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ORIGINAL ARTICLE

Prophylaxis for paediatric emergence delirium in desflurane-based anaesthesia: a network meta-analysis

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Abstract

Purpose The prevalence of postoperative emergence delirium in paediatric patients (pedED) following desflurane anaesthesia is considerably high at 50–80%. Although several pharmacological prophylactic strategies have been introduced to reduce the risk of pedED, conclusive evidence about the superiority of these individual regimens is lacking. The aim of the current study was to assess the potential prophylactic effect and safety of individual pharmacotherapies in the prevention of pedED following desflurane anaesthesia.

Methods This frequentist model network meta-analysis (NMA) of randomized controlled trials (RCTs) included peer-reviewed RCTs of either placebo-controlled or active-controlled design in paediatric patients under desflurane anaesthesia.

Results Seven studies comprising 573 participants were included. Overall, the ketamine + propofol administration [odds ratio (OR) = 0.05, 95% confidence intervals (95%CIs) 0.01–0.33], dexmedetomidine alone (OR = 0.13, 95%CIs 0.05–0.31), and propofol administration (OR = 0.30, 95%CIs 0.10–0.91) were associated with a significantly lower incidence of pedED than the placebo/control groups. In addition, only gabapentin and dexmedetomidine were associated with a significantly higher improvement in the severity of emergence delirium than the placebo/control groups. Finally, the ketamine + propofol administration was associated with the lowest incidence of pedED, whereas gabapentin was associated with the lowest severity of pedED among all of the pharmacologic interventions studied.

Conclusions The current NMA showed that ketamine + propofol administration was associated with the lowest incidence of pedED among all of the pharmacologic interventions studied. Future large-scale trials to more fully elucidate the comparative benefits of different combination regimens are warranted.

Trial registration PROSPERO CRD42021285200.

Keywords Emergence delirium · Emergence agitation · Desflurane · Pediatric anesthesia · Network meta-analysis

Abbreviations

CI	Confidence interval
Dex	Dexmedetomidine
ES	Effect size
FeMi	Fentanyl + midazolam
Gab	Gabapentin
GABA	Gamma-aminobutyric acid
KeP	Ketamine + propofol
Mid	Midazolam
NMA	Network meta-analysis
OR	Odds ratio
pedED	Postoperative emergence delirium in pediatric population
Pla	Placebo/control
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
Pro	Propofol
RCT	Randomized controlled trial
SMD	Standardized mean difference
SUCRA	Surface under the cumulative ranking curve

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Introduction

The occurrence of postoperative emergence delirium in paediatric participants (pedED) was one of the complications in paediatric surgery. Several potentially underlying aetiology regarding the occurrence of pedED had been explored. The residual anesthetics might be related to the pedED [1]. There had been debate regarding the selection of sevoflurane versus desflurane in pedED prevention [2]. Desflurane might be potentially related to less pedED because of its shorter recovery time and elimination time than sevoflurane [3–5]. However, the incidence of pedED following desflurane anaesthesia has been reported to be as high as 50–80% [6, 7], and this limits its usage in clinical practice [8]. Importantly, pedED may cause patients to fall or injure themselves and thus require additional treatment with analgesics and/or sedatives [9]. Therefore, the prevention of pedED has become an important issue in paediatric anaesthesiology.

The physiopathology of pedED remains unclear. Previous research has hypothesized that pre-operative anxiety and the rapid increase in pain sensation are possible causes of pedED [2]. Based on this hypothesis, several randomized controlled trials (RCTs) using analgesics, anxiolytics, or sedatives as pedED prophylaxis have been conducted. Recently, one huge network meta-analysis (NMA) of 70 RCTs had revealed that most combination therapies with midazolam or antiemetics were superior to monotherapies for delirium prophylaxis in pediatric patients undergoing sevoflurane anesthesia [10]. However, these trends could not be found in those RCTs in pediatric patients undergoing desflurane anaesthesia. One of these trials showed that children undergoing strabismus surgery and receiving dexmedetomidine exhibited significantly lower pedED than those who did not receive the dexmedetomidine (12.8% versus 74.5%, $p < 0.001$) [11], and another showed that desflurane anaesthesia with dexmedetomidine resulted in significantly lower pedED in children undergoing infra-umbilical surgery than in those who did not receive the dexmedetomidine (9.4% versus 40.6%, $p = 0.030$) [12]. In contrast, no significant differences in the prophylactic effects on pedED were reported with midazolam [8] or fentanyl [2] compared to placebo/control groups.

