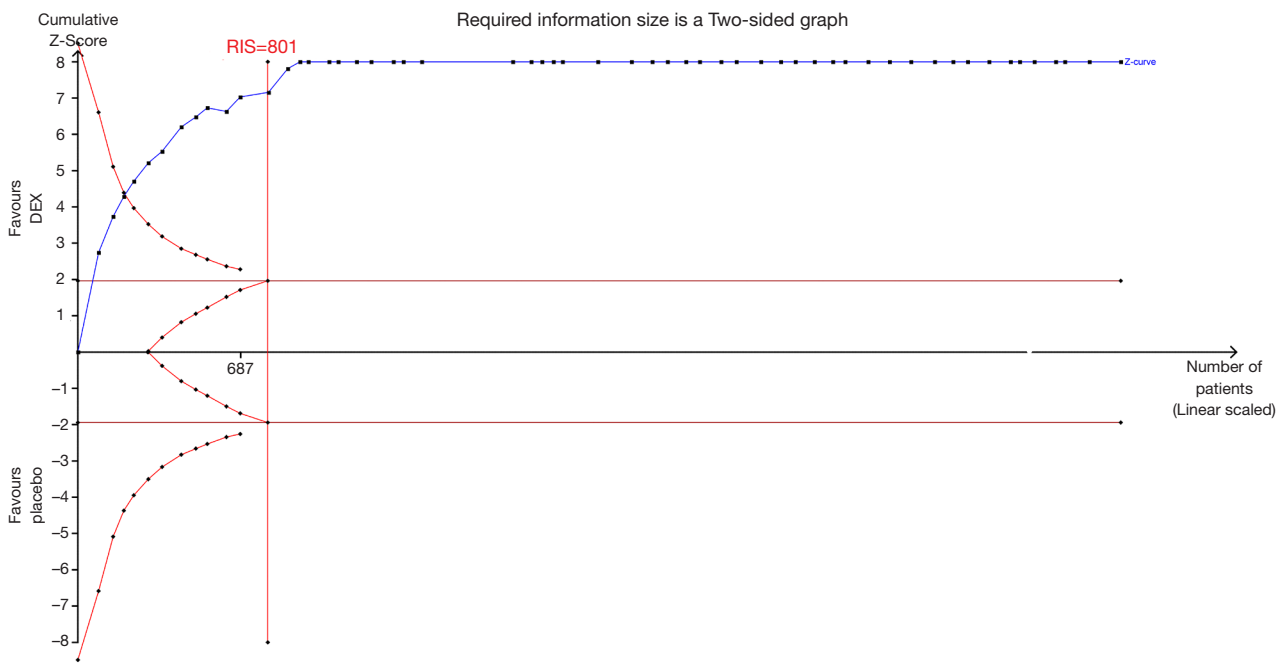

Figure 7 Trial sequential analyses for EA incidence: DEX *vs.* placebo. EA, emergence agitation; DEX, dexmedetomidine.

Table 2 TSA for subgroup analysis of EA incidence and secondary outcomes

Outcomes/subgroup	RRR% (MD)	IIA% (Variance)	ICA%	D^2%	Required IS	Reach IS	Cross TSMB	Cross FB	Evidence
Dichotomous outcomes									
Incidence of EA									
DEX *vs.* placebo	30	34.63	49.47	57	801	Yes	Yes	No	FE
Different administration routes									
Intravenous	30	36.95	52.78	60	781	Yes	Yes	No	FE
Intranasal	30	33.01	47.16	47	716	No	Yes	No	FE
Oral	30	19.09	27.27	45	1,508	No	No	No	AE
Perineural	30	22.00	31.43	0	692	Yes	Yes	No	FE
Different administration timing									
Premedication	30	32.93	47.04	23	489	Yes	Yes	No	FE
After induction of anesthesia	30	32.23	46.04	44	698	Yes	Yes	No	FE
Before the end of surgery	30	42.76	61.08	85	1,550	No	Yes	No	FE
Different administration patterns									
Bolus dosage	30	34.27	48.96	59	870	Yes	Yes	No	FE
Continuous dosage	30	35.97	51.39	0	325	Yes	Yes	No	FE
Different administration dose									
Low dose	30	39.22	56.03	56	624	Yes	Yes	No	FE
Medium dose	30	34.60	49.43	67	1,068	Yes	Yes	No	FE
High dose	30	31.99	45.70	0	397	Yes	Yes	No	FE
DEX *vs.* midazolam	30	23.94	34.20	34	928	No	Yes	No	FE
DEX *vs.* fentanyl	30	20.05	28.65	56	1,790	No	No	No	AE
DEX *vs.* propofol	30	16.04	22.92	0	1,041	No	No	No	AE
DEX *vs.* ketamine	30	14.73	21.05	0	1,155	No	No	No	AE
DEX *vs.* ketofol	30	16.55	23.64	0	1,003	No	No	No	AE
Incidence of severe EA									
DEX *vs.* placebo	30	22.83	32.62	0	657	Yes	Yes	No	FE
Patients requiring rescue analgesia									
DEX *vs.* placebo	30	26.18	37.40	87	4,217	No	Yes	No	FE
DEX *vs.* midazolam	30	11.07	15.82	0	1,620	No	No	No	AE
DEX *vs.* fentanyl	30	21.68	30.97	0	706	No	No	No	AE
Incidence of PONV									
DEX *vs.* placebo	30	11.99	17.13	0	1,479	Yes	Yes	No	FE
DEX *vs.* midazolam	30	8.67	12.38	0	2,149	No	No	No	AE
DEX *vs.* ketamine	30	23.33	33.33	89	5,584	No	No	No	AE
Incidence of hypotension	–30	2.95	2.27	0	17,259	No	No	No	AE

