Association of pharmacological prophylaxis with the risk of pediatric emergence delirium after sevoflurane anesthesia: An updated network meta-analysis

Running title: NMA of delirium prevention

Hung-Yu Wang[1], Tien-Yu Chen[2,3], Dian-Jeng Li [4], Pao-Yen Lin[5,6], Kuan-Pin Su[7,8,9,10], Min-Hsien Chiang[11], Andre F. Carvalho [12,13], Brendon Stubbs[7,14,15], Yu-Kang Tu [16,17], Yi-Cheng Wu[18], Michael Roerecke[19], Lee Smith[20], Ping-Tao Tseng[21,22,23,*], Kuo-Chuan Hung[24,*]

[1] Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Kaohsiung City, Taiwan

[2] Department of Psychiatry, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei, Taiwan

[3] Institute of Brain Science, National Yang Ming Chiao Tung University, Taipei, Taiwan

[4] Department of Addiction Science, Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Kaohsiung City, Taiwan

[5] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

[6] Institute for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital

[7] Department of Psychological Medicine, Institute of Psychiatry, Psychology and

Neuroscience, King's College London, London, UK

[8] Department of Psychiatry & Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan

[9] College of Medicine, China Medical University, Taichung, Taiwan

[10] An-Nan Hospital, China Medical University, Tainan, Taiwan

[11] Department of Anesthesiology, Shin Huey Shin Hospital, Kaohsiung, Taiwan

[12] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

[13] Centre for Addiction & Mental Health (CAMH), Toronto, Ontario, Canada

[14] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, UK

[15] Positive Ageing Research Institute (PARI), Faculty of Health, Social Care Medicine and Education, Anglia Ruskin University, Chelmsford, UK

[16] Institute of Epidemiology & Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

[17] Department of Dentistry, National Taiwan University Hospital, Taipei, Taiwan

[18] Department of Sports Medicine, Landseed International Hospital, Taoyuan, Taiwan

[19] Independent Scientist, Institute for Mental Health Policy Research, PAHO/WHO Collaborating Centre for Addiction and Mental Health, Centre for Addiction and Mental Health (CAMH),

Dalla Lana School of Public Health (DLSPH), University of Toronto, Canada

[20] The Cambridge Center for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK

[21] Prospect Clinic for Otorhinolaryngology & Neurology, Kaohsiung City, Taiwan

[22] Institute of Biomedical Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan

[23] Department of Psychology, College of Medical and Health Science, Asia University, Taichung, Taiwan

[24] Department of Anesthesiology, Chi Mei Medical Center, Tainan, Taiwan

*: contributed equally as corresponding author

*** Please corresponding to:**

Ping-Tao Tseng

Prospect Clinic for Otorhinolaryngology & Neurology, Kaohsiung City, Taiwan

No. 252, Nanzixin Road, Nanzi District, Kaohsiung City 81166, Taiwan

Tel: +886-7-3524100

Email: ducktseng@gmail.com

OR

Kuo-Chuan Hung

Department of Anesthesiology, Chi Mei Medical Center, Tainan, Taiwan

No. 901, Zhonghua Road, Yongkang District, Tainan City 710, Taiwan

Tel: +886-6-2812811

Email: ed102605@gmail.com

Abstract

Study Objective: This updated network meta-analysis aims at exploring whether the concurrent use of midazolam or antiemetics may enhance the efficacy of other pharmacological regimens for delirium prophylaxis in pediatric population after general anesthesia (GA).

Design: network meta-analysis (PROSPERO registration: CRD42020179483)

Setting: Postoperative recovery area.

Patients: Pediatric patients undergoing GA with sevoflurane

Interventions: Pharmacological interventions applied during GA with sevoflurane

Measurements: This network meta-analysis of randomized controlled trials (RCTs) was conducted with a frequentist model. PubMed, Embase, ProQuest, ScienceDirect, Cochrane CENTRAL, ClinicalKey, Web of Science, and ClinicalTrials.gov were searched from their inception dates to April 12, 2020, for RCTs of either placebo-controlled or active-controlled design containing information on the incidence of emergence delirium in pediatric patients undergoing sevoflurane anesthesia.

Main Results: Seventy studies comprising 6,904 participants were included for the analysis of 30 pharmacological interventions. Based on surface under the cumulative ranking curve (SUCRA) analysis, midazolam was ranked the lowest in therapeutic effect (SUCRA: 20%), while antiemetics as a monotherapy had no effect on delirium prophylaxis. However, there was a trend that most combination therapies with midazolam or antiemetics were superior to monotherapies for delirium prophylaxis. Subgroup analyses based on age (i.e., ≤7 years) and a validated scoring system (i.e., the Pediatric Anesthesia Emergence Delirium scale) for delirium also suggested a better efficacy of combination therapies than monotherapies. Overall, combination therapies with midazolam or antiemetics did not have a negative impact on the

incidence of postoperative nausea and vomiting, length of stay in the postanesthesia care unit, or time to extubation. The dexmedetomidine-midazolam-antiemetic combination was the most effective strategy for the prevention of emergence delirium.