In addition to the inconclusive evidence relating to the prophylactic effects on pedED with analgesics, anxiolytics, and sedatives under desflurane anaesthesia, evidence about the superiority of these regimens in relation to their prophylactic effect is also lacking. To date, no meta-analysis or network meta-analysis (NMA) has compared the prophylactic effect of pharmacologic regimens on pedED. Therefore, we conducted this study to compare the relative prophylactic effects of various pharmacologic regimens to prevent pedED under desflurane anaesthesia using an NMA, with the goal of providing more detailed evidence-based information to guide clinical practice [13]. The primary aim was to compare the incidence of pedED, and the secondary aim was to compare the severity of pedED with different pharmacologic regimens under desflurane anaesthesia in paediatric patients.

Methods

General guidelines applied in the current study

The study protocol of this NMA had been registered in PROSPERO (CRD42021285200). The current NMA followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guideline (eTable 1) [14] and AMSTAR2 appraisal tool [15]. The current study complies for the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-109-29).

Search strategy and selection criteria

We conducted a systematic review of publications retrieved from PubMed, Embase, ProQuest, ScienceDirect, Cochrane CENTRAL, ClinicalKey, Web of Science, and ClinicalTrials.gov, and the first search was performed on October 21st, 2022 (eTable 2). No language restriction or restrictions on publication type were applied. To avoid missing the eligible studies, we manually searched the reference lists of relevant review articles or meta-analyses.

Inclusion and exclusion criteria

Following the PICO design, we searched for (1) participant: paediatric patients (age under 18 years undergoing desflurane general anesthesia; (2) intervention: pharmacological interventions applied during general anesthesia with desflurane; (3) comparator: placebo-controlled or active-controlled; and (4) outcome: the incidence of emergence delirium after desflurane anaesthesia. We only included peer-reviewed RCTs of either placebo-controlled or active-controlled design in paediatric patients under desflurane anaesthesia. The definition of paediatric was age under 18. If there is any RCT providing information of the presence or absence of delirium but not the severity of delirium, this study would be also included in this analysis. The targets of comparison arms were defined as pharmacologic interventions applied in paediatric patients scheduled to receive general anaesthesia with desflurane. Therefore, the inclusion criteria were as follows: (1) RCTs in paediatric patients (i.e. < 18 years old), (2) trials investigating different pharmacologic interventions applied in paediatric patients who were scheduled to receive general anaesthesia with desflurane; (3) trials with target outcome of incidence of pedED; (4) either

placebo-controlled or active-controlled design, and (5) trials undergoing general anaesthesia with desflurane.

The exclusion criteria were as follows: (1) studies that were not RCTs, (2) those in which the incidence or ***severity of pedED was not reported, (3) those not related to pharmacologic interventions targeted at the risk of developing pedED, and (4) not receiving desflurane anaesthesia. In cases of duplicate data (i.e., different articles based on the same sample sources), we only included the reports with more information and larger sample sources.

Data extraction

Two authors independently screened the studies, extracted relevant data from the articles, and assessed the risk of bias among the included studies. In cases of discrepancy, another corresponding author was involved. If there was a lack of available data from the manuscripts, we contacted the corresponding authors or co-authors to obtain the original data. We followed the flowchart reported in previous NMAs.

Outcomes

The primary outcome was the incidence of pedED with different prophylactic regimens. The secondary outcome was changes in the severity of pedED following the investigated interventions. Specifically, pedED was evaluated according to the Pediatric Anesthesia Emergence Delirium (PAED) scale, Emergence Agitation Scales, Aono's four-point scale score (AFPS), and Davis's three-point scale. Because there is currently no consensus on the cut-off points for the incidence of pedED, the cut-off points varied among the included RCTs. The safety profiles included the following two outcomes: time to extubation and time to leave the post-anaesthesia care unit. In addition, because of the presumed few RCTs to be included, we did not strictly limit our target RCTs to be "set incidence of pedED as their primary outcome". Therefore, any RCTs providing information regarding the incidence of pedED, either as their primary outcome or secondary outcome, could be included in the current NMA.

Cochrane risk of bias tool

We evaluated the quality of included studies according to previous NMAs published in *Lancet* [16, 17]. To be specific, two independent authors evaluated the risk of bias (interrater reliability, 0.86) for each domain described in the Cochrane risk of bias tool [18].

Statistical analysis

The NMA was performed using STATA version 16.0 (StataCorp LLC Statistics/Data Analysis StataCorp, TX, 77845 USA). For continuous data, we calculated the summary standardized mean difference (SMD) with 95% confidence intervals (95%CIs). For categorical data, we estimated summary odds ratio (OR) with 95%CIs. For categorical data, we used 0.5 zero-cell correction during the meta-analysis procedure. However, if there was zero in both intervention and control arms in one study, we did not apply this correction procedure because of the risk of increasing bias [19]. We used frequentist models of NMA to compare the effect sizes among studies with the same interventions. All comparisons were made with a two-tailed test, and a p value cut-off point of 0.05 was taken to indicate statistical significance. Heterogeneity among the included studies was evaluated using the tau value, which was calculated as the estimated standard deviation of the effect across the included studies.