Table 2 (*continued*)

Table 2 (*continued*)

Outcomes/subgroup	RRR% (MD)	IIA% (Variance)	ICA%	D^2%	Required IS	Reach IS	Cross TSMB	Cross FB	Evidence
Incidence of bradycardia	−30	1.14	0.88	0	46,434	No	No	No	AE
Continuous outcomes									
Emergence time									
DEX *vs.* placebo	2.48	5.41	–	97	1,054	Yes	Yes	No	FE
DEX *vs.* midazolam	0.16	5.62	–	97	234,573	No	No	No	AE
DEX *vs.* fentanyl	−0.10	14.44	–	83	286,217	No	No	No	AE
Discharge time from PACU			–						
DEX *vs.* placebo	−0.75	36.06	–	99	176,960	No	No	No	AE
DEX *vs.* midazolam	−0.94	31.10	–	0	1,107	No	No	No	AE
DEX *vs.* fentanyl	3.68	205.11	–	81	2,551	No	No	No	AE

TSA, trial sequential analysis; EA, emergence agitation; RRR, relative risk reduction; IIA, the incidence in the intervention arm; ICA, the incidence in the control arm; D^2, diversity; IS, information size; TSMB, trial sequential monitoring boundary; FB, futility boundary; FE, firm evidence; AE, absent evidence; MD, mean difference. Error a and 1-β were defined as 5% and 80%, respectively, in each model; For dichotomous data, RRR was defined as 30%, ICA was calculated from the average incidence in the control group, D^2 was set as model variance-based; For continuous data, MD and Variance were calculated from the low risk of bias studies, D^2 was set as model variance-based.

The pooled results showed that low (RR 0.33, 95% CI: 0.24–0.45, P<0.00001, I^2=51%), medium (RR 0.38, 95% CI: 0.29–0.50, P<0.00001, I^2=45%) or high dose (RR 0.24, 95% CI: 0.18–0.31, P<0.00001, I^2=0%) of DEX could significantly reduce the incidence of EA (Figure S4, *Table 3*). There is a significant difference among the three subgroups (P=0.04), suggesting that the high dose of DEX may be more effective in reducing EA incidence. TSA showed Z-curves crossed TSMB and reached the IS for all three subgroups (*Table 2*). GRADE evidence for the low and medium dose of DEX showed low quality due to inconsistency and publication bias. While GRADE for high dose DEX was classified as moderate-quality evidence (Appendix 1).

Relationship between the dose of DEX and incidence of EA

Nine studies reported the incidence of EA according to the different dose of DEX compared to placebo (22,30,33,43,44,56,75,76,79). We conducted a meta-regression analysis to show the relationship between the dose of DEX and EA incidence, which revealed statistically significant evidence for an association between the log risk ratio for EA and the dose of DEX (P=0.013) (*Figure 11*). This underlines that the incidence of EA decreases as the dose of DEX increases.

Secondary outcomes

Emergence time

Compared with placebo, DEX had a significantly delayed effect on emergence time in children (MD 2.28, 95% CI: 1.49–3.08, P<0.00001, I^2=97%) (*Table 4*). The TSA showed Z-curves reached the IS and crossed the TSMB (*Table 2*). However, the quality of evidence was judged to be exceptionally low due to serious inconsistency and publication bias (Egger's tests P=0.000) (Appendix 1). The pooled results revealed no significant differences between DEX and midazolam (MD 0.45, 95% CI: −1.45–2.35, P=0.64, I^2=96%) or fentanyl (MD −0.46, 95% CI: −1.94–1.02, P=0.54, I^2=80%) (*Table 4*) while lacking firm evidence by TSA (*Table 2*) and very low quality (Appendix 1).

Time to discharge from PACU

Compared with midazolam, DEX significantly reduced the time to discharge from the PACU (MD −0.94, 95% CI: −1.82–0.06, P=0.04, I^2=0%) (*Table 4*). The TSA showed Z-curves crossed the conventional boundary for benefit but did not cross both TSMB and IS (*Table 2*). It might reveal a possible false-positive effect of DEX in

