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ORIGINAL ARTICLE

Prophylactic pharmacological interventions against perioperative respiratory adverse events in children undergoing noncardiac surgery: a systematic review and meta-analysis

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Abstract

Purpose Perioperative respiratory adverse event (PRAE) is one of the most common complications in pediatric anesthesia. We aimed to evaluate the efficacy of perioperative pharmacological interventions to prevent the development of PRAE in children undergoing noncardiac surgery.

Methods PubMed, Embase, Cochrane Library and ClinicalTrials.gov were searched for randomized controlled trials (RCT) of prophylactic pharmacological interventions for PRAE among surgical children from inception to 5 August 2024. Pairwise meta-analyses were conducted to compare the effects of an intervention with placebo or another intervention on overall PRAE and their subtypes, including laryngospasm, bronchospasm, oxygen desaturation, airway obstruction, coughing and stridor. Risk of bias was assessed using the Cochrane Collaboration tool.

Results Seven categories of prophylactic interventions were identified. Twenty-nine RCTs with 4452 children were included. Compared with placebo, lidocaine reduced the odds ratio (OR) of overall PRAE (0.27 [95% CI] [0.17, 0.42]) and laryngospasm (0.38 [0.22, 0.67]); dexmedetomidine reduced the OR of PRAE (0.31 [0.12, 0.76]), laryngospasm (0.31 [0.10, 0.91]), coughing (0.24 [0.14, 0.41]) and oxygen desaturation (0.54 [0.35, 0.84]); β_2-adrenoreceptor agonists reduced the OR of PRAE (0.45 [0.24, 0.83]), coughing (0.36 [0.13, 0.95]) and oxygen desaturation (0.66 [0.45, 0.98]). Compared with sevoflurane induction, intravenous propofol induction lowered the OR of PRAE (0.35 [0.16, 0.74]), laryngospasm (0.17 [0.06, 0.48]) and airway obstruction (0.32 [0.17, 0.63]).

Conclusions The meta-analysis demonstrated prophylactic potential of lidocaine, dexmedetomidine, β_2-adrenoreceptor agonists and propofol induction technique against PRAE, but it should be interpreted cautiously due to inconsistent PRAE definition and correlation of subtypes within the composite outcome.

Trial registration PROSPERO (CRD42020220028). Registered 11 December 2020. Updated 3 September 2024.

Keywords Perioperative respiratory adverse events · Pediatric anesthesia · Pharmacological interventions · Prophylaxis · Meta-analysis

Introduction

Perioperative respiratory adverse events (PRAE) encompass a range of respiratory incidents encountered in pediatric anesthesia. Examples range from mild oxygen desaturation to severe laryngospasm. The prevalence of PRAE is approximately 15% in general pediatric population, with the rate as high as 50% in high-risk children [1]. Severe PRAE are associated with prolonged hospital admissions, higher healthcare costs and even one-third of anesthesia-related cardiac arrests [2, 3].

Optimizing airway management is a long-standing challenge in pediatric anesthesia. Compared with adults, children

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have smaller airways, lower oxygen reserve and increased airway sensitivity. Moreover, they tend to have recurrent respiratory tract infection, which links with airway inflammation and hypersensitivity. Actually, the respiratory symptoms are present in 25% of children scheduled for surgery [4], and there are no robust data demonstrating that rescheduling surgery reduces the incidence of PRAE.

Randomized controlled trials (RCT) were designed to evaluate the efficacy of prophylactic pharmacological interventions on PRAE, including the use of β_2-adrenoreceptor agonists, dexmedetomidine, local anesthetics, M-cholinoreceptor blockers and propofol induction technique. Unfortunately, these studies demonstrated contradictory results. A substantial proportion of RCTs showed treatment benefit, while the others found no prophylactic effects against PRAE. To date, prophylactic pharmacological strategies for PRAE lack consensus. The aim of this meta-analysis was to summarize the available evidence and evaluate the effects of prophylactic pharmacological interventions on the incidence of PRAE in children undergoing noncardiac surgery.

Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane guidelines [5, 6]. The protocol of the systematic review and meta-analysis has been registered in PROSPERO (CRD42020220028).

Search strategy and study selection

Three authors (Q.W.D., W.C.T., and Y.Q.Z.) conducted literature search and study selection independently. We searched PubMed, Embase, Cochrane Library, and ClinicalTrials.gov for eligible trials from inception to 30 December 2020. The last search was updated on 5 August 2024. Further studies were identified from previous reviews and meta-analyses. The search strategy in PubMed was ((perioperative respiratory adverse events [MeSH Terms] OR laryngospasm OR bronchospasm OR desaturation OR "airway obstruction" OR coughing OR stridor) AND (infants OR children OR adolescent OR pediatric) AND (surgery OR operation)) with filters to clinical trial (article type) and birth–18 years (age). The complete search strategies for each database are shown in Online Resource: Appendix S1.

We included RCTs of prophylactic pharmacological interventions for PRAE in patients from birth to 18 years of age undergoing noncardiac surgery. We only included children receiving general anesthesia with airway devices (laryngeal mask airway [LMA] or endotracheal tube [ETT]). Premature infants of gestational age less than 37 weeks or birth weight less than 2500 g with potential airway malformations were excluded. Eligible trial designs were RCTs comparing the effects of a particular pharmacological agent with that of placebo or another intervention on the incidence of PRAE. Primary outcome was overall PRAE, a composite outcome of the major respiratory adverse events (laryngospasm and bronchospasm) and at least two of the minor events (oxygen desaturation, airway obstruction, coughing or stridor), or at least including three of the six PRAE subtypes. Secondary outcomes were subtypes of PRAE. The definition of PRAE and its subtypes is shown in Online Resource: Table S1.

Data extraction

Two authors (Q.W.D. and W.C.T.) extracted the study characteristics and outcomes of each eligible trial to a predesigned form independently. The following variables were collected: first author, year of publication, type of surgery, sample size, airway devices, participant characteristics (age, American Society of Anesthesiologists [ASA] physical status classification system, risk classification [high-risk children or not], difficult airway), intervention characteristics (dosage, administration route and timing of prophylactic pharmacological agents, premedication, use of muscle relaxants), and outcome measures (incidence of overall PRAE, laryngospasm, bronchospasm, oxygen desaturation, airway obstruction, coughing, stridor, and phase of outcome measurement).