Regarding the meta-analysis procedure, we used mixed comparisons with generalized linear mixed models to perform the direct and indirect comparisons for the NMA [20]. Specifically, indirect comparisons were calculated by transitivity, through which differences between treatment A and B could be calculated from their comparisons with the third treatment, C. For comparisons among multiple treatment arms, we combined the direct and indirect evidence from the included studies [21]. In this NMA, we used a suite of Stata programs using *mvmeta* for data manipulation [22]. We used the restricted maximum likelihood method to evaluate the between-study variance [23].

To increase the clinical applicability, we calculated the relative ranking probabilities between the preventive effects of all treatments for the target outcomes. In brief, the surface under the cumulative ranking curve (SUCRA) is the percentage of the mean rank of each pharmacology intervention relative to an imaginary intervention that is the best without uncertainty [24]. Finally, we evaluated potential inconsistency between the direct and indirect evidence within the network using the loop-specific approach and local inconsistency using the node-splitting method. Further, we used a design-by-treatment model to evaluate the global inconsistency among the whole NMA [25]. We used comparison-adjusted funnel plots [26] and Egger regression to evaluate the potentially small study effects and publication bias. To reduce the potential heterogeneity, we further arrange subgroup analysis focusing on the timing of the pharmacology administration. To be specific, we arrange subgroup analysis of "administration during surgery" and "administration prior to induction of anesthesia".

Results

Eligibility of retrieved studies and treatment arms

After the initial screening procedure, a total of 103 articles were considered for full-text review (Fig. 1), of which 96 were excluded for various reasons (see Fig. 1 and eTable 3). Finally, seven articles were included in the current study (Table 1) [2, 8, 11, 12, 27–29]. The whole geometric distribution of the treatment arms is provided in Fig. 2A–B.

Characteristics of the included studies

A total of 573 children (the average of "mean age" in the included RCTs was 4.4 years, range = 3.0–5.3 years; the average of "female proportion" in the included RCTs was 45.6%, range = 20.6–71.9%) were included. The baseline conditions of these children included the following: (a) children scheduled for elective infra-umbilical surgery; (b) children scheduled for elective strabismus surgery; and (c) children scheduled for adenotonsillectomy. The mean follow-up duration of pedED was 32.9 min (range = 30–40 min). Although we set the age limitation as "under 18 years old" in our inclusion criteria, all the included studies select their participants age ranging 1–9 years old (Table 1).

Primary outcome: incidence of emergence delirium

The ketamine + propofol administration (KeP) (OR = 0.05, 95%CIs 0.01–0.33), dexmedetomidine alone (OR = 0.13, 95%CIs 0.05–0.31) and propofol administration (OR = 0.30, 95%CIs 0.10–0.91) were associated with a significantly lower incidence of pedED than the placebo/control groups after desflurane anesthesia (Table 2, Fig. 2A, and Fig. 3A). According to the SUCRA, KeP was associated with the lowest incidence of pedED among all of the pharmacologic interventions, followed by dexmedetomidine (eTable 4A). In addition, there had been no significant heterogeneity detected according to the tau value and corresponding *p* value (eTable 8).

In the subgroup of "administration during surgery", only the dexmedetomidine alone (OR = 0.21, 95%CIs 0.09–0.48), midazolam (OR = 0.27, 95%CIs 0.07–1.00), and propofol administration (OR = 0.33, 95%CIs 0.14–0.78) were associated with a significantly lower incidence of pedED than the placebo/control groups after desflurane anesthesia (eFig. 1C and 2C), whereas in the subgroup of "administration prior to induction of anesthesia", the network structure could not be connected because of too few RCTs. Therefore, the analysis of subgroup of "administration prior to induction of anesthesia" could not be performed.

Secondary outcome: severity of emergence delirium

Overall, only gabapentin (SMD = − 0.64, 95%CIs − 1.13 to − 0.15) and dexmedetomidine (SMD = − 0.61, 95%CIs − 0.91 to − 0.31) were associated with a significantly higher improvement in the severity of emergence delirium compared to the placebo/control groups (Figs. 2B, 3B and Table 3). According to the SUCRA, gabapentin was associated with the lowest severity of pedED among all of the pharmacologic interventions, followed by dexmedetomidine (eTable 4B).