Conclusions: This network meta-analysis suggested that the incorporation of midazolam or antiemetics as adjuncts for combination therapies may have synergistic effects against pediatric postoperative emergence delirium. Future large-scale placebo-controlled RCTs are warranted to validate our findings.

Keywords*: combination therapy; emergence delirium; network meta-analysis; pediatric anesthesia; sevoflurane*

1. INTRODUCTION

Sevoflurane is a commonly used agent for the induction and maintenance of anesthesia, but its use is associated with the occurrence of postoperative emergence delirium in the pediatric population [1]. Postoperative emergence delirium has an incidence ranging from 25% to 80% [2, 3] and is characterized by hallucination, thrashing, nonpurposeful restlessness, crying, and disorientation [4]. Its occurrence in the postanesthesia care unit (PACU) may carry the risk of self-injury, delayed hospital discharge, and increased medical expenditure (e.g., extra nursing care) [5]. A number of factors have been reported that may predispose pediatric patients to the occurrence of emergence delirium, including pain, rapid emergence, preoperative anxiety, young age, and a suboptimal physiological condition [6]. Therefore, the consensus-based guideline on postoperative delirium from the European Society of Anaesthesiology (ESA) emphasizes the importance of risk factor assessment, monitoring, and preventive and treatment measures for emergence delirium [7].

Previous randomized control trials (RCTs) have demonstrated potential synergistic effects of combination therapies on the prevention of emergence delirium [8-10]. Although midazolam premedication and antiemetics (e.g., dexamethasone) have been shown to have an impact on the incidence of emergence delirium [10, 11], a number of previous RCTs that have included midazolam or antiemetics in their intraoperative medical regimens [10, 12-15] did not address the possible synergistic effects of combination therapies. Therefore, the efficacy of pharmacological interventions based on the information of those RCTs may have been incorrectly estimated in a previous NMA [11]. Contrary to the potential beneficial effects, there have been concerns that the use of midazolam may prolong emergence time [16, 17]

and delay patient recovery [18]. To address the hypotheses that combined regimens may be more effective than monotherapies for prophylaxis against emergence delirium and that an association may exist between the use of combined regimens and a delayed recovery, this current NMA was primarily aimed at evaluating the efficacies of various monotherapies and combination therapies through a comprehensive review of the currently available clinical evidence. We also performed analyses to differentiate the impacts on the recovery characteristics between monotherapies and combined regimens.

2. Materials and Methods

2.1. General guideline and registration

The current NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 guideline (eTable 1) [19] and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) guidelines [20] and was registered at PROSPERO (CRD42020179483).

2.2. Research 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 from their inception dates to April 12, 2020. Articles were searched with the following keywords: "pediatric anesthesia", "combination therapy", "sevoflurane", "ancillary drug", "propofol", "ketamine", "dexmedetomidine", "delirium", "agitation", "midazolam", "clonidine", "fentanyl", "remifentanil", "antiemetic drugs", "sufentanil", "melatonin", “randomized control trial (RCT)”, and their synonyms. No language restrictions or publication dates were applied. We also conducted manual searches for potentially eligible articles from the reference lists of review articles or pairwise meta-analysis [11, 21-28].

2.3. Inclusion and exclusion criteria

The PICO applied in the current NMA was as follows: (1) patient or problem: pediatric patients (age under 18 years old) undergoing general anesthesia with sevoflurane; (2) intervention: pharmacological interventions applied during general anesthesia with sevoflurane; (3) comparator: placebo-controlled or active-controlled; and

(4) outcome: the incidence of emergence delirium after sevoflurane anesthesia. Of the three commonly used inhalational anesthetics for children (i.e., desflurane, sevoflurane, and isoflurane), sevoflurane is the most frequently used. To reduce the heterogeneity of included articles, we included only peer-reviewed and formally published RCTs of either placebo-controlled or active-controlled designs in pediatric patients undergoing sevoflurane anesthesia. The targets of the comparison arms were set to include pharmacological interventions applied in pediatric patients scheduled to receive general anesthesia with sevoflurane.

The exclusion criteria consisted of (1) studies that were not randomized controlled trials, (2) those in which the incidence of emergence delirium was not reported, (3) those not related to pharmacological interventions targeted at the risk of emergence delirium, or (4) those involving patients not subjected to sevoflurane anesthesia. In the situation of duplicated usage of data (i.e., different articles based on the same sample sources), we included only the reports with more information and larger sample sizes.

2.4. Data extraction

Two authors (HY Wang and PT Tseng) independently examined the studies, extracted relevant data from the articles, and evaluated the risk of bias among the included studies. When discrepancies were encountered, the corresponding author (KC Hung) was also involved. If there was a lack of available data from the manuscripts, we contacted the corresponding authors or coauthors to obtain the original data. We followed the flowchart reported in a previous NMA [29-32].