Quality assessments

Two authors (Q.W.D. and Y.Q.Z.) conducted the critical appraisals of the included trials using the Cochrane Collaboration tool [7]. The Cochrane Collaboration tool focused on selection bias, performance bias, detection bias, attrition bias and reporting bias. Two independent reviewers (X.W.W. and H.J.L.) rated the quality of evidence for each comparison according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group system [8, 9]. Briefly, the GRADE system classified the quality of evidence in one of four levels: high, moderate, low and very low. Evidence based on RCTs started as high-quality evidence. The confidence in the evidence might be decreased for several reasons, including risk of bias, inconsistency of the results, indirectness of evidence, imprecision and reporting bias. Disagreement was resolved by consensus or consultation with the third author (S.H.W.).

Statistical analysis

Data of overall PRAE were included in the quantitative analysis only when it met the inclusion criteria for primary outcome of the current meta-analysis. For each prophylactic pharmacological intervention, we conducted conventional

pairwise meta-analyses when two or more studies were estimating the same underlying treatment effect on PRAE outcomes. Both primary and secondary outcomes were dichotomous data. We used odds ratio (OR) as the effect measure with 95% confidence intervals (CI) estimated using Mantel–Haenszel methods. Random effects models were used when producing an overall summary estimate. Statistical heterogeneity between studies was assessed using the I^2 statistics. Next, we conducted post hoc subgroup analyses based on different types of surgery, different administration routes of pharmacological agents, with or without the use of muscle relaxants or different phases of outcome measurement to clarify their impacts on the results. Airway-related surgery was defined as surgery related to upper or lower respiratory tract, including cleft palate repair surgery, tonsillectomy and/or adenoidectomy, fiberoptic or rigid bronchoscopy. We also conducted post hoc sensitivity analyses excluding studies with premedication or children with difficult airway. Conventional pairwise meta-analyses were performed using Review Manager, version 5.3.3 (Cochrane Collaboration).

Results

Search results and study characteristics

Of 2741 records identified, 1829 studies remained after removal of duplication. 44 studies were selected for full-text review after title and abstract screening. 29 RCTs including 4452 children finally fulfilled the inclusion criteria [10–38]. The process of literature searching and study selection is presented in Fig. 1.

Seven categories of prophylactic pharmacological interventions were identified: β_2-adrenoreceptor agonists (salbutamol and tulobuterol), dexmedetomidine, lidocaine,

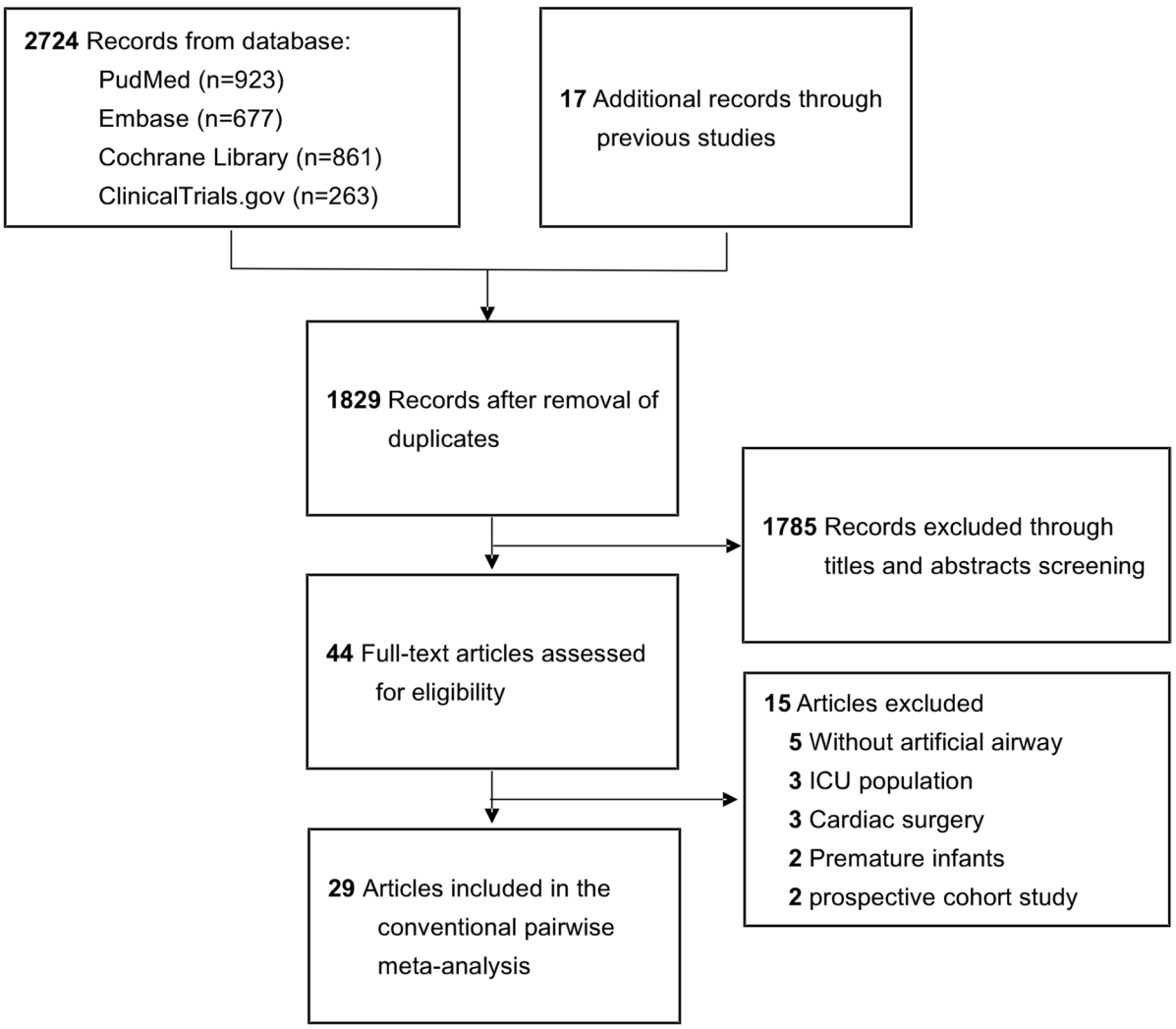

Fig. 1 The process of literature searching and study selection. *ICU* intensive care unit

magnesium, M-cholinoreceptor blockers (atropine and glycopyrrolate), propofol, and sevoflurane. Specially, the effect of propofol was compared with that of placebo when used as a bolus before emergency, while it was compared with that of sevoflurane when used as induction technique. The characteristics of included studies are summarized in Table 1. The definition of overall PRAE in each included study is shown in Table 2.