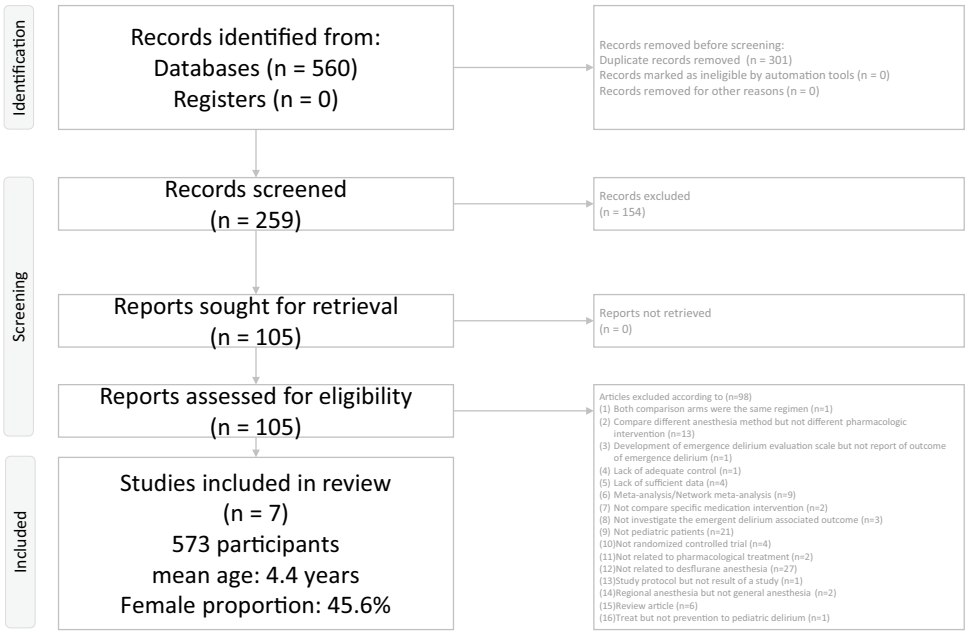

Fig. 1 The flowchart of the current network meta-analysis. Figure 1 depicts the whole flowchart of the current network meta-analysis

Table 1 Characteristics of the included studies

Study	Baseline illness	pedED tool/time/criteria	Time of prescription	Route	Comparison	Subject	Mean age	Female %	Follow up	Country
Badawy (2018) [1]	2–6 years old, with an ASA physical status I–II who were undergoing strabismus surgery	Emergence agitation scale/in PACU/emergence agitation scale grade at least 4	1 h before the start of anesthesia and operation	Oral solution	Gabapentin (5 mg/kg) Placebo	33 34	3.7 ± 1.4 4.2 ± 1.2	27.3 20.6	30 min	Egypt
Makkar (2016) [2]	Aged between 2 and 8 years, of ASA physical status 1 or 2 and scheduled for elective infraumbilical surgery	Pediatric anesthesia emergence delirium scale/recorded every 5 min after the removal of the laryngeal mask/at least 10 scores	15 min before the end of surgery	Intravenous	Dexmedetomidine (0.3 μg/kg) Propofol (1 mg/kg) Placebo	32 36 32	5.0 4.8 3.0	37.5 38.9 40.6	30 min	India
Song (2016) [3]	ASA class I pediatric patients, aged 2–6 years, undergoing elective strabismus surgery	Pediatric anesthesia emergence delirium scale/in PACU/at least 10 scores	During anesthesia in the operation	Intravenous	Dexmedetomidine (0.25–1.0 μg/kg) Placebo	84 28	4.5 ± 1.5 3.8 ± 1.5	47.6 50.0	n/m	Republic of Korea
Kim (2014) [4]	Aged 1–5 years, ASA I–II, undergoing strabismus surgery	Pediatric anesthesia emergence delirium scale/recorded every 10 min in PACU/more than 11 scores	During anesthesia in the operation	Intravenous	Fentanyl (1 μg/kg) Fentanyl + dexmedetomidine (1 μg/kg)/(0.2 μg/kg)	47 47	4.3 ± 1.0 4.3 ± 1.4	44.7 61.7	40 min	Republic of Korea
Demirbilek (2004)* [5],	Age 2–7 years, ASA status I, scheduled for adenoidectomy and/or tonsillectomy	Agitation score/in recovery room/at least 3 scores	During anesthesia in the operation	Intravenous	Fentanyl + midazolam (2.5 μg/kg)/(0.5 mg/kg) Midazolam (0.5 mg/kg)	30 30	5.3 ± 1.5 5.2 ± 1.4	36.7 40.0	30 min	Turkey
Kararmaz, A. (2004)[6]	aged 3–6 years, ASA I and II, undergoing adenotonsillectomy with/without bilateral myringotomy and insertion of tubes	5-point agitation score/in recovery room/at least 4 scores	30 min before the induction of anesthesia	Oral solution for ketamine / intravenous for propofol	Ketamine + propofol (6 mg/kg) / (2–3 mg/kg) Placebo + propofol (2–3 mg/kg)	39 32	4.2 ± 0.9 4.4 ± 0.7	64.1 71.9	n/m	Turkey

Table 1 (continued)

Study	Baseline illness	pedED tool/time/criteria	Time of prescription	Route	Comparison	Subject	Mean age	Female %	Follow up	Country
Cohen (2002) [7]	Children aged 2–9 years, ASA status I or II, undergoing adenotonsillectomy with or without bilateral myringotomy and insertion of tubes	Agitation score/in the PACU/at least 3 scores	During anesthesia in the operation	Intravenous	Midazolam (0.1 mg/kg) Propofol (2 mg/kg) Control	24 22 23	4.6 ± 1.8 5.0 ± 2.2 5.2 ± 1.9	37.5 50.0 47.8	n/m	USA