2.5. Outcomes

The primary outcome was the incidence of emergence delirium after the administration of sevoflurane anesthesia and different prophylactic regimens, while the secondary outcomes included recovery characteristics, namely, the incidence of postoperative nausea and vomiting (PONV), length of PACU stay, and time to extubation, as reported in most of the RCTs included in this study. The diagnosis of emergence delirium was based on the criteria that individual studies applied [e.g., the Pediatric Anesthesia Emergence Delirium scale (PAEDS), the Watcha scale, Emergence Behavior scales, Aono's four-point scale score, Cole's five-point scale, and Davis's three-point scale]. For the analysis of the length of PACU stay, we included only studies adopting the Aldrete score or its modified versions in the criteria for discharge from the PACU. In addition, we included the incidence of PONV as one of the secondary outcomes, taking into account the possible prophylactic action of antiemetics against delirium independent of their known effects (i.e., the suppression of nausea/vomiting) as well as the concern that certain anesthetics (e.g., fentanyl) may be associated with an increased risk of PONV.

The incidence of emergence delirium is influenced by patient characteristics (e.g., young age) or diagnostic criteria [6]. In addition, effective pain control is vital for the accurate diagnosis of emergence delirium [6, 7]. To minimize bias, we performed subgroup analyses on three prespecified subgroups. The first subgroup included only studies on patients aged ≤ 7 years. The second subgroup included only studies using a validated scoring system [i.e., the Pediatric Anesthesia Emergence Delirium scale (PAEDS)] in the diagnostic criteria. The third subgroup comprised only trials in which (a) the patient age was ≤ 7 years, (b) the PAEDS score was used as a diagnostic criterion, and (c) surgical patients with specific information regarding intraoperative pain control or

nonsurgical patients (e.g., those receiving general anesthesia for painless procedures [i.e., MRI]) were included.

2.6. Node definition and treatment arm selection

For the present NMA, studies on the same pharmacological intervention were merged into one group regardless of the dosage or route of administration with the exception of melatonin, of which the dosage has been shown to have a physiological impact on the incidence of delirium in adult patients [31]. In addition, we studied the impact of dosage on the median incidence of emergence delirium for the most commonly used agent(s) in the included trials with subgroup analysis if the agent(s) showed a significant dose-dependent effect on the primary outcome. To investigate the potential impacts of concurrent use of intraoperative midazolam or antiemetic drugs, studies involving the use of such medications were regarded as “combination therapies” and categorized into different treatment arms. For the present study, we used the term “-based” (e.g., "propofol-based", "fentanyl-based") to describe an anesthetic regimen to denote the role of a drug as a prophylactic agent against emergence delirium rather than referring to its being used as the main anesthetic for a procedure.

2.7. Assessment of risk of bias of the included studies

Two authors (HY Wang and PT Tseng) independently evaluated the risk of bias (interrater reliability, 0.85) for each domain described in the Cochrane risk of bias tool [33]. Disagreements were resolved by discussion. The overall risk of bias of all studies and the risk of bias of individual studies were analyzed. We rated the potential risk of bias by applying a rating of “low”, “high,” or “unclear” to each trial.

2.8. Statistical analysis

The NMA was performed using STATA version 16.0 (StataCorp LLC Statistics/Data Analysis StataCorp, Texas, USA). For continuous data, we computed the summary mean difference (MD) with 95% confidence intervals (CIs). For categorical data, we estimated the summary odds ratio (OR) with 95% CIs and applied a 0.5 zero-cell correction during the process of meta-analysis. However, if, in one study, there were zero values in both the intervention arm and the control arm, we did not apply such a correction procedure because of the risk of increasing bias [34, 35]. We used frequentist models of NMA to compare the affected sizes (ESs) among studies with the same interventions. All comparisons were made with a two-tailed t-test with a *p*-value cutoff point set at 0.05 to denote statistical significance. The heterogeneity among the included studies was evaluated by the tau value, which is the estimated standard deviation of the effect across the included studies.

Regarding the procedure of meta-analysis applied in the current study, we used a mixed comparison with generalized linear mixed models to analyze the direct and indirect comparisons for the NMA [36]. For comparisons among multiple treatment arms, we combined the direct and indirect evidence from the included studies [37]. For the current NMA, a suite of Stata programs using mvmeta for data manipulation was utilized [38]. We used the restricted maximum likelihood method to evaluate the between-study variance [39].

To provide more clinical application, we calculated the relative ranking probabilities between the preventive effects of all treatments for the target outcomes. In brief, surface under the cumulative ranking curve (SUCRA) analysis is the percentage method used for

ranking each pharmacology intervention [40]. The larger the area under the curve, the higher the rank of effectiveness of an intervention against emergence delirium.

Finally, we evaluated the potential inconsistency between the direct and indirect evidence within the network with the loop-specific approach and local inconsistency with the node-splitting method. Furthermore, we used the design-by-treatment model to evaluate the global inconsistency among the whole NMA [41]. We used the comparison-adjusted funnel plot [42] and Egger regression to evaluate the potential small study effects and publication bias.