Quality assessments

Methods of random sequence generation, allocation concealment, blinding of participants and outcome assessment were clearly reported in most of the included studies. The risk of incomplete outcome data and selective report was unclear in half of the studies. The details of risk of bias assessment for the included studies are presented in Online Resource: Figures S1 and S2. The overall certainty of evidence in our study was graded as moderate to very-low using GRADE's approach. The confidence of evidence was decreased mostly due to risk of bias, inconsistency of the results and imprecision. The certainty of evidence for each comparison is presented in Figs. 2 and 3. The details of certainty assessment of evidence for each comparison are shown in Online Resource: Table S2.

Meta-analyses

Primary outcome

Evidence from 14 RCTs with 2707 patients showed that compared with placebo, the use of lidocaine, dexmedetomidine and β_2-adrenoreceptor agonists was associated with reduced OR of overall PRAE (0.27 [95% CI] [0.17, 0.42] [moderate certainty of evidence], 0.31 [0.12, 0.76] [moderate certainty of evidence], 0.45 [0.24, 0.83] [low certainty of evidence], respectively). Intravenous induction with propofol was associated with lower OR of overall PRAE compared with inhalational induction with sevoflurane (0.35 [95% CI] [0.16, 0.74] [low certainty of evidence]). The use of M-cholinoreceptor blockers did not significantly reduce the OR of overall PRAE (Fig. 2).

Secondary outcomes

Laryngospasm

A total of 26 RCTs with 3608 children included laryngospasm as outcome measure. The result of meta-analysis showed that the use of magnesium, dexmedetomidine and lidocaine was associated with lower OR of laryngospasm compared with placebo (0.11 [95% CI] [0.01, 0.95] [low certainty of evidence], 0.31 [0.10, 0.91] [moderate certainty of evidence], 0.38 [0.22, 0.67] [moderate certainty of evidence], respectively). Intravenous induction with propofol was associated with reduced OR of laryngospasm when compared with inhalational induction with sevoflurane (0.17 [95% CI] [0.06, 0.48] [moderate certainty of evidence]). However, the use of propofol before emergency, β_2-adrenoreceptor agonists and M-cholinoreceptor blockers was not superior to placebo with respect to laryngospasm (Fig. 3).

Bronchospasm

Bronchospasm was reported in 14 RCTs with 2312 patients. The results of meta-analysis indicated that the use of dexmedetomidine, β_2-adrenoreceptor agonists and intravenous induction with propofol was not associated with lower OR of bronchospasm (Fig. 3).

Oxygen desaturation

A total of 21 RCTs with 3817 patients reported oxygen desaturation as outcome measure. Compared with placebo, the use of dexmedetomidine and β_2-adrenoreceptor agonists was associated with reduced OR of oxygen desaturation (0.54 [95% CI] [0.35, 0.84] [moderate certainty of evidence], 0.66 [0.45, 0.98] [moderate certainty of evidence], respectively). Other pharmacological interventions did not decrease the OR of oxygen desaturation (Fig. 3).

Airway obstruction

Airway obstruction was reported in seven RCTs with 1854 patients. The results of meta-analysis indicated that intravenous induction with propofol was associated with lower OR of airway obstruction compared with inhalational induction with sevoflurane (0.32 [95% CI] [0.17, 0.63] [moderate certainty of evidence]) (Fig. 3).

Coughing

Twenty-three RCTs with 3961 children reported severe coughing as outcome measure. The results of meta-analysis showed that the use of dexmedetomidine and β_2-adrenoreceptor agonists was associated with lower OR of coughing compared with placebo (0.24 [95% CI] [0.14, 0.41] [moderate certainty of evidence], 0.36 [0.13, 0.95] [low certainty of evidence], respectively). Other pharmacological interventions did not decrease the OR of coughing (Fig. 3).

Table 1 Characteristics of the included trials

Study	Type of surgery	Age/yr	High-risk	ASA	Pre-medication	Muscle relaxant	Airway devices	Intervention	Comparator	PRAE incidence		Outcome measuring phase	Adverse events
										I	C		
Dexmedetomidine VS placebo													
Bi 2019 [8][a]	Fiberoptic bronchoscopy	0-4	Y	I ~ II	Y	N	LMA	1 ug/kg dexmedetomidine intranasally before induction	0.9% NaCl intranasally before induction	NR/20	NR/20	Perioperative	NR
Chen 2014 [9][a]	Rigid bronchoscopy	0-5	Y	I ~ II	N	N	LMA[c]	4 μg/kg dexmedetomidine followed by 1–2 μg/kg/h infusion	Remifentanil started at 0.05 μg/kg/min and adjusted later	NR/38	NR/39	Perioperative	Bradycardia: 5.1%
Di 2014 [10]	Cleft palate repair surgery	3-7	N	I ~ II	N	N	ETT	0.5 ug/kg dexmedetomidine intravenously before the end of surgery	0.9% NaCl intravenously before the end of surgery	NR/30	NR/30	Postoperative	NR
Guler 2005 [11]	Tonsillectomy and adenoidectomy	3-7	N	I	Y	Y	ETT	0.5 ug/kg dexmedetomidine intravenously before the end of surgery	0.9% NaCl intravenously before the end of surgery	0/30	6/30	Postoperative	NR
He 2013 [12]	Minor surface surgery	3–7	N	I ~ II	N	N	LMA	1 ug/kg dexmedetomidine intravenously after LMA insertion	0.9% NaCl intravenously after LMA insertion	2/32	10/26	Postoperative	–
Shen 2022 [13]	Tonsillectomy and adenoidectomy	0–12	Y	I ~ II	N	Y	ETT	2 ug/kg dexmedetomidine intranasally before induction	0.9% NaCl intranasally before induction	30/124	51/125	Perioperative	–

Table 1 (continued)