*In this study, the authors totally had four arms of intervention, including sevoflurane, sevoflurane + fentanyl, desflurane, and desflurane + fentanyl. We selected the groups with desflurane anesthesia (i.e. the groups of desflurane, and desflurane + fentanyl)

ASA American Society of Anesthesiologists; *min* minutes; *n/m* not mentioned; *PACU* post-anesthesia care unit; *pedED* postoperative emergence delirium in pediatric population

Fig. 2 The network structure of (**A**) the overall incidence of emergence delirium with the investigated interventions, and (**B**) overall severity of emergence delirium with the investigated interventions. **A** and **B** depicts the overall network structure of the current network meta-analysis. The lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the size of the population involved in each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network

Safety profile: aspect of time to extubation

Overall, fentanyl *plus* midazolam (FeMi) (SMD = 1.75, 95%CIs 0.88–2.61), oral midazolam (SMD = 1.13, 95%CIs 0.45–1.80), KeP (SMD = 0.94, 95%CIs 0.07–1.80), propofol administration (SMD = 0.85, 95%CIs 0.16–1.54), and gabapentin (SMD = 0.76, 95%CIs 0.26–1.26) but not dexmedetomidine (SMD = 0.27, 95%CIs − 0.14 to 0.68) were associated with a significantly longer time to extubation compared to the placebo/control groups (eFigs. 1A, 2A and eTable 5A). According to the SUCRA, FeMi was associated with the longest time to extubation (eTable 4C).

Table 2 League table of the prophylactic effect of postoperative emergence delirium in pediatric population following desflurane anesthesia: aspect of postoperative emergence delirium incidence rate

KeP				***0.17 (0.06, 0.50)**		
0.41 (0.06, 2.91)	Dex			0.64 (0.14, 2.93)		***0.12 (0.05, 0.33)**
0.28 (0.01, 5.08)	0.68 (0.05, 9.23)	FeMi	0.72 (0.15, 3.55)			
0.20 (0.02, 1.83)	0.49 (0.08, 2.96)	0.72 (0.11, 4.78)	Mid	0.68 (0.16, 2.94)		0.31 (0.08, 1.21)
***0.17 (0.04, 0.75)**	0.42 (0.11, 1.53)	0.62 (0.05, 7.57)	0.85 (0.16, 4.44)	Pro		***0.32 (0.13, 0.76)**
0.13 (0.01, 1.38)	0.33 (0.06, 1.76)	0.48 (0.03, 8.49)	0.67 (0.08, 5.77)	0.79 (0.13, 4.77)	Gab	0.39 (0.14, 1.05)
***0.05 (0.01, 0.33)**	***0.13 (0.05, 0.31)**	0.19 (0.02, 2.24)	0.26 (0.05, 1.30)	***0.30 (0.10, 0.91)**	0.39 (0.09, 1.61)	Pla

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of the incidence rate of postoperative emergence delirium. Interventions are reported in order of mean ranking of the prophylactic effect, and outcomes are expressed as odds ratio (OR) (95% confidence intervals). For the pairwise meta-analyses, an OR of less than 1 indicated that the treatment specified in the row had a stronger prophylactic effect than that specified in the column. For the network meta-analysis (NMA), an OR of less than 1 indicated that the treatment specified in the column had a stronger prophylactic effect than that specified in the row. Bold results marked with * indicate statistical significance

CI confidence interval; *Dex* dexmedetomidine; *ES* effect size; *FeMi* fentanyl + midazolam; *Gab* gabapentin; *GABA* gamma-aminobutyric acid; *Mid* midazolam; *KeP* ketamine + propofol; *NMA* network meta-analysis; *OR* odds ratio; *pedED* postoperative emergence delirium in pediatric population; *Pla* placebo/control; *PRISMA* preferred reporting items for systematic reviews and meta-analyses; *Pro* propofol; *RCT* randomized controlled trial; *SMD* standardized mean difference; *SUCRA* surface under the cumulative ranking curve