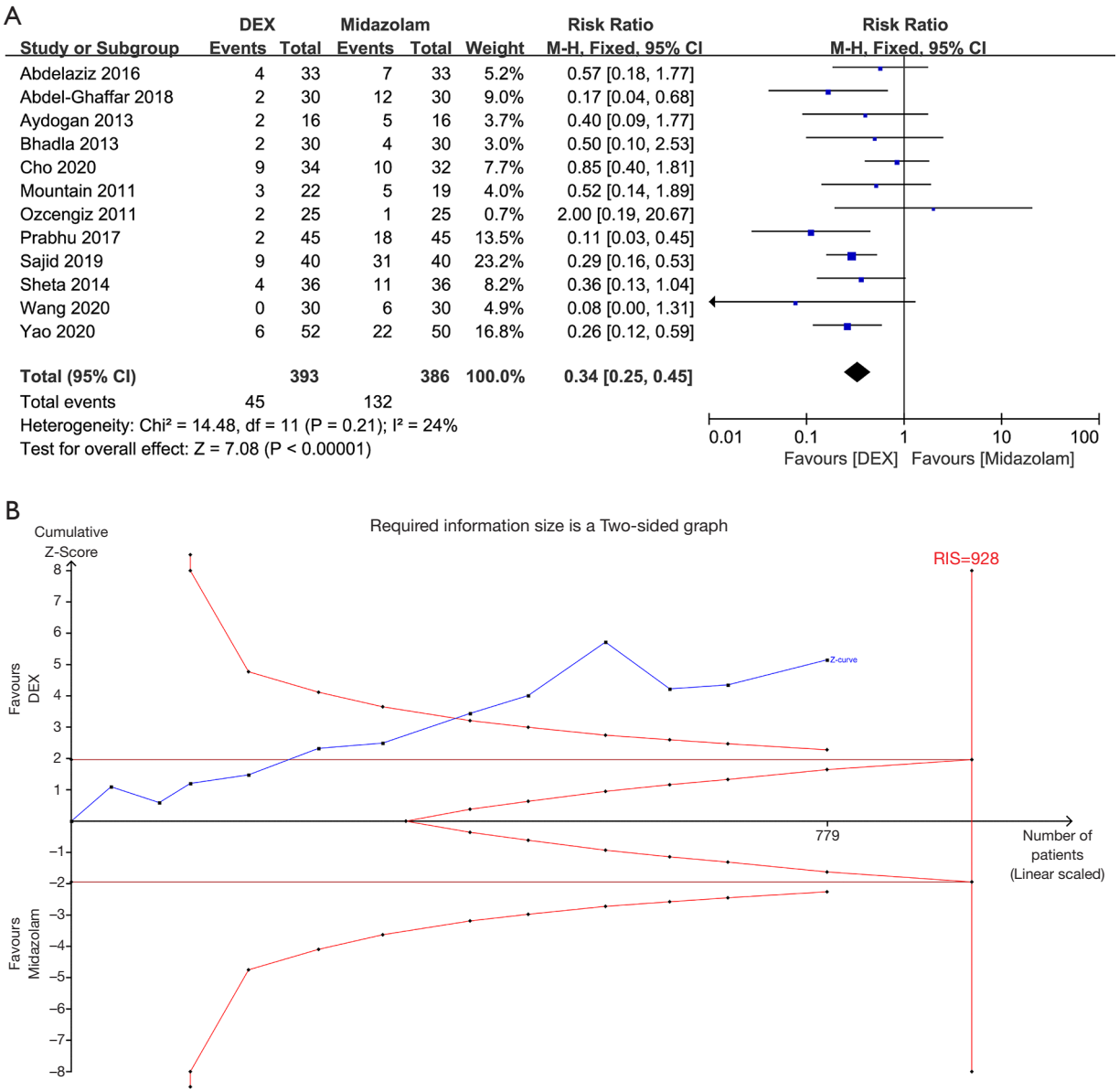

Figure 8 EA incidence: DEX *vs.* midazolam. (A) forest plot for EA incidence. (B) trial sequential analyses for EA incidence. EA, emergence agitation; DEX, dexmedetomidine.

reducing the time to discharge from the PACU compared to midazolam. GRADE quality of evidence was moderate due to imprecision (Appendix 1). No significant differences were observed between the DEX and placebo (MD 1.27, 95% CI: −2.43–4.96, P=0.50, I^2=99%) or fentanyl (MD 3.68, 95% CI: −3.00–10.37, P=0.28, I^2=63%) (*Table 4*), while lacking firm evidence by TSA (*Table 2*). The quality of evidence was graded as very low for the placebo group and low for the fentanyl group (Appendix 1).

The number of patients requiring rescue analgesia

Compared with placebo, the number of patients requiring rescue analgesia was significantly lower in the DEX group (RR 0.43, 95% CI: 0.31–0.59, P<0.00001, I^2=77%) (*Table 4*). TSA showed that although the pooled sample size did not exceed the IS, the Z-curve crossed the conventional boundary and TSMB (*Table 2*). However, the GRADE quality of evidence was low due to inconsistency and publication bias (Egger's tests P=0.002) (Appendix 1). We also