3. Results

3.1. Eligibility of retrieved studies and treatment arms

Figure 1 is the flow diagram that summarizes the reasons for study exclusion. Of a total of 5,871 eligible records retrieved from the database search, 4,137 were removed because of duplications. Another 1,591 records were then excluded after initial screening of the titles and abstracts. Of the 143 articles considered for full-text review (Figure 1), 73 were excluded for various reasons (see Figure 1 and eTable 2). Finally, 70 articles were included in the current study (eTable 3)[3, 4, 8, 9, 12-18, 43-100]. As the network for some pharmacological interventions was poorly connected, only sixty-two articles with thirty individual pharmacological intervention arms were investigated in the current NMA. The whole geometric distribution of the treatment arms is provided in Figure 2.

3.2. Characteristics of the included studies

A total of 6,904 children (age range: 1.0 to 9.5 years; female 39.5%, range: 0.0% to 70.0%) with different health conditions were covered in the studies, including children scheduled for (1) elective oral surgery; (2) diagnostic intervention under sevoflurane anesthesia [i.e., MRI]; (3) elective abdominal surgery; and (4) elective ophthalmic surgery (eTable 3). Regarding the impact of drug dosage on study outcomes, an assessment of the impact of the dosage of a wide variety of pharmacological agents in the included studies on their efficacies against emergence delirium was infeasible in the current NMA. Dexmedetomidine was the most commonly studied drug in the included trials (28 out of 62 trials, 45.2%) [12, 14, 15, 51, 53, 57, 59, 60, 65, 68-72, 74, 78, 83-87, 89, 90, 93-96, 100], with a loading dose ranging from 0.15 μg/kg to 2.5 μg/kg with or without continuous infusion. By dividing the loading dose into <1 μg/kg and ≥1 μg/kg,

the median incidence of emergence delirium was found to be 12.9% in patients receiving a bolus dose of <1 μg/kg and 10.6% in those receiving a bolus dose of ≥1 μg/kg (eTable 4A). Because of the small difference in the incidence of emergence delirium together with the existence of other possible confounders in those studies (e.g., discrepancies in diagnostic criteria and the age of patients) that may bias the results, subgroup analysis on dosage was also not performed for dexmedetomidine.

Of the 26 studies mentioning perioperative use of midazolam, 22 used midazolam as a premedication and four administered midazolam before the end of surgery (eTable 4B). The routes of administration were oral (18 trials; range of dosage: 0.2 to 0.5 mg/kg), intravenous (six trials; range of dosage: 0.03 to 0.1 mg/kg), and nasal (two trial; dosage: 0.2 mg/kg). Of the 26 studies, 16 (61.5%) used an oral dose of 0.5 mg/kg. For antiemetics, dexamethasone was administered as a single antiemetic (7 trials) [12, 14, 15, 49, 70, 82, 89] or combined with other antiemetics (4 trials) [46, 51, 65, 95]. Another three trials [80, 84, 86] used tropisetron as a single antiemetic. Subgroup analysis based on the mechanism of action of antiemetics was not performed either because of their combined use or due to the small number of studies (e.g., tropisetron as a single antiemetic in three trials).

3.3. Primary outcome: Incidence of emergency delirium following monotherapies or combination therapies

The results of SUCRA analysis (eTable 5A) showed that the majority of the pharmacological interventions were associated with a significantly lower incidence of emergence delirium compared to that in the placebo/control groups. Among all the pharmacological interventions, the dexmedetomidine/midazolam/antiemetic combination was associated with the lowest incidence of emergence delirium,

followed by the midazolam/propofol/antiemetic combination. Some prophylactic regimens, such as tramadol/antiemetic or antiemetic monotherapies, were not associated with a decreased incidence of emergence delirium compared to that in the placebo/control groups (Table 1 and Figure 3). Among monotherapies, high-dose melatonin (i.e., 0.4 mg/kg) ranked highest in effectiveness for preventing emergence delirium, followed by nalbuphine.

Based on SUCRA analysis, most combination therapies showed a higher cumulative ranking probability than monotherapies, suggesting a trend of the superiority of the former to the latter (eTable 5A). In addition, the use of antiemetics or midazolam appeared to improve the efficacy of other pharmacological interventions (e.g., SUCRA for dexmedetomidine-based interventions: dexmedetomidine: 38.7%; dexmedetomidine/antiemetics: 59%; and dexmedetomidine/midazolam/antiemetics: 92.3%). Similar findings were also noted for propofol-based interventions (i.e., propofol: 38.9%; propofol/midazolam: 55.7%; propofol/midazolam/antiemetic drugs: 85.1%) or fentanyl-based interventions (i.e., fentanyl: 35.5%; fentanyl/midazolam: 63.8%; fentanyl/propofol/midazolam: 75.4%).