Study	Type of surgery	Age/yr	High-risk	ASA	Pre-medication	Muscle relaxant	Airway devices	Intervention	Comparator	PRAE incidence		Outcome measuring phase	Adverse events
										I	C		
Shi 2019 [14]	Tonsillectomy and/or adenoidectomy	0–7	N	I ~ II	N	Y	ETT	0.5ug/kg dexmedetomidine intravenously after induction	0.9% NaCl intravenously after induction	2/45	3/45	Postoperative	Bradycardia: 4.4%
Xu 2012 [15]	Vitreoretinal surgery	0–7	N	I ~ II	N	Y	ETT	0.5 ug/kg dexmedetomidine intravenously before induction	0.9% NaCl intravenously before induction	NR/30	NR/30	Postoperative	–
β_2-adrenoreceptor agonists VS placebo													
Kim 2023 [18]	Tonsillectomy	0–6	N	N	N	Y	ETT	1 mg tulobuterol patch the day before surgery	Bandage without any ingredients the day before surgery	13/88	40/94	Perioperative	–
Ramgolam 2017 [16]	Minor elective surgery	6–16	Y	I ~ III	N	N	LMA	200 ug salbutamol inhaled before surgery	Placebo inhaled before surgery	276/230	32/232	Perioperative	–
Von Ungern-Sternberg 2019 [17]	Tonsillectomy	0–8	Y	I ~ III	N	N	LMA or ETT	200 ug salbutamol inhaled before surgery	Placebo inhaled before surgery	67/241	114/238	Perioperative	–
Lidocaine VS placebo													
Baraka 1978 [19]	Tonsillectomy	0–6	N	N	Y	N	ETT	2 mg/kg lidocaine intravenously before extubation	No treatment	NR/20	NR/20	Postoperative	–

Table 1 (continued)

Study	Type of surgery	Age/yr	High-risk	ASA	Pre-medication	Muscle relaxant	Airway devices	Intervention	Comparator	PRAE incidence		Outcome measuring phase	Adverse events
										I	C		
Khattak 2018 [20]	Surgery requiring airway device	0–6	N	I ~ II	N	Y	ETT	1.5 mg/kg lidocaine intravenously before extubation	No treatment	NR/355	NR/355	Postoperative	–
Kheirabadi 2020 [21]	Cleft palate repair surgery	0–2	N	I ~ II	Y	Y	ETT	1 mg/kg lidocaine intravenously before induction	Distilled water intravenously before induction	8/28	16/29	Postoperative	–
Koc 1998 [22]	Tonsillectomy and/or adenoidectomy	N	N	N	Y	Y	ETT	1 mg/kg 2% lidocaine intravenously before extubation	0.9% NaCl intravenously before extubation	NR/34	NR/34	Postoperative	–
Leicht 1985 [23]	Tonsillectomy	> 1	N	N	Y	N	ETT	1.5 mg/kg lidocaine intravenously before extubation	0.9% NaCl intravenously before extubation	NR/50	NR/50	Postoperative	–
Sanikop 2010 [24]	Cleft palate surgery	0–6	N	I ~ II	Y	Y	ETT	1.5 mg/kg lidocaine intravenously before extubation	0.9% NaCl intravenously before extubation	NR/37	NR/37	Postoperative	–
Koc 1998 [22][b]	Tonsillectomy and/or adenoidectomy	N	N	N	Y	Y	ETT	4 mg/kg lidocaine sprayed to glottic area before intubation	0.9% NaCl sprayed to glottic area before intubation	NR/33	NR/33	Postoperative	–
Li 2016 [25]	Surgery requiring airway	0–12	Y	I ~ III	N	Y	ETT	4 mg/kg lidocaine sprayed to glottic area before intubation	0.9% NaCl sprayed to glottic area before intubation	21/162	61/160	Perioperative	–

Table 1 (continued)

Study	Type of surgery	Age/yr	High-risk	ASA	Pre-medication	Muscle relaxant	Airway devices	Intervention	Comparator	PRAE incidence		Outcome measuring phase	Adverse events
										I	C		
O'Neill 1994 [26]	Minor surgical procedure	0–14	N	N	Y	Y/N	LMA	LMA lubricated with lidocaine gel before insertion	LMA lubricated with gel before insertion	NR/63	NR/57	Perioperative	–
Schebesta 2010 [27]	Minor surgical procedures	1–10	Y	I ~ II	Y	N	LMA	LMA lubricated with lidocaine gel before insertion	LMA lubricated with gel before insertion	8/29	20/37	Postoperative	–
Magnesium VS placebo													
Gulhas 2003 [28]	Tonsillectomy and/or adenoidectomy	1–12	N	I ~ II	N	Y	ETT	15 mg/kg magnesium intravenously after intubation	0.9% NaCl intravenously after intubation	NR/20	NR/20	Postoperative	–
Marzban 2014 [29]	Tonsillectomy and adenoidectomy	1–12	N	I ~ II	N	Y	ETT	15 mg/kg magnesium intravenously after intubation	0.9% NaCl intravenously after intubation	NR/35	NR/35	Postoperative	–
M-cholinoreceptor blockers VS placebo													
Shaw 2000 [30]	Surgery requiring airway	0–1	Y	I ~ II	N	Y	ETT	40 ug/kg atropine orally before anesthesia induction	No treatment	15/59	30/61	Postoperative	——
Tait 2007 [31]	Elective outpatient surgery	0–18	Y	I ~ III	N	N	LMA or ETT	0.01 mg/kg glycopyrrolate intravenously before airway placement	0.9% NaCl intravenously before airway placement		21/59	Perioperative	Tachycardia: 68.3%
Propofol VS placebo										28/71			

Table 1 (continued)

Study	Type of surgery	Age/yr	High-risk	ASA	Pre-medication	Muscle relaxant	Airway devices	Intervention	Comparator	PRAE incidence		Outcome measuring phase	Adverse events
										I	C		
Batra 2005 [32]	Tonsillectomy and/or adenoidectomy	1–14	N	I ~ II	Y	Y	ETT	0.5 mg/kg propofol intravenously before extubation	0.9% NaCl intravenously before extubation	NR/60	NR/60	Postoperative	–
Kumar 2019 [33]	Infra-umbilical surgery	0–10	N	I ~ II	Y	N	LMA	1 mg/kg propofol intravenously before LMA removal	No treatment	NR/25	NR/25	Postoperative	–
Propofol VS sevoflurane													
Guard BC 1998 [34]	Urological surgery	0–8	N	I ~ II	N	Y	ETT	Inhalation induction with sevoflurane maintenance with propofol	Inhalation induction and maintenance with sevoflurane	NR/25	NR/25	Postoperative	–
Karam 2022 [35]	Minor procedures	0–7	Y	I ~ III	N	N	LMA	Intravenous induction and maintained with propofol	Inhalation induction and maintained with sevoflurane	7/65	25/69	Postoperative	Refusing IV catheter: 4.6%
Ramgolam 2018 [36]	Elective surgery	0–8	Y	I ~ III	N	N	LMA	Intravenous induction with propofol	Inhalation induction with sevoflurane	39/149	64/149	Perioperative	Refusing IV catheter: 4.7%