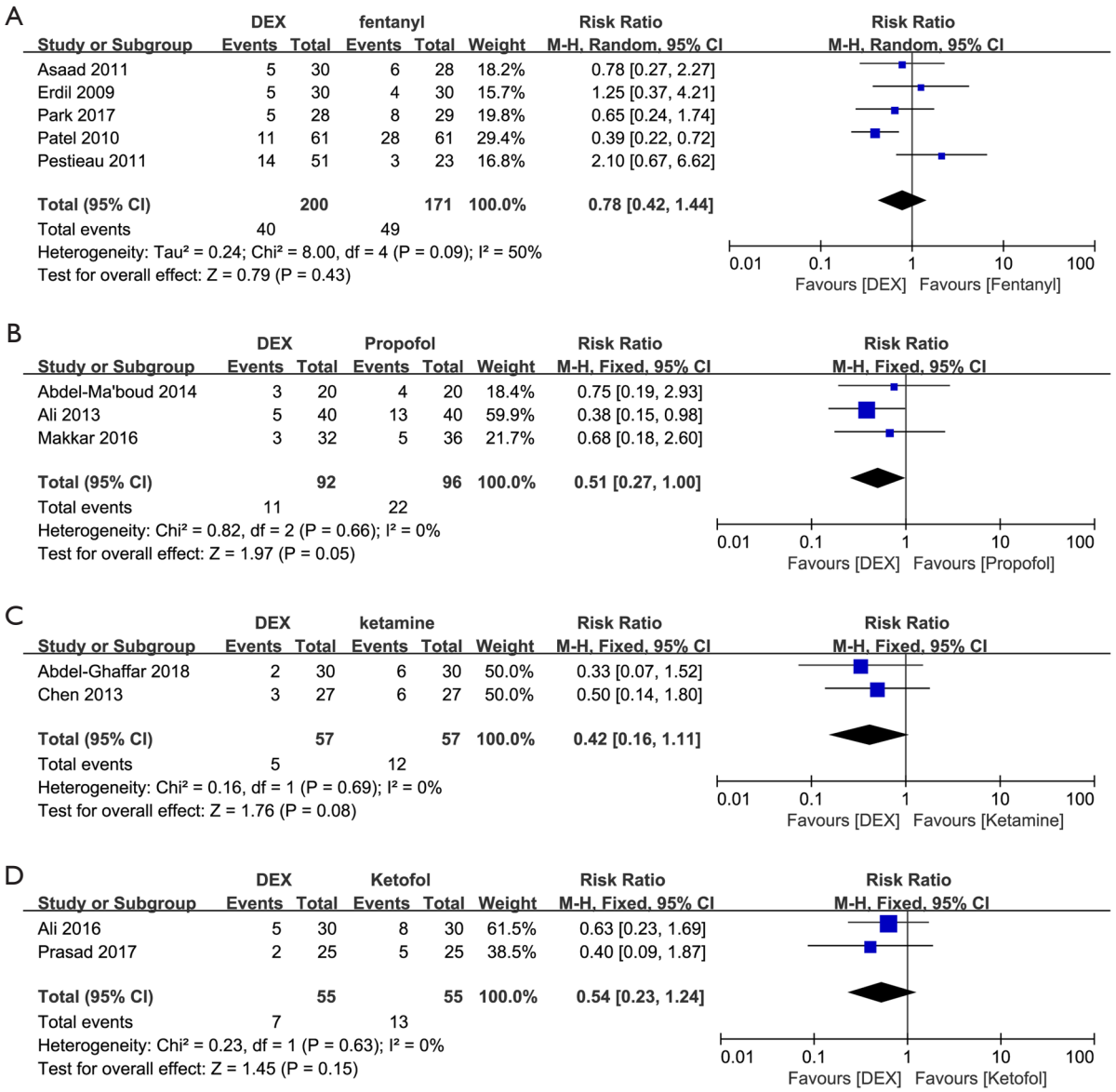

Figure 9 Forest plot for EA incidence: DEX *vs.* other active comparators. (A) DEX *vs.* fentanyl. (B) DEX *vs.* propofol. (C) DEX *vs.* ketamine. (D) DEX *vs.* ketofol. EA, emergence agitation; DEX, dexmedetomidine.

found the proportion of patients requiring rescue analgesia was significantly lower in the DEX group compared with midazolam (RR 0.58, 95% CI: 0.36–0.94, P=0.03, I^2=0%) or fentanyl (RR 0.39, 95% CI: 0.22–0.66, P=0.0005, I^2=0%) (*Table 4*). However, TSA revealed an absence of evidence (*Table 2*) with moderate quality (Appendix 1).

Incidence of PONV

The pooled results showed that DEX reduced the incidence of PONV compared to placebo (RR 0.43, 95% CI: 0.33–0.55, P<0.00001, I^2=0%) (*Table 4*). The TSA showed the Z-curves crossed the conventional boundary, TSMB, and IS (calculated as 1,479). TSA of pooled meta-analysis had firm evidence for the expected intervention effect (*Table 2*), while GRADE evidence was strong (Appendix 1). We also found the incidence of PONV was significantly lower in the DEX subgroup compared with the midazolam subgroup (RR 0.48, 95% CI: 0.27–0.85, P=0.01, I^2=0%) (*Table 4*). However,