SUCRA analysis of the results from the age subgroup analysis revealed a superior efficacy of the combined regimen clonidine/midazolam to that of other monotherapies (eFigure 1A; eFigure 2A; eTable 5B; eTable 6A), while data from the PAEDS criteria subgroup analysis demonstrated that ketamine/midazolam was more effective than other monotherapies (eFigure 1B; eFigure 2B; eTable 5C; eTable 6B). Overall, the findings supported a better efficacy of combined regimens than of monotherapies (e.g., clonidine/midazolam vs. clonidine). On the other hand, although SUCRA analysis also assigned the highest rank to a combined regimen (i.e.,

midazolam/hydroxyzine) for the third subgroup (i.e., age ≤7 years, PAEDS criteria, positive pain control), only seven regimens were available for comparison (eFigure 1C; eFigure 2C; eTable 5D; eTable 6 C).

3.4. Secondary outcomes: Recovery characteristics

Our results showed that most pharmacological interventions did not have a significant impact on the risks of PONV, length of PACU stay, or time to extubation (eFigure 3A-C and eFigure 4A-C). SUCRA analysis of the incidence of PONV, length of PACU stay, and time to extubation in the intervention arms are shown in eTable 7A-C and eTable 8A-C, respectively. The use of clonidine/midazolam combination or dexmedetomidine monotherapy decreased the risk of PONV, while the use of fentanyl was associated with a significantly higher incidence of PONV than that in the placebo group (eFigure 3A; eFigure 4A; eTable7A; eTable 8A). The use of dexmedetomidine [MD = 1.28 minutes (95% CIs: 0.21 to 2.34)] or dexmedetomidine/midazolam combination [MD = 6.22 minutes (95% CIs: 0.72 to 11.72)] statistically prolonged the time to extubation compared to that in the placebo group despite the probable lack of clinical significance of this finding (eFigure 3C; eFigure 4C; eTable 7C; eTable 8 C). Similarly, the use of dexmedetomidine monotherapy was correlated with a statistically significant but clinically nonsignificant prolonged PACU stay [MD = 6.68 minutes (95% CIs: 6.68 to 11.71)] compared to that in the placebo group (eFigure 3B; eFigure 4B; eTable 7B; eTable 8 B). Interestingly, only the tramadol/antiemetics regimen was associated with a significantly shorter PACU stay [MD = -28.13 minutes (95% CIs: -54.15 to -2.12)] than placebo.

3.5. Risk of bias and publication bias

We found that 86.7% (425/490 items), 5.1% (25/490 items), and 8.2% (40/490 items) of the included studies had overall low, unclear, and high risks of bias, respectively. Vague reporting with “allocation concealment” or “incomplete outcome data” was the main reason for such bias (eFigures 5A-5B).

Funnel plots of publication bias across the included studies (eFigure 6A; 6C; 6E; 6G; 6I) revealed general symmetry, and the results of Egger’s test indicated no significant asymmetry, which might suggest publication bias among the articles included in the present NMA (eFigure 6B; 6D; 6F; 6H; 6J). In general, the examination of local inconsistency with the loop-specific approach and the node-splitting method as well as global inconsistency with the design-by-treatment method demonstrated no significant inconsistency in the present NMA (eTable 9-10).

4. DISCUSSION

As each anesthetic adjunct has a unique benefit and unwanted side effects [101], the choice of optimal monotherapy may be difficult. By analyzing all available RCTs with the inclusion of midazolam and antiemetics in our treatment arms, we investigated the efficacy and recovery characteristics of various pharmacological interventions (i.e., up to 30 intervention strategies) with a systematic approach. We found that most combination therapies were superior to monotherapies in the prevention of emergence delirium. For dexmedetomidine- or propofol-based regimens, triple combinations with concurrent use of midazolam/antiemetics were superior to dual combinations, followed by monotherapies. These findings may suggest a trend that concomitant use of midazolam or antiemetics may enhance the efficacy of other commonly used anesthetic adjuncts to prevent emergence delirium. Furthermore, combination therapies with midazolam or antiemetics did not significantly increase the incidence of PONV, length of PACU stay, or time to extubation at the doses used in the studies that we included. Since the majority of studies on midazolam (16 out of 26, 61.5%) used an oral dose of 0.5 mg/kg, our findings implied that such an oral dose may not be associated with a prolonged PACU stay and time to extubation, taking into account a probable dose-dependent relationship. Current international guidelines on the management of emergence delirium recommend the prophylactic use of midazolam, dexmedetomidine, or propofol during pediatric anesthesia [7] without considering the potentially beneficial effects of combination therapies. The findings of our NMA further showed that combination therapies, especially those with the inclusion of midazolam and antiemetics, may be feasible strategies to optimize patient care.