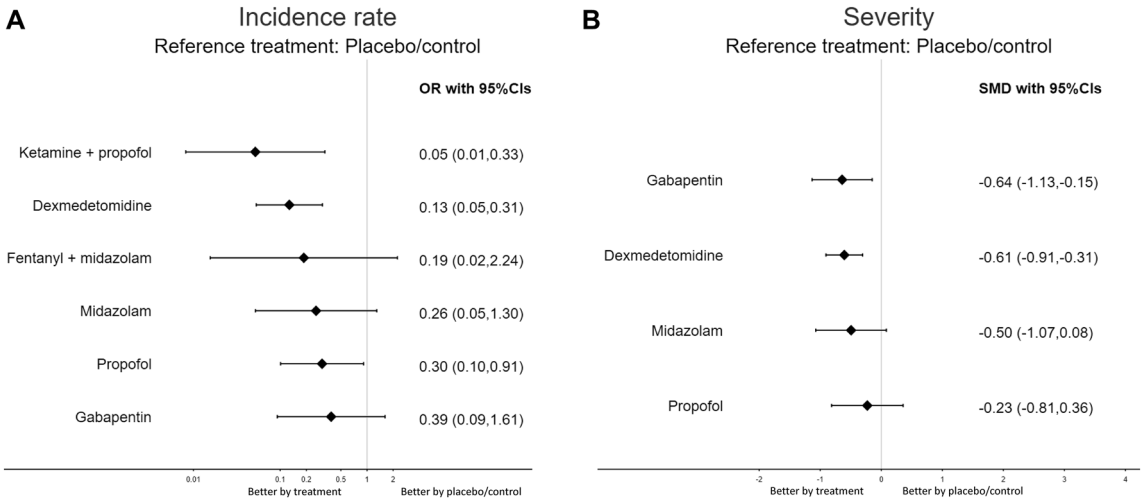

Fig. 3 Forest plot of (**A**) the overall incidence of emergence delirium with the investigated interventions, and (**B**) overall severity of emergence delirium with the investigated interventions. **A** and **B** indicate that, **A** when the effect size (presented as OR) < 1, the incidence of emergence delirium with a specific intervention was lower compared to the placebo/control groups; **B** when the effect size (presented as SMD) < 0, the severity of emergence delirium with a specific intervention was compared to the placebo/control groups

Safety profile: aspect of time to leave the post-anaesthesia care unit

Overall, none of the investigated regimens were associated with a significantly different time to leave the post-anaesthesia care unit compared to the placebo/control groups (eFigs. 1B, 2B and eTable 5B). According to the SUCRA, KeP was associated with the shortest time to leave the post-anaesthesia care unit (SMD = − 0.28, 95%CIs − 1.92 to 1.37 compared to the placebo/control groups) (eTable 4D).

Risk of bias and publication bias

We found that 67.3% (33/49 items), 28.6% (14/49 items), and 4.1% (2/49 items) of the included studies had an overall low, unclear, and high risk of bias, respectively. The vague reporting of randomization procedures or blindness of the studies further contributed to the risk of bias (eFigs. 3A, B). Funnel plots of publication bias across the included studies (eFig. 4A–D) revealed general symmetry, and the results of Egger's test indicated no significant asymmetry that might suggest publication bias among the articles included in the

Table 3 League table of the prophylactic effect of postoperative emergence delirium in pediatric population following desflurane anesthesia: aspect of postoperative emergence delirium severity

Gab				***– 0.64 (– 1.13, – 0.15)**
– 0.03 (– 0.61, 0.54)	Dex			***– 0.61 (– 0.91, – 0.31)**
– 0.15 (– 0.91, 0.61)	– 0.11 (– 0.76, 0.54)	Mid	– 0.27 (– 0.85, 0.31)	– 0.50 (– 1.07, 0.08)
– 0.41 (– 1.18, 0.35)	– 0.38 (– 1.04, 0.28)	– 0.27 (– 0.85, 0.31)	Pro	– 0.23 (– 0.82, 0.36)
***– 0.64 (– 1.13, – 0.15)**	***– 0.61 (– 0.91, -0.31)**	– 0.50 (– 1.07, 0.08)	– 0.23 (– 0.81, 0.36)	Pla

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of the changes of severity of postoperative emergence delirium. Interventions are reported in order of mean ranking of the prophylactic effect, and outcomes are expressed as standardized mean difference (SMD) (95% confidence intervals). For the pairwise meta-analyses, an SMD of less than 0 indicated that the treatment specified in the row had a stronger improvement than that specified in the column. For the network meta-analysis (NMA), an SMD of less than 0 indicated that the treatment specified in the column had a stronger improvement than that specified in the row. Bold results marked with * indicate statistical significance

CI confidence interval; *Dex* dexmedetomidine; *ES* effect size; *FeMi* fentanyl + midazolam; *Gab* gabapentin; *GABA* gamma-aminobutyric acid; *Mid* midazolam; *KeP* ketamine + propofol; *NMA* network meta-analysis; *OR* odds ratio; *pedED* postoperative emergence delirium in pediatric population; *Pla* placebo/control; *PRISMA* preferred reporting items for systematic reviews and meta-analyses; *Pro* propofol; *RCT* randomized controlled trial; *SMD* standardized mean difference; *SUCRA* surface under the cumulative ranking curve

NMA. In general, inconsistency, concerning either local inconsistency as assessed using the loop-specific approach and the node-splitting method or global inconsistency as determined using the design-by-treatment method, was not demonstrated in this NMA (eTable 6–7).