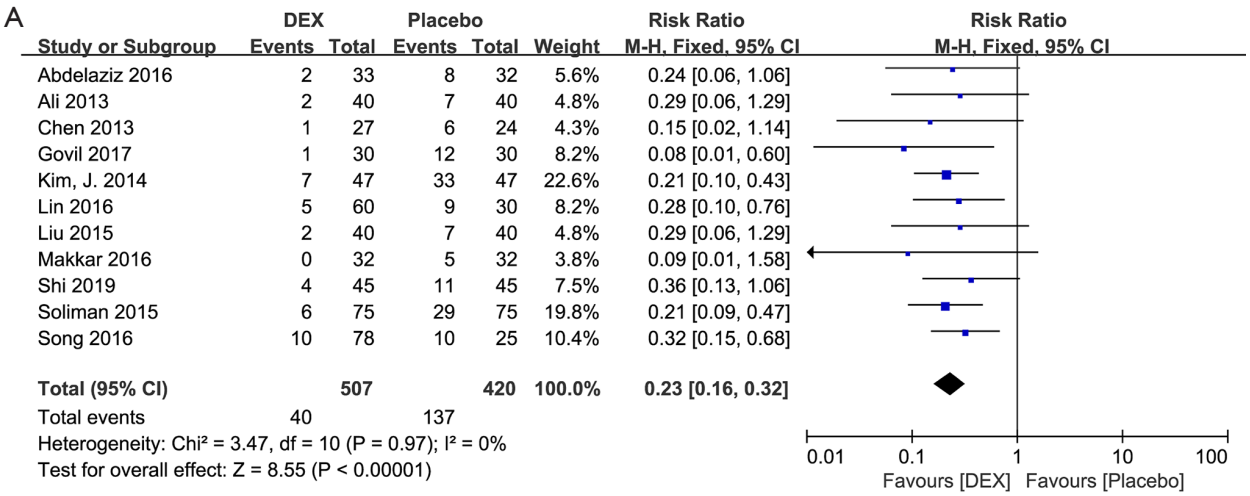

Figure 10 Severe EA incidence: DEX vs. placebo. (A) forest plot for severe EA incidence. (B) trial sequential analyses for severe EA incidence. EA, emergence agitation; DEX, dexmedetomidine.

TSA showed an absence of evidence for this result (*Table 2*). There was no significant difference between DEX and ketamine (RR 0.58, 95% CI: 0.19–1.82, P=0.35, I^2=69%) (*Table 4*), while lacking firm evidence by TSA (*Table 2*) and low quality (Appendix 1).

Incidence of hypertension

Twenty studies (20,22,23,29,37-42,45,46,51,53,57,70,74,80-82) including 1,868 patients showed there was no difference in hypotension incidence between DEX and placebo group (RR 1.50, 95% CI: 0.90–2.50, P=0.12, I^2=0%) (*Table 4*). The results are lacking firm evidence in TSA (*Table 2*), and quality of evidence was graded as low due to serious imprecision (Appendix 1).

Incidence of bradycardia

Twenty-six studies with 2,333 patients were included in the present meta-analysis for incidence of bradycardia.

Table 3 Subgroup analysis results

Outcomes/subgroup	No. of studies	No. of participants	Heterogeneity	Model of pool	Effect size (95% CI:)	P value	Subgroup Difference
Different administration routes							P=0.65
Intravenous	39	3,173	I^2=47%	Random effect	RR 0.29 [0.24,0.35]	<0.00001	
Intranasal	8	685	I^2=45%	Random effect	RR 0.29 [0.20,0.43]	<0.00001	
Oral	2	140	I^2=35%	Random effect	RR 0.50 [0.18,1.34]	0.17	
Perineural	8	459	I^2=0%	Random effect	RR 0.24 [0.14,0.41]	<0.00001	
Different administration timing							P=0.71
Premedication	11	941	I^2=20%	Random effect	RR 0.27 [0.20,0.36]	<0.00001	
After induction of anesthesia	36	2,615	I^2=35%	Random effect	RR 0.30 [0.25,0.37]	<0.00001	
Before the end of surgery	8	846	I^2=66%	Random effect	RR 0.26 [0.16,0.43]	<0.00001	
Different administration patterns							P=0.21
Bolus dosage	43	3,565	I^2=46%	Random effect	RR 0.30 [0.25,0.36]	<0.00001	
Continuous dosage	12	837	I^2=0%	Random effect	RR 0.25 [0.18,0.33]	<0.00001	
Different administration dose							P=0.04
Low dose	15	972	I^2=51%	Random effect	RR 0.33 [0.24,0.45]	<0.00001	
Medium dose	16	1,427	I^2=45%	Random effect	RR 0.38 [0.29,0.50]	<0.00001	
High dose	20	1,109	I^2=0%	Random effect	RR 0.24 [0.18,0.31]	<0.00001	

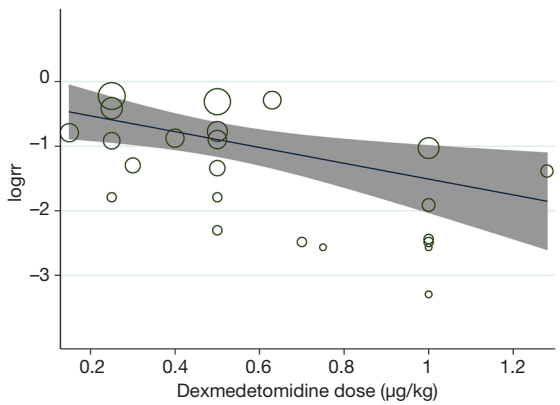

Figure 11 Scatterplot of the relationship between the dose of DEX and Log risk ratio for the incidence of EA. EA, emergence agitation; DEX, dexmedetomidine.