As perioperative anxiety is a predictor of emergence delirium in the PACU, midazolam premedication is commonly used during pediatric anesthesia to alleviate emotional stress [24, 64, 75]. In addition to its anxiolytic and sedative properties, the use of midazolam has been reported to significantly decrease analgesic requirements [101] and prevent PONV [102, 103]. Moreover, the use of midazolam did not increase the extubation time, emergency time, or duration of PACU stay at the dose used in certain studies [101], highlighting its possible lack of adverse effects on patient recovery. Our study further suggests a trend that combination therapies with the incorporation of midazolam may be superior to monotherapies in the prevention of emergence delirium, underscoring that midazolam may enhance the prophylactic effect of other anesthetic adjuncts at the doses used in the included studies. It should be noted that midazolam monotherapy had a low efficacy against emergence delirium based on SUCRA analysis (cumulative ranking probability for midazolam: 20%). This finding was consistent with that of a previous meta-analysis [104]. Therefore, concurrent use of midazolam with other drugs, rather than its administration as monotherapy, may be a feasible choice for clinicians.

Although combination therapies with midazolam did not significantly increase the length of PACU stay or time to extubation at the doses used in the studies that we included. There are still some concerns about the impact of midazolam on recovery from anesthesia. Because the onset of action and the duration of action of oral midazolam are 10-20 minutes and 60-90 minutes, respectively, with a bioavailability in children of about 36% [105], a previous study reported that oral premedication with midazolam delays early recovery (e.g., awake from general anesthesia) after a short procedure (i.e., mean time of 13 minutes)[106]. Therefore, despite the benefi of

midazolam in the prevention of emergence delirium, it may still affect patient recovery from short procedures.

As antiemetics, ondansetron or tropisetron (i.e., 5-HT_3 antagonists) have been successfully used in the treatment of postcardiotomy delirium in adults [107] or as a prophylactic agent against emergence delirium without prolonging PACU stay [80]. In the current NMA, we found that the use of antiemetics as monotherapies did not reduce the risk of emergence delirium compared to placebo [OR = 0.31 (95% CIs: 0.09 to 1.05)]. Interestingly, the incorporation of antiemetics into other regimens seemed to improve the prophylactic efficacies of the latter against emergence delirium (e.g., the SUCRA for dexmedetomidine/antiemetics and dexmedetomidine was 59% and 38.7%, respectively). On the other hand, because our results demonstrated no significant difference in the incidence of PONV between antiemetics (both as monotherapies or as components of combined treatments) and placebos, the findings may imply that the mechanism underlying the synergic effect of antiemetics may be independent of their established actions of preventing nausea/vomiting. Therefore, our results based on indirect evidence suggested that antiemetics could be routinely used as an adjunct for combination therapies during pediatric sevoflurane anesthesia. Further RCTs are warranted to support our findings.

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesized primarily by the pineal gland. Despite its hypnotic effects, whether it is as effective as midazolam for reducing preoperative anxiety remains controversial [75, 108]. Consistent with the results of a previous study showing a direct dose-dependent prophylactic effect against emergence delirium after sevoflurane anesthesia [75], our NMA demonstrated the effectiveness of high-dose melatonin (i.e., 0.4 mg/kg or 0.2

mg/kg) rather than lower doses (i.e., 0.05 mg/kg or 0.1 mg/kg) for preventing emergence delirium compared to placebo. Furthermore, we found that 0.4 mg/kg melatonin was significantly better than other monotherapies for prophylaxis against emergence delirium. The hypnotic effects and the unique role of melatonin in the treatment of sleep-wake dysregulation [109] may contribute to this finding. Consistently, a recent NMA found that melatoninergic agents are effective and safe for delirium prevention in adults [31]. Based on our findings and those of others, melatonin 0.4 mg/kg may be recommended as an intervention strategy in clinical practice. However, the impact of high-dose melatonin on the length of PACU stay and time to extubation could not be investigated in the current NMA because related outcomes were unavailable in the included studies. Further studies are required to address this issue. Moreover, the possibility of additional or synergistic effects when melatonin is combined with midazolam or antiemetics as a prophylactic regimen remains to be elucidated in further large-scale and placebo-controlled RCTs.

Dexmedetomidine is a highly selective alpha-2 agonist that acts on the brain, peripheral nervous system, and spinal cord [110]. As a highly selective alpha-2 agonist[110], dexmedetomidine has anxiolytic, sedative, and analgesic properties and is the preferred anesthetic adjunct in the prevention of emergence delirium during sevoflurane anesthesia [11]. ESA guidelines recommend the use of alpha-2 agonists (e.g., dexmedetomidine or clonidine) for prophylaxis against emergence delirium [7]. For dexmedetomidine-based regimens in our NMA, the cumulative ranking probability was highest for dexmedetomidine/midazolam/antiemetics (SUCRA: 92.3%), followed by dexmedetomidine/antiemetics (SUCRA: 59%) and dexmedetomidine (SUCRA: 38.7%). These findings suggest a trend of enhancement of the prophylactic effects of dexmedetomidine when combined with midazolam

and/or antiemetics, especially in triple combination. Our results may support the clinical application of dexmedetomidine/midazolam/antiemetics as a pharmacological strategy for patients undergoing high-risk surgeries. Compared with the finding of a previous meta-analysis [11], our study results imply that the efficacy of dexmedetomidine may be overestimated in that study.