ASA American society of anesthesiologists physical status classification system, *C* control group, *ETT* endotracheal tube, High-risk: Children with risk factors for PRAE were considered as high-risk children. The risk factors for PRAE were defined according to the included studies. *I* intervention group, *IV* intravenous, *LMA* laryngeal mask, *N* not high-risk/without premedication/without muscle relaxants, *NR* not reported, *Y* high-risk/with premedication/with muscle relaxants, *yr* years old

[a]: The two studies focused on children with inhaled foreign body, which were considered as difficult airway. [b]: The data was derived from another comparison of a previous study (Koc 1998). [c]: Laryngeal mask was inserted after the completion of rigid bronchoscopy

Table 2 Definition of perioperative respiratory adverse events in each trial

Study	Overall PRAE	Laryngospasm	Bronchospasm	Oxygen desaturation	Airway obstruction	Coughing	Stridor
Bi 2019 [8]	Not reported	Y	Y	Y	N	Y	N
Chen 2014 [9]	Not reported	N	N	Y	N	Y	N
Di 2014 [10]	Not reported	Y	Y	Y	N	Y	N
Guler 2005 [11]	PRAEs referred to a composite outcome including laryngospasm, bronchospasm, oxygen desaturation or coughing	Y	Y	Y	N	Y	N
He 2013 [12]	PRAEs referred to a composite outcome including laryngospasm, bronchospasm, oxygen desaturation or coughing	Y	Y	Y	N	Y	N
Shen 2022 [13]	PRAEs were defined as a composite outcome including laryngospasm, bronchospasm, oxygen desaturation, airway obstruction, coughing or stridor	Y	Y	Y	Y	Y	Y
Shi 2019 [14]	"Adverse events" were defined as a composite outcome including postoperative nausea and vomiting, laryngospasm, coughing, oxygen desaturation or bradycardia	Y	N	Y	N	Y	N
Xu 2012 [15]	Not reported	Y	Y	Y	N	Y	N
Kim 2023 [18]	PRAEs were defined as a composite outcome including laryngospasm, bronchospasm, oxygen desaturation, airway obstruction, coughing or stridor	Y	Y	Y	Y	Y	Y
Ramgolam 2017 [16]	PRAEs were defined as a composite outcome including laryngospasm, bronchospasm, oxygen desaturation, airway obstruction, coughing or stridor	Y	Y	Y	Y	Y	Y
Von Ungern-Sternberg 2019 [17]	PRAEs were defined as a composite outcome including laryngospasm, bronchospasm, oxygen desaturation, airway obstruction, coughing or stridor	Y	Y	Y	Y	Y	Y
Baraka 1978 [19]	Not reported	Y	N	N	N	N	N
Khattak 2018 [20]	Not reported	N	N	Y	N	Y	N
Kheirabadi 2020 [21]	"Respiratory complications" were defined as a composite outcome including laryngospasm, bronchospasm or coughing	N	N	N	N	N	N
Koc 1998 [22]	Not reported	Y	N	N	N	N	N
Leicht 1985 [23]	Not reported	Y	N	N	N	N	Y
Sanikop 2010 [24]	Not reported	Y	N	N	N	Y	N
Li 2016 [25]	"Respiratory adverse events" were defined as a composite outcome including laryngospasm, desaturation or coughing	Y	N	Y	N	Y	N
O'Neill 1994 [26]	Not reported	Y	N	Y	N	Y	N
Schebesta 2010 [27]	"Adverse events" were defined as a composite outcome including coughing, excessive oral and pharyngeal secretions, bronchospasm, laryngospasm or oxygen desaturation	Y	N	Y	N	Y	N
Gulhas 2003 [28]	Not reported	Y	N	N	N	N	N
Marzban 2014 [29]	Not reported	Y	N	N	N	Y	N
Shaw 2000 [30]	"Airway conditions" were defined as a composite outcome including laryngospasm, cough, excessive secretions or breath holding	Y	N	Y	N	Y	N
Tait 2007 [31]	"Perioperative respiratory events" were defined as a composite outcome including laryngospasm, bronchospasm, oxygen desaturation, cough or breath holding	Y	Y	Y	N	Y	N
Batra 2005 [32]	Not reported	Y	N	N	N	N	Y
Kumar 2019 [33]	Not reported	Y	Y	Y	Y	Y	N

Table 2 (continued)

Study	Overall PRAE	Laryngospasm	Bronchospasm	Oxygen desaturation	Airway obstruction	Coughing	Stridor
Guard BC 1998 [34]	Not reported	Y	Y	Y	N	Y	N
Karam 2022 [35]	PRAEs were defined as a composite outcome including laryngospasm, bronchospasm, oxygen desaturation, airway obstruction, coughing, LMA mask biting/teeth clenching or breath holding	Y	Y	Y	Y	Y	N
Ramgolam 2018 [36]	PRAEs were defined as a composite outcome including laryngospasm, bronchospasm, oxygen desaturation, airway obstruction, coughing or stridor	Y	Y	Y	Y	Y	Y

Y The specific PRAE subtype was reported as outcome measure in the study. *N* The specific PRAE subtype was not reported as outcome measure in the study. Not reported: The study did not report overall PRAE but reported the individual subtypes of PRAE

Stridor

Stridor was reported in seven RCTs with 1890 patients. Only data of studies on β_2-adrenoreceptor agonists were appropriate to be synthesized for meta-analysis. The result showed that there was no significant difference between β_2-adrenoreceptor agonists and placebo (Fig. 3).

Subgroup analyses and sensitivity analyses

The prophylactic effects of lidocaine, dexmedetomidine, and propofol induction technique still remained after subgroup analyses based on types of surgery, administration routes of pharmacological intervention, use of muscle relaxants and phase of outcome measurement. However, the beneficial effects of β_2-adrenoreceptor agonists remained only in subgroups of airway-related surgery (tonsillectomy), transdermal route, and with the use of muscle relaxants (Table 3). The results on overall PRAE remained unchanged in sensitivity analyses excluding studies with premedication or children with difficult airway (Online Resource: Table S3).

Discussion

The meta-analysis identified seven categories of prophylactic pharmacological interventions and assessed their efficacy on PRAE in children undergoing noncardiac surgery. Our study demonstrated the effectiveness of lidocaine, dexmedetomidine, β_2-adrenoreceptor agonists, and propofol induction technique against PRAE. Furthermore, laryngospasm, coughing, and oxygen desaturation might be the adverse events most significantly reduced.