It revealed that DEX was associated with an increased bradycardia incidence compared to placebo (RR 3.47, 95% CI: 1.86–6.44, P<0.0001, I^2=0%) (*Table 4*). The TSA showed Z-curves crossed the conventional boundary but did not cross both TSMB and IS (*Table 2*), and the quality of evidence was graded as very low due to serious imprecision and publication bias (Appendix 1).

Discussion

To the best of our knowledge, this is the first comprehensive systematic review and meta-analysis of RCTs assessing the effects of different administration and dosage of DEX on EA in children using TSA and GRADE tools. This meta-analysis's main finding can be summarized as follows: (I) DEX could decrease the EA incidence and severe EA incidence after general anesthesia in children with the firm and moderate-to high-quality evidence evaluated by TSA and GRADE. (II) DEX was superior to midazolam for preventing EA in children with the firm and high-quality evidence. (III) Subgroup analyses revealed that, except for oral administration, DEX reduced EA incidence regardless of administration routes, timing, patterns, and doses. However, the firm and high-grade evidence were found only in the perineural route, premedication, continuous dosage, and high dose subgroups. (IV) DEX reduced the incidence of PONV compared to placebo, with firm

Table 4 Meta-analytic findings of secondary outcomes

Outcomes/subgroup	No. of studies	No. of participants	Heterogeneity	Model of pool	Effect size (95% CI)	P value
Emergence time						
DEX *vs.* placebo	45	3,451	I^2=97%	Random effect	MD 2.28 [1.49, 3.08]	<0.00001
DEX *vs.* midazolam	6	456	I^2=96%	Random effect	MD 0.45 [–1.45, 2.35]	0.64
DEX *vs.* Fentanyl	5	371	I^2=80%	Random effect	MD –0.46 [–1.94, 1.02]	0.54
Discharge time from PACU						
DEX *vs.* placebo	31	2,725	I^2=99%	Random effect	MD 1.27 [–2.43, 4.96]	0.50
DEX *vs.* midazolam	4	307	I^2=0%	Fixed effect	MD –0.94 [–1.82, –0.06]	0.04
DEX *vs.* fentanyl	3	189	I^2=63%	Random effect	MD 3.68 [–3.00, 10.37]	0.28
Patients requiring rescue analgesia						
DEX *vs.* placebo	23	2,031	I^2=77%	Random effect	RR 0.43 [0.31, 0.59]	<0.00001
DEX *vs.* midazolam	5	396	I^2=0%	Fixed effect	RR 0.58 [0.36, 0.94]	0.03
DEX *vs.* fentanyl	3	253	I^2=0%	Fixed effect	RR 0.39 [0.22, 0.66]	0.0005
Incidence of PONV						
DEX *vs.* placebo	32	2,616	I^2=0%	Fixed effect	RR 0.43 [0.33, 0.55]	<0.00001
DEX *vs.* midazolam	5	366	I^2=0%	Fixed effect	RR 0.48 [0.27, 0.85]	0.01
DEX *vs.* ketamine	3	204	I^2=69%	Random effect	RR 0.58 [0.19, 1.82]	0.35
Incidence of hypotension	20	1,868	I^2=0%	Fixed effect	RR 1.50 [0.90, 2.50]	0.12
Incidence of bradycardia	26	2,333	I^2=0%	Fixed effect	RR 3.47 [1.86, 6.44]	<0.0001

evidence by TSA and high quality of GRADE. (V) Evidence for DEX's influence on emergence time, time in PACU, rescue analgesia, hypotension, and bradycardia is thus far insufficient to draw any valid conclusion.

The high incidence and extensive harm of EA in children have brought many troubles to clinical practice. Various drugs have been investigated to prevent EA in pediatric patients (2). Earlier network meta-analyses (85,86) suggested that DEX may be the most effective drug to prevent EA in children. At present, the exact mechanism by which DEX reduces the incidence of EA is still poorly understood. Several unique pharmacological properties of DEX may account for this effect. First, unlike other sedatives, DEX does not interfere with physiologic sleep patterns and lacks significant anticholinergic effects (6). Second, DEX has proven to have opioid-sparing properties, and pain is one of the most important risk factors for EA in children (1). Third, recent studies revealed that DEX might have anti-inflammatory, organ-protective, and neuroprotective effects, which may play a key role in preventing EA (1,87,88).