Several limitations need to be considered for accurate interpretation of the findings of the present NMA. First, the heterogeneity in the characteristics of the participants (e.g., age) and surgical procedures as well as the use of different scoring systems for emergence delirium may bias the results. Indeed, it has been reported that the prevalence of emergence delirium in children varies widely from 25% to 80%, depending on the scoring system used [111]. Although we addressed this issue by subgroup analyses, the limited numbers of pharmacological regimens available for analysis in each subgroup precluded a robust conclusion. Second, evidence that supported the benefit of some anesthetic adjuncts (e.g., nalbuphine or melatonin) and the synergistic effects of midazolam or antiemetics was derived from only a limited number of RCTs, so there was insufficient direct evidence acquired from comparisons among different treatment arms to reinforce the overall findings of the present NMA. Third, the comparative efficacy of these anesthetic adjuncts reflected by the incidence of emergence delirium after non-sevoflurane anesthesia was not evaluated because of a limited number of available RCTs. Fourth, the relative efficacy of the antiemetics in the current study remains unknown because we considered all antiemetics to be a single category without subdividing them into different subgroups according to their mechanisms of action. Fifth, the potential therapeutic benefits of nonpharmacological interventions were not assessed. Finally, the exclusion of some RCTs because of their

poor connections with other studies for network comparison may also bias our findings.

In conclusion, by comprehensively and systematically reviewing the updated information on various pharmacological interventions (i.e., up to 30 intervention strategies), our results showed that a triple combination intervention with dexmedetomidine, midazolam, and antiemetics was the best pharmacological strategy for preventing postoperative emergence delirium in pediatric patients receiving sevoflurane anesthesia. The findings of the current network meta-analysis also suggested a trend that most combination therapies may be superior to monotherapies for delirium prophylaxis, without a negative impact on patient recovery. Despite the promising outcomes, future large-scale placebo-controlled RCTs are warranted to validate our findings.

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FIGURE LEGENDS

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

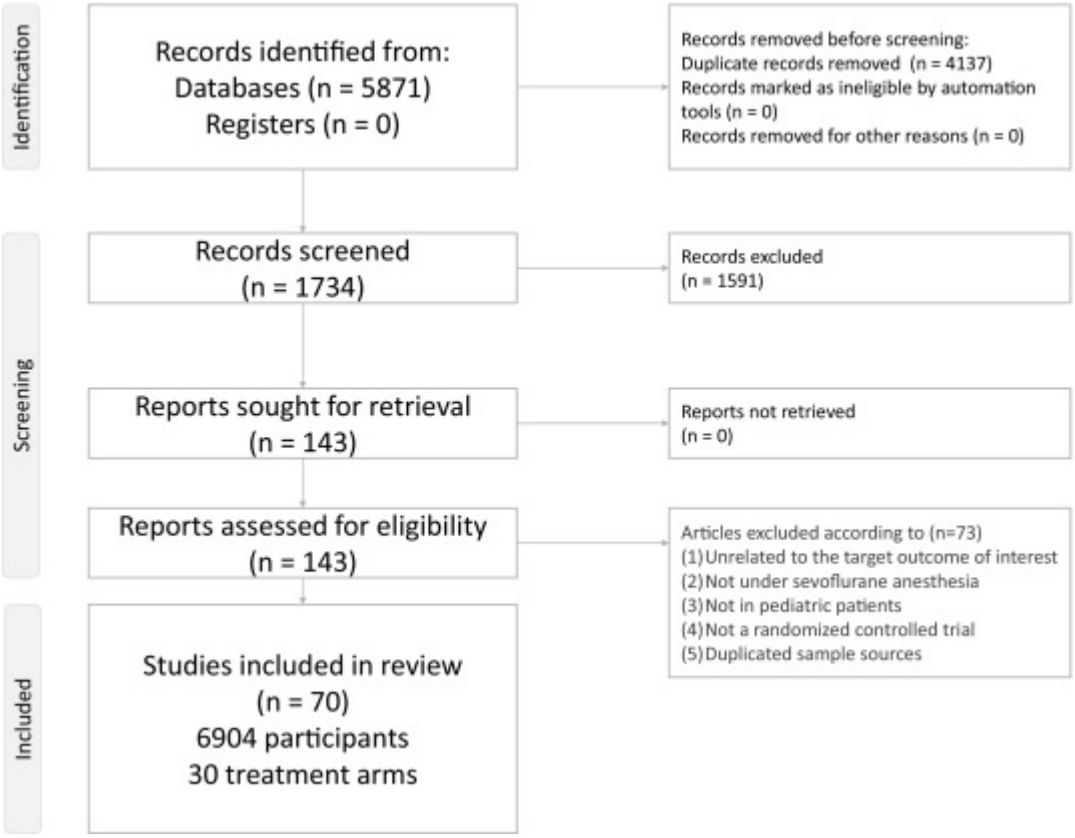


Figure 2. The network structure of the included trials on intraoperative pharmacological interventions for the prevention of emergence delirium. The lines between nodes represent direct comparisons among various regimens, and the size of each circle is proportional to the size of the population involved in each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network.