Discussion

To the best of our knowledge, this is the first NMA to address the prophylactic efficacy of individual pharmacotherapy for post-anaesthesia emergence delirium in children under desflurane anaesthesia. The results of the NMA demonstrated that KeP was associated with the lowest incidence of pedED among all of the pharmacologic interventions, followed by dexmedetomidine, whereas gabapentin was associated with the lowest severity of pedED among all of the pharmacologic interventions, followed by dexmedetomidine. However, most of the pharmacologic interventions were associated with a significantly longer time to extubation than in the placebo/control groups.

The most important finding of the current NMA is that oral ketamine plus intravenous propofol was associated with the lowest incidence of pedED among all of the pharmacologic interventions. In the previous NMA of pedED prevention under sevoflurane anaesthesia, the regimens which consisted of ketamine could exert significantly superior preventive effect compared to placebo [10]. Similar findings could be found in the RCT under desflurane anaesthesia [28]. The potentially beneficial effect to reduce pedED might be derived from the sedative and analgesic effect by ketamine and its metabolite, norketamine [30]. However, the major concern of the administration of ketamine was its psychomimetic side effects of "drawback phenomenon". This potential risk could be minimized by lowering its dosage to 6 mg/kg [28]. Further, the additional oral ketamine/intravenous propofol into inhalation desflurane might also serve as another kind of "combined anesthesia", which might be associated with increased complication. Although, in the original RCT of this combination [28], there was only increased nystagmus and vomiting but not any serious adverse events related to ketamine use, the clinicians still need pay special attention when applied ketamine in their clinical practice.

Secondly, the dexmedetomidine alone was associated with the second lowest incidence of pedED and second lowest severity of pedED among all of the pharmacologic interventions. Similar to previous RCTs, the current NMA addressed the efficacy of dexmedetomidine in the prevention of pedED [11, 12, 29]. Dexmedetomidine is an agonist with high affinity to the alpha2-adrenergic receptor, and it exerts sedative, analgesic and anxiolytic effects [11, 12]. A previous NMA demonstrated the prophylactic effects of dexmedetomidine on pedED in children under sevoflurane anaesthesia, with an OR of 0.19 (95%CIs 0.14–0.27) compared to placebo groups [31]. In the current NMA, dexmedetomidine was associated with a prophylactic effect on pedED in children under desflurane anaesthesia with an OR of 0.13 (95%CIs 0.05–0.31) compared to placebo groups, which is similar to that reported for sevoflurane anaesthesia. Furthermore, the current NMA demonstrated that dexmedetomidine was not associated with a significantly different time to extubation (SMD = 0.27, 95%CIs − 0.14 to 0.68) or time to leave the post-anaesthesia care unit (SMD = 0.20, 95%CIs − 0.49 to 0.90) compared to the placebo/control groups. This finding is consistent with the safety profiles reported in previous RCTs. Specifically, there was no significant difference in the incidence of postoperative respiratory complications between the dexmedetomidine and control groups [11]. Furthermore,

only minimal coughing and mild laryngospasms were observed after removing the laryngeal mask [12]. Finally, with regards to desaturation after anaesthesia, there was no significantly difference in the incidence of postoperative desaturation between the dexmedetomidine and control groups, and these desaturation events could be resolved by encouragement to breathe [29]. Given the current evidence, dexmedetomidine could be considered to be a potential prophylactic regimen for pedED in children under desflurane anaesthesia.

The third finding of the current NMA is that gabapentin was associated with the lowest severity of pedED among all of the pharmacologic interventions. Gabapentin is a gamma-aminobutyric acid (GABA) analogue that can bind to voltage-gated calcium channels [32]. Through inhibiting the release of excitatory neurotransmitters, gabapentin has shown effectiveness in the management of preoperative anxiety, agitation, postoperative pain, postoperative delirium and nausea and vomiting in paediatric settings [33, 34]. Although the results of the secondary outcome (changes in the severity of pedED with gabapentin) achieved statistical significance (SMD = − 0.64, 95%CIs − 1.13 to − 0.15 compared to the placebo), the results of the NMA of the primary outcome (incidence of pedED) did not achieve statistical significance. This may be due to the small sample sizes of the gabapentin groups. In the original RCT of gabapentin [27], the authors suggested that gabapentin resulted in a significantly lower incidence of pedED compared to the control group ($p = 0.03$). Further, although gabapentin was associated with a significantly longer time to extubation than the placebo/control groups (SMD = 0.76, 95%CIs 0.26–1.26) in the current NMA, the general safety profile of gabapentin in the original RCT of gabapentin was acceptable, and there was no statistical difference in the incidence of postoperative nausea and vomiting between the gabapentin and control groups [27]. Therefore, future large-scale RCTs addressing the potential efficacy of gabapentin in preventing pedED are warranted to validate the results of the current NMA.