The preventive effect of DEX on EA in children has been documented in several meta-analyses (7-13). Although four relevant meta-analyses (7-10) published during 2014–2015 seemed to confirm the superiority of DEX on EA in children, the limited number of included studies reduced the reliability of outcomes. In 2020, three meta-analyses were conducted to study the effect of DEX on EA in children. Tang *et al*. (11) included 24 trials and reported that DEX has positive effects on preventing EA in children undergoing general anesthesia with sevoflurane. Yang *et al*. (12) included 33 studies and revealed using DEX was associated with a reduced incidence of EA in children. Recently, Rao *et al*. (13) conducted a meta-analysis with 63 trials, which showed the effectiveness of DEX in preventing EA in children. However, including non-randomized case-control and high heterogeneity studies decreased the reliability of the conclusion.

None of these meta-analyses evaluated the evidence quality using either TSA or GRADE tools, which conclusions would be unreliable. Compared with the earlier

meta-analyses, we added the latest evidence from 67 RCTs and confirmed the beneficial effects of DEX on EA in pediatric patients. Notably, we found that DEX significantly reduced severe EA incidence in children, which is more harmful and requires added drug therapy. Also, in our study, TSA showed firm evidence, and the quality of evidence was graded as moderate to high. Therefore, the evidence from our meta-analysis suffices to support that DEX should be considered for children to prevent EA and severe EA.

Our meta-analysis suggested that DEX was superior to midazolam for preventing EA in children, in line with the findings of Lang *et al*. (89) and Rao *et al*. (13). TSA and GRADE results revealed that the level of evidence about the DEX's superiority over midazolam in reducing EA incidence was sufficient. However, compared with fentanyl, propofol, ketamine, or ketofol, DEX did not significantly reduce the EA incidence. TSA results showed that Z-curves did not cross any of the boundaries, and further evidence with a large sample size is needed.

The European Society of Anaesthesiology suggested that DEX should be used intravenously, intranasally, or epidurally to reduce the risk of EA in children (90). However, no suggestions were given for the best administration, timing, patterns, or dosages of DEX in EA prevention. Therefore, we performed the pre-specified subgroup analyses with different administration routes, timing, patterns, and DEX dosages.

Subgroup analysis revealed that DEX significantly reduced EA incidence when administered intravenously, intranasally, and perineurally. However, no significant difference was found when DEX was administered orally, with only two trials included (20,60). Zhang *et al*. (7) and Zhu *et al*. (10) reported that intravenous or intranasal DEX could decrease EA incidence in children undergoing general anesthesia. Our meta-analysis confirmed the beneficial effects of DEX by including a larger number of studies. Interestingly, perineural DEX improved EA incidence with high-quality and firm evidence. DEX was found to supply analgesic effects through supraspinal, ganglionic, spinal, and peripheral actions when it is perineurally administered (91), reducing EA incidence. Andersen *et al*. (92) reported that perineural DEX could double the nerve block duration better than intravenous administration.

A recent meta-analysis (93) showed that caudal DEX could prolong postoperative analgesia with less pain and decrease intraoperative end-tidal sevoflurane concentration. Collectively, combining this study with earlier research, one can state with great confidence that perineural DEX can effectively reduce EA incidence in children. However, the best dose and side effects of perineural DEX cannot be set up due to insufficient detailed data, and the effects of other routes of DEX administration on EA in children also need to be further studied.

Subgroup analysis was performed for the timing of DEX administration, and the result showed that DEX decreases EA incidence regardless of the timing when DEX was administered preoperatively, after induction of anesthesia, and before the end of surgery. TSA revealed firm evidence for each subgroup. The GRADE-rated evaluation showed the moderate and low quality of evidence for after-induction and the before-the-end-of-surgery subgroup due to inconsistency and publication bias. However, the evidence for the premedication subgroup was of high quality. This may be due to the higher dose (0.5–4 μg/kg) and the more uniform route (transnasal or oral) of DEX administration in the premedication subgroup, leading to a more consistent DEX effect in reducing the incidence of EA. Preoperative administration of DEX has been shown to have several significant benefits, including a lower incidence of EA, reduced agitation severity, and a shorter duration of agitation (94). Therefore, high-quality evidence supports preoperative DEX administration to prevent EA in children. Further, studies focusing on the merits of other DEX administration timing would be of the greatest benefit.

Our further subgroup analysis, with different DEX administration patterns, revealed that DEX administered as bolus dosage or as continuous dosage has a similar effect in reducing EA incidence in children. This result was consistent with the finding of the earlier meta-analysis by Zhu *et al*. (10). TSA showed Z-curves reached the IS and crossed TSMB for both patterns, suggesting a sufficient level of evidence has been reached. GRADE evidence for bolus dosage subgroup showed low due to inconsistency and publication bias. However, GRADE for the continuous dosage subgroup had high-quality evidence, proving that the beneficial effects of continuous administration of DEX on EA incidence were more reliable. Continuous infusion of DEX resulted in higher dosage and longer duration of DEX action, leading to more robust EA prevention effects. Thus, our evidence supported continuous DEX injection to prevent EA in children. Further studies should compare the efficacy and safety of different DEX administration patterns for EA in children.