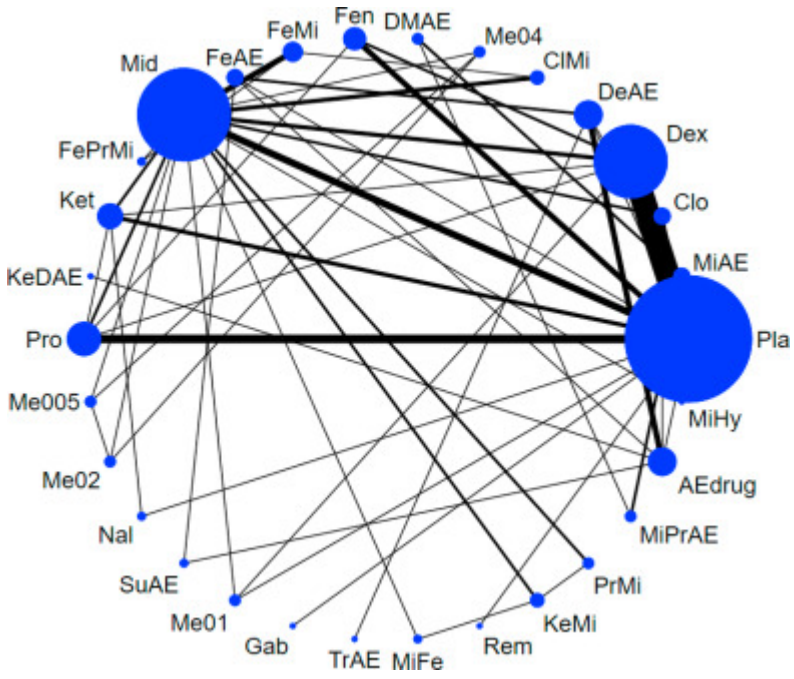
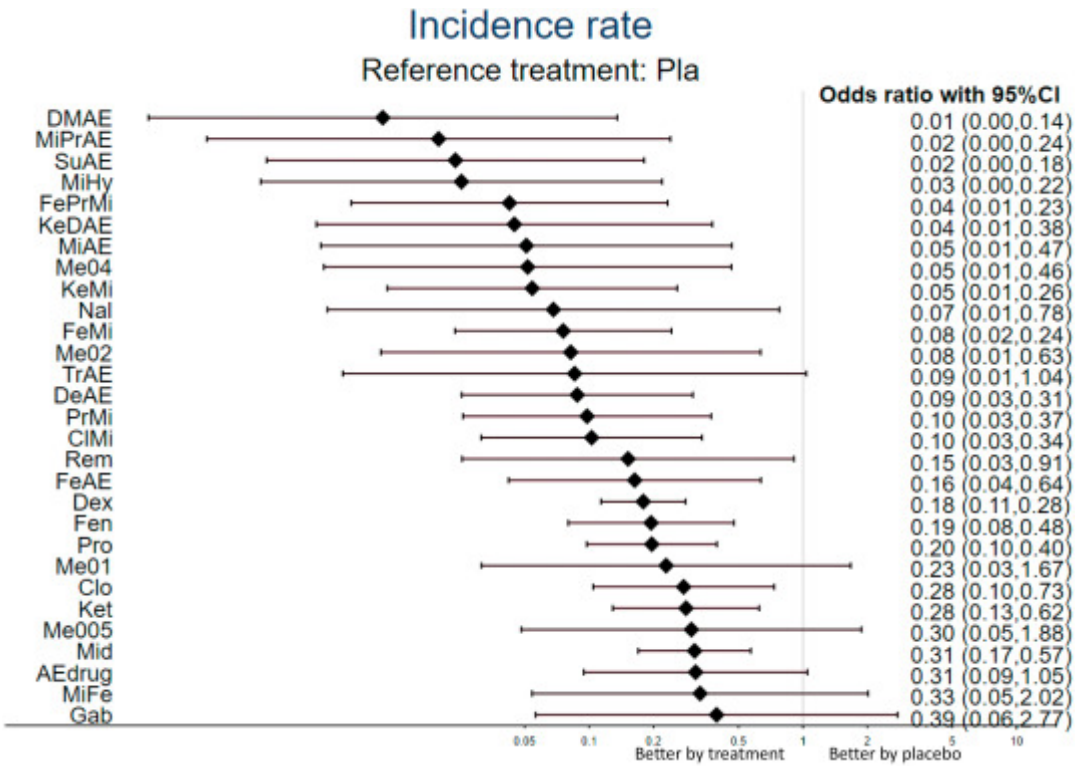


Figure 3. Forest plot comparing the incidence of emergence delirium between different pharmacological interventions and placebos with an effect size [i.e., odds ratio (OR)] < 1 signifying a lower incidence of emergence delirium associated with a specified intervention than that in placebo/control groups.