Finally, among all the included RCTs, the evaluation of incidence of pedED was token in the post-anesthesia care unit or in the recovery room. However, although the desflurane had a shorter recovery time and elimination time than other inhaling anesthetics [3–5], if the pedED occurs in a later stage, such as in the ordinary ward, these pedED events will not be counted in. Therefore, for the future clinical research regarding the safety of desflurane anesthesia, it should take the complication in the ward into consideration. In addition, there had been no conclusive evidence regarding the superiority, timing, and frequency of individual pedED rating scales. Therefore, different ratings might result in different incidence of pedED. We would recommend future clinical research to achieve a widely acceptable consensus regarding the selection of pedED rating scale.

There are several limitations to this NMA that need to be considered. First, the NMA may be affected by the heterogeneous characteristics of the participants (e.g., baseline diseases, different surgery received, ethnic background, and trial duration), small number of trials for some treatment arms, and heterogeneity in pedED assessment tools. Second, as the network structure was weakened, there was no direct evidence about comparisons between some of the treatment arms. Third, although there had not been significant inconsistency (eTable 6) or heterogeneity (eTable 8) detected within the current network meta-analysis, there might still be some potential heterogeneity to be addressed. To be specific, within the treatment arm of Propofol, two RCTs provided data of the propofol administration to prevent pedED [8, 12]. However, in the study by Makkar, J.K. (2016) [12], the authors applied a single intravenous bolus of propofol 1 mg/kg five minutes before the end of surgery; rather, in the study by Cohen, I.T. (2002) [8], they administered a single intravenous bolus of propofol 2 mg/kg in the beginning. Therefore, the clinicians should pay special attention when apply the propofol during the desflurane anaesthesia, especially the timing and dosage of administration under different anaesthesia situation [35, 36]. Fourth, in the previous studies, there were inconclusive evidences about the potentially beneficial effect by the additive dexmedetomidine to paediatric patients receiving total intravenous anaesthesia. However, currently, the available evidences mainly focused on other anaesthesic agents (for example, propofol) rather than desflurane [37, 38] so that the current NMA did not include such studies. Finally, not all of the included RCTs used a placebo as their control groups.

Conclusion

The results of this NMA demonstrated that KeP was associated with the lowest incidence of pedED among all of the pharmacologic interventions, followed by dexmedetomidine; whereas gabapentin was associated with the lowest severity of pedED among all of the pharmacologic interventions, followed by dexmedetomidine. However, most of the pharmacologic interventions were associated with a significantly longer time to extubation compared to the placebo/control groups. Future large-scale RCTs are warranted to validate our results.

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Author contributions HCK contributed as the first author and took the whole responsibility of manuscript drafting and data analysis. KCH contributed as the first author and study design, concept formation, data analysis, and drafting manuscript. HYW contributed as the first author and concept formation, manuscript revision, data validataion, data extraction, visualization, and manuscript drafting. BSZ contributed as

the first author and took the whole responsibility of data extraction, data analysis, data approval, and manuscript drafting. TYC contributed in study design, concept formation, data extraction, and data analysis. DJL contributed in concept formation, method design, literature screen and selection. PYL contributed in data curation, data analysis, statitical process, and manuscript revision. KPS contributed in study design, data analysis, validation of data, and visualization. MHC contributed in concept formation, literature screen/selection, supervision of data extraction, and validation. AFC contributed in data curation and validation, visualization, and manuscript revision. BS contributed in concept formation, literature screen, and data extraction. YKT contributed in data analysis, data validation, data analysis, and supervision. YCW contributed in data analysis, visualization, manuscript revision, and data validatation. MR contributed in concept formation, study design, literature screen and selection. LS contributed in study design, manuscript revision, and data validation. SPH contributed in manuscript revision, supervision, and data extraction. YWC contributed in data analysis, data extraction, analysis process, and manuscript revision. PYY contributed in concept formation, study design, and manuscript revision. CWH contributed equally as the corresponding author and manuscript revision, data extraction, data analysis, and manuscript submission. PTT contributed equally as the corresponding author and manuscript revision, data analysis, data collection, and manuscript submission. MWS contributed equally as the corresponding author and manuscript revision, data analysis, data collection, and manuscript submission.

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Availability of data and materials All the data of the current study were available upon reasonable request to the corresponding authors.

Declarations

Conflict of interest Authors declare that they have no conflict of interest.

Ethical approval and consent to participate The current study complies for the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-105-12). The current study did not direct involve individual participant so that we did not have the chance to approach individual participant or explore individual participant's information. Therefore, it would be impossible to obtain Consent to Participate in the current study.

Consent for publication The current study did not direct involve individual participant so that we did not have the chance to approach individual participant or explore individual participant's information. Therefore, it would be impossible to obtain Consent to Publish in the current study.

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