The meta-analysis demonstrated that the use of lidocaine, administrated in intravenous route or topicalization of airway, reduced the OR of overall PRAE and laryngospasm in children. Another meta-analysis focusing on adult patients showed that intravenous lidocaine reduced the risk of coughing but not laryngospasm [39]. The difference might be explained by the occurrence of laryngospasm in patients of different age. Laryngospasm occurred more frequently in children than in adults due to higher airway sensitivity. Lidocaine acted through the inhibition of the voltage-dependent channels of airway smooth muscle, which might blunt laryngeal reflexes and decrease the sensitivity of airway.

Dexmedetomidine is widely used in pediatric anesthesia to facilitate sedation and reduce the incidence of agitation [40, 41], but its effect on PRAE remains unclear. Our study demonstrated that the use of dexmedetomidine, administrated intravenously or intranasally, was associated with lower OR of overall PRAE, laryngospasm, coughing and oxygen desaturation compared with placebo. It indicated that dexmedetomidine could also facilitate the tolerance of invasive airway devices. The result further supported the conclusion of a recent meta-analysis, which based on a broader population and PRAE definition including breath-holding or apnea, fever and pulmonary rales in addition to laryngospasm, bronchospasm, oxygen desaturation and coughing [42]. It seemed that dexmedetomidine was an attractive approach in pediatric anesthesia because it uniquely provided sedation, reduced PRAE, and could be administrated in an intranasal route. However, bradycardia was reported with the use of intravenous dexmedetomidine. We should be alert to its adverse effect on cardiovascular system.

Evidence from three RCTs showed that the use of β_2-adrenoreceptor agonists decreased the OR of overall PRAE, coughing and oxygen desaturation. As a bronchodilator, β_2-adrenoreceptor agonist was thought to blunt the reflex bronchoconstriction. However, the results of the meta-analysis only showed an insignificant trend toward lower OR of bronchospasm. It might attribute to the extremely low occurrence of bronchospasm in both groups. Subgroup analyses indicated that the prophylactic effects of β_2-adrenoreceptor agonists remained in patients undergoing airway-related surgery, which had higher incidence of airway complications than general surgery [43]. Among these RCTs, two of them

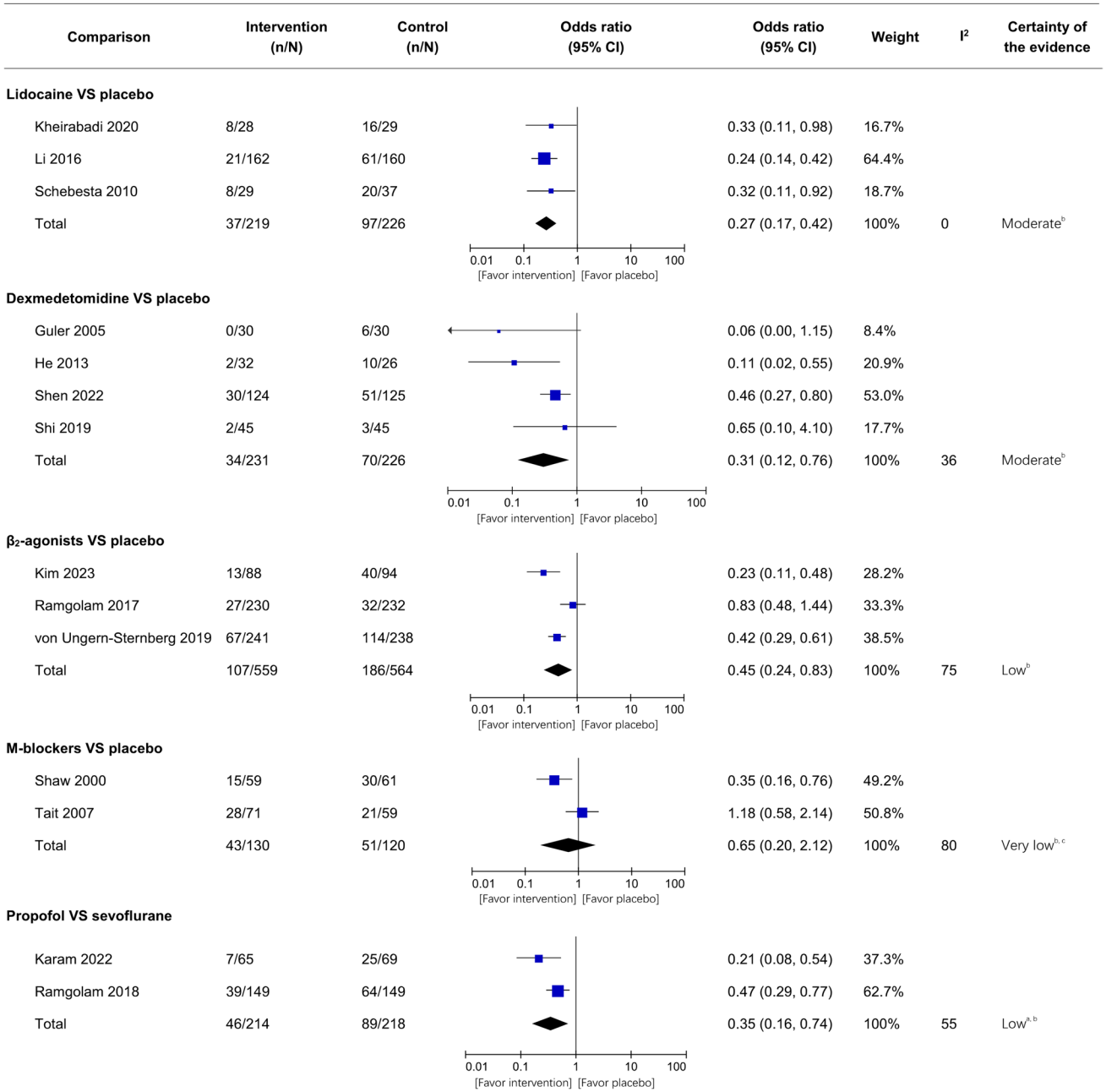

Fig. 2 Results of pairwise meta-analyses of included trials for overall perioperative respiratory adverse events. *β_2-agonists* β_2-adrenoreceptor agonists; *CI* confidence interval, *M-blockers* M-cholinoreceptor blockers. [a]: downgraded for risk of bias; [b]: downgraded for inconsistency; [c]:downgraded for imprecision

recruiting children younger than eight years old undergoing airway-related surgery showed beneficial effects, while the other recruiting six- to 16-year-old children undergoing general surgery showed negative results. It might imply that β_2-adrenoreceptor agonists benefited high-risk children of younger age or undergoing airway-related surgery.