To further investigate the preventive effect of DEX on EA in children, we performed an added subgroup analysis

for different intravenous DEX doses. The pooled results showed that all doses of DEX significantly reduced the incidence of EA in children. There is a significant difference among the three subgroups (P=0.04), suggesting that a high dose of DEX (≥1 μg/kg) may be more effective than a low and medium dose of DEX in reducing the incidence of EA. TSA showed firm evidence for all three subgroups. However, only the high-dose DEX subgroup had moderate-quality GRADE evidence. In our included studies, DEX showed its effect in decreasing EA from the lowest dose of 0.15 μg/kg (26) to the highest dose of 1.86 μg/kg (41). Nine studies directly compared the effects of different doses of DEX on EA in children (22,30,33,43,44,56,75,76,79). The meta-regression analysis for these nine studies showed a statistically significant association between EA incidence and DEX dose (P<0.05). It is not surprising that EA incidence decreases with an increase in DEX dose. A high dose of DEX may be associated with some side effects, including hypotension, bradycardia, and delayed emergence (95). However, we did not analyze the relationship between different doses of DEX and side effects due to insufficient detailed data. At present, there is no clear conclusion on the greatest dose of DEX for preventing EA in children. Zhang *et al*. (96) revealed that intravenous DEX infusion at 0.30 μg/kg could prevent half of or all EA after general anesthesia during pediatric tonsillectomy and adenoidectomy. Manning *et al*. (97) suggested that intravenous DEX 0.5 μg/kg could significantly reduce EA incidence in children with minimal side effects. However, Bhat *et al*. (30) reported that a single dose of DEX 1 μg/kg was more effective than 0.5 μg/kg in reducing EA. Therefore, further studies are needed to find the best DEX dose, considering the different administration routes, timing, and side effects.

PONV is a frequent complication after general anesthesia in children. The analysis for PONV showed that patients who received DEX were associated with a lower incidence of PONV than placebo. The results strengthened the findings of earlier meta-analyses (10-12). The TSA results showed that the current sample size exceeded the required IS, and the present evidence for anticipated intervention effects was sufficient. While high-quality evidence from GRADE strongly supported the results. The prophylactic effect of DEX on PONV may be related to the sparing effects of opioids and inhaled anesthetics (98,99). We also found that DEX had a better preventive effect on PONV than midazolam. However, TSA showed an absence of evidence with low quality. Therefore, high-quality studies with a large sample size are needed to confirm this result.

We also investigated the emergency time, time to discharge from PACU, and the number of patients requiring rescue analgesia. Our pooled results showed that DEX prolonged the emergence time but did not increase the time to discharge from PACU, which was consistent with the recent meta-analysis found by Yang *et al*. (12). However, the results should be interpreted with caution due to the high levels of heterogeneity across the studies. Some data were re-calculated; the median and range were transformed into the mean and variance. These may be the main source of heterogeneity. Our study suggested that DEX could reduce the proportion of rescue analgesia than placebo with TSA firm evidence. Compared with other anesthetics, including midazolam and fentanyl, DEX may be more effective in reducing rescue analgesia. However, low-to moderate-quality evidence reveals further research is needed to draw definitive conclusions.

The most reported adverse events of DEX are hypotension and bradycardia. In our meta-analysis, DEX significantly increased the occurrence of bradycardia but did not increase the risk of hypotension. The TSA suggested the evidence was insufficient for both results, and the quality of evidence was graded as low or very low due to serious imprecision and publication bias. Data on side effects were sparse in all studies, while some studies reported no hypotension or bradycardia was collected, which was known as "zero events". Therefore, it is currently unreasonable to conclude the relationship between DEX and bradycardia or hypotension due to insufficient information. More clinical trials and samples are needed to verify the safety of DEX.

This systematic review and meta-analysis have several potential limitations. First, the included studies' sample sizes were small, with only 10 of the 67 studies having more than 100 subjects. Therefore, our meta-analysis may be subject to small study effect bias. Second, patient age, type of operation, and EA evaluation method differ among the included studies. These variables might have produced the clinical heterogeneity that influenced the results, but we did not perform subgroup analyses for such variables. According to the Galbraith plot analysis, we found a moderate heterogeneity within EA incidence, which is due to the inclusion of three studies (42,70,75). A sensitivity analysis that excluded the three studies confirmed the robustness of the conclusion. We identified high heterogeneity in some secondary outcomes, including emergence time, time to discharge from PACU, and the

number of patients requiring rescue analgesia. These results should be interpreted with caution. Third, Egger's test results suggested a potential publication bias in one of the primary outcomes (EA incidence). Although the trim-and-fill analysis was performed to reduce the missing studies' influence, the potential publication bias could still affect the conclusions' reliability. Finally, our study suggested a dose-dependent effect of DEX on preventing EA in children, but we did not study the effects of different doses of DEX on side effects due to insufficient sufficient data. It is unreasonable to emphasize the benefit of DEX in preventing EA without considering its side effects. The optimal dose of DEX for preventing EA with minimal side effects in children requires further investigation.

Conclusions

In summary, the present meta-analysis showed that perioperative administration of DEX significantly reduced the incidence of EA, severe EA, and PONV in children. TSA and GRADE supplied sufficient evidence to support the efficacy of DEX in the prevention of EA in children when the perineural route administered DEX, as premedication, as continuous dosage, and at a high dose. However, the best dose, route, and timing of DEX and influence on other outcomes call for further studies.

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Footnote

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