Our study found that propofol induction technique was superior to sevoflurane in pediatric anesthesia, which

Comparison	Study	Intervention (n/N)	Control (n/N)	Odds ratio (95% CI)	Odds ratio (95% CI)	I^2	Certainty of the evidence
Laryngospasm							
Magnesium VS placebo	2	0/55	7/55		0.11 (0.01 , 0.95)	0	Low[c]
Propofol VS placebo	2	1/85	6/85		0.22 (0.04 , 1.35)	0	Low[c]
Dexmedetomidine VS placebo	7	5/311	14/306		0.31 (0.10 , 0.91)	0	Moderate[c]
Lidocaine VS placebo	7	20/428	52/428		0.38 (0.22 , 0.67)	0	Moderate[a]
β_2-agonists VS placebo	3	19/559	36/564		0.61 (0.20 , 1.85)	55	Low[b, c]
M-blockers VS placebo	2	10/130	5/120		1.97 (0.63 , 6.12)	0	Low[c]
Propofol VS sevoflurane	3	4/239	24/243		0.17 (0.06 , 0.48)	0	Moderate[a]
Bronchospasm				.1 1 10 [Favor intervention] [Favor placebo]			
β_2-agonists VS placebo	3	1/559	5/564		0.30 (0.05 , 1.95)	0	Low[b, c]
Dexmedetomidine VS placebo	6	1/266	1/261		1.00 (0.10 , 9.85)	0	Low[c]
Propofol VS sevoflurane	3	1/239	3/243		0.49 (0.06 , 3.86)	0	Very low[a, c]
Oxygen desaturation				.1 1 10 [Favor intervention] [Favor placebo]			
Dexmedetomidine VS placebo	8	43/349	69/345		0.54 (0.35 , 0.84)	0	Moderate[b]
β_2-agonists VS placebo	3	52/559	74/564		0.66 (0.45 , 0.98)	0	Moderate[b]
M-blockers VS placebo	2	38/130	36/120		1.02 (0.58 , 1.78)	0	Low[b, c]
Lidocaine VS placebo	4	106/609	64/609		1.21 (0.32 , 4.59)	90	Very low[a, b, c]
Propofol VS sevoflurane	3	29/239	49/243		0.49 (0.23 , 1.05)	31	Low[a, c]
Airway obstruction				.1 1 10 [Favor intervention] [Favor placebo]			
β_2-agonists VS placebo	3	34/559	70/564		0.44 (0.19 , 1.00)	66	Low[b, c]
Propofol VS sevoflurane	2	13/214	37/218		0.32 (0.17 , 0.63)	0	Moderate[a]
Coughing				.1 1 10 [Favor intervention] [Favor placebo]			
Dexmedetomidine VS placebo	8	68/349	95/345		0.24 (0.14 , 0.41)	0	Moderate[b]
β_2-agonists VS placebo	3	38/559	99/564		0.36 (0.13 , 0.95)	69	Low[b, c]
Lidocaine VS placebo	5	299/646	270/646		0.44 (0.12 , 1.57)	92	Very low[a, b, c]
M-blockers VS placebo	2	16/130	23/120		0.57 (0.28 , 1.17)	0	Low[b, c]
Propofol VS sevoflurane	3	30/239	62/243		0.39 (0.11 , 1.37)	72	Very low[a, b, c]
Stridor				.1 1 10 [Favor intervention] [Favor placebo]			
β_2-agonists VS placebo	3	15/559	17/564		0.85 (0.41 , 1.74)	0	Low[b, c]
				.1 1 10 [Favor intervention] [Favor placebo]			

Fig. 3 Results of pairwise meta-analyses of included trials for subtypes of perioperative respiratory adverse events. *β_2-agonists* β_2-adrenoreceptor agonists; *CI* confidence interval; *M-blockers* M-cholinoreceptor blockers. [a]: downgraded for risk of bias; [b]: downgraded for inconsistency; [c]: downgraded for imprecision

Table 3 Subgroup analyses on primary outcome overall PRAE

Comparison	Study	Intervention (n/N)	Control (n/N)	Weight (%)	Odds ratio (95% CI)	I^2
Type of surgery						
Lidocaine VS placebo	3	37/219	97/226	100	0.27 (0.17, 0.42)	0
Airway-related surgery[a]	1	8/28	16/29	16.7	0.33 (0.11, 0.98)	–
General surgery	2	29/129	81/197	83.3	0.26 (0.16, 0.42)	0
Dexmedetomidine VS placebo	4	34/231	70/226	100	0.31 (0.12, 0.76)	27.4
Airway-related surgery	3	32/199	60/200	79.1	0.45 (0.27, 0.75)	0
General surgery	1	2/32	10/26	20.9	0.11 (0.02, 0.55)	–
β_2-adrenoreceptor agonists VS placebo	3	107/559	186/564	100	0.45 (0.24, 0.83)	75.0
Airway-related surgery	2	80/329	154/332	66.7	0.34 (0.20, 0.59)	49
General surgery	1	27/230	32/232	33.3	0.83 (0.48, 1.44)	–
M-cholinoreceptor blockers VS placebo	2	43/130	51/120	100	0.65 (0.20, 2.12)	80
General surgery	2	43/130	51/120	100	0.65 (0.20, 2.12)	80
Propofol VS sevoflurane	2	46/214	89/218	100	0.35 (0.16, 0.74)	55
General surgery	2	46/214	89/218	100	0.35 (0.16, 0.74)	55
Administration routes						
Lidocaine VS placebo	3	37/219	97/226	100	0.27 (0.17, 0.42)	0
Intravenous	1	8/28	16/29	16.7	0.33 (0.11, 0.98)	–
Endotracheal	2	29/191	81/197	83.3	0.26 (0.16, 0.42)	0
Dexmedetomidine VS placebo	4	34/231	70/226	100	0.31 (0.12, 0.76)	27.4
Intravenous	3	4/107	19/101	47.0	0.19 (0.05, 0.76)	29
Intranasal	1	30/124	51/125	53.0	0.46 (0.27, 0.80)	–
β_2-adrenoreceptor agonists VS placebo	3	107/559	186/564	100	0.45 (0.24, 0.83)	75.0
Transdermal	1	13/88	40/94	28.2	0.23 (0.11, 0.48)	–
Inhalational	2	94/471	146/470	71.8	0.57 (0.29, 1.12)	75
M-cholinoreceptor blockers VS placebo	2	43/130	51/120	100	0.65 (0.20, 2.12)	80
Oral	1	15/59	30/61	49.2	0.35 (0.16, 0.76)	–
Intravenous	1	28/71	21/59	50.8	1.18 (0.58, 2.41)	–
Propofol VS sevoflurane	2	46/214	89/218	100	0.35 (0.16, 0.74)	55
Propofol (intravenous) sevoflurane (inhaled)	2	46/214	89/218	100	0.35 (0.16, 0.74)	55
Use of muscle relaxants						
Lidocaine VS placebo	3	37/219	97/226	100	0.27 (0.17, 0.42)	0
With muscle relaxants	2	29/190	77/189	81.3	0.26 (0.16, 0.42)	0
Without muscle relaxants	1	8/29	20/37	18.7	0.32 (0.11, 0.92)	–
Dexmedetomidine VS placebo	4	34/231	70/226	100	0.31 (0.12, 0.76)	36
With muscle relaxants	3	32/199	60/200	79.1	0.45 (0.27, 0.75)	0
Without muscle relaxants	1	2/32	10/26	20.9	0.11 (0.02, 0.55)	–
β_2-adrenoreceptor agonists VS placebo	3	107/559	186/564	100	0.45 (0.24, 0.83)	75.0
With muscle relaxants	1	13/88	40/94	28.2	0.23 (0.11, 0.48)	–
Without muscle relaxants	2	94/471	146/470	71.8	0.57 (0.29, 1.12)	75
M-cholinoreceptor blockers	2	43/130	51/120	100	0.65 (0.20, 2.12)	80
With muscle relaxants	1	15/59	30/61	49.2	0.35 (0.16, 0.76)	–
Without muscle relaxants	1	28/71	21/59	50.8	1.18 (0.58, 2.41)	–
Propofol VS sevoflurane	2	46/214	89/218	100	0.35 (0.16, 0.74)	55
Without muscle relaxants	2	46/214	89/218	100	0.35 (0.16, 0.74)	55
Phase of PRAE measurement						
Lidocaine VS placebo	3	37/219	97/226	100	0.27 (0.17, 0.42)	0
Perioperative	1	21/162	61/160	64.6	0.24 (0.14, 0.42)	–
Postoperative	2	16/57	36/66	35.4	0.32 (0.15, 0.69)	0
Dexmedetomidine VS placebo	4	34/231	70/226	100	0.31 (0.12, 0.76)	36

Table 3 (continued)

Comparison	Study	Intervention (n/N)	Control (n/N)	Weight (%)	Odds ratio (95% CI)	I^2
Perioperative	1	30/124	51/125	53	0.46 (0.27, 0.80)	–
Postoperative	3	4/107	19/101	47	0.19 (0.05, 0.76)	29
β_2-adrenoreceptor agonists VS placebo	3	107/559	186/564	100	0.45 (0.24, 0.83)	75.0
Perioperative	3	107/559	186/564	100	0.45 (0.24, 0.83)	75.0
M-cholinoreceptor blockers VS placebo	2	43/130	51/120	100	0.65 (0.20, 2.12)	80
Perioperative	1	28/71	21/59	50.8	1.18 (0.58, 2.41)	–
Postoperative	1	15/59	30/61	49.2	0.35 (0.16, 0.76)	–
Propofol VS sevoflurane	2	46/214	89/218	100	0.35 (0.16, 0.74)	55
Perioperative	1	39/149	64/149	62.7	0.47 (0.29, 0.77)	–
Postoperative	1	7/65	25/69	37.3	0.21 (0.08, 0.54)	–

CI confidence interval. –: Only one study was included in these subgroups, so I^2 was not estimated. [a]: Airway-related surgery was defined as surgery related to upper or lower respiratory tract, including cleft palate repair surgery, tonsillectomy and/or adenoidectomy, fiberoptic or rigid bronchoscopy

opposed the results from an earlier meta-analysis [44]. Two large-scale RCTs demonstrating protective effects of propofol induction technique dominated the results of our meta-analysis, one of which was not included in the earlier meta-analysis. This might explain why our meta-analysis showed opposite results from the previous one. Compared with inhalational induction, intravenous induction was thought to be less acceptable for children due to the distress and anxiety when establishing an intravenous line. Surprisingly, acceptability for intravenous induction was very high (greater than 95%) with the use of local anesthetic cream or accompany by their parents in the included studies. It highlighted the high feasibility of intravenous induction in children. Interestingly, when propofol was administrated as a bolus before emergency, its prophylactic effect on laryngospasm disappeared. It might imply that different timing of administration affected the efficacy of propofol against laryngeal reflexes.

These results should be interpreted carefully in light of their limitations. First, variation in definition of primary outcome PRAE posed a problem for evidence synthesis. To reduce the heterogeneity of the definition of PRAE, we defined it as a composite outcome including the major events (laryngospasm and bronchospasm) and at least two of the minor events (oxygen desaturation, airway obstruction, coughing or stridor), or at least including three of the six PRAE subtypes. We also used a random-effects model to reduce false positives and provide conservative estimates of treatment effects. Furthermore, the correlation of each complication within PRAE also had an impact on the results of our meta-analysis. For instance, laryngospasm or bronchospasm might clinically be correlated with oxygen desaturation. To address the problem, we evaluated the individual outcomes of PRAE subtypes in our study. Second, heterogeneity of the type of surgery, the use of premedication, administration routes of pharmacological agents, the use of muscle relaxants and phase of outcome measurement existed among the included RCTs. Therefore, we conducted subgroup and sensitivity analyses based on these factors. However, we should be cautious about the results of these post hoc analyses because type I error might be inflated in these exploratory analyses. Third, the quality of evidence in our meta-analysis was downgraded by risk of bias, inconsistency and imprecision. More high-quality research was needed to test the robustness of the results.

Our study indicated the prophylactic effects of lidocaine, dexmedetomidine, β_2-adrenoreceptor agonists and propofol induction technique against PRAE. The findings should be interpreted cautiously due to the inconsistent definition of PRAE and the correlation of each subtype within the composite outcome. Future high-quality research with standard definition for PRAE was needed to add to our understanding of their roles in pediatric anesthesia. Further investigation was also required to explore the optimal administration route, dosage, and timing of the prophylactic pharmacological interventions.

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Authors' contributions Qi-Wen Deng and Shi-Hong Wen: study conception and design, acquisition, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content. Wen-Cheng Tan and Ya-Qing Zhan: acquisition, analysis and interpretation of data, revising the article critically for important intellectual content. Xi-Wen Wang and Han-Jin Lai: acquisition, analysis and interpretation of data. All authors read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

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Data availability All datasets analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and consent to participate Not applicable.

Consent for publication Not applicable.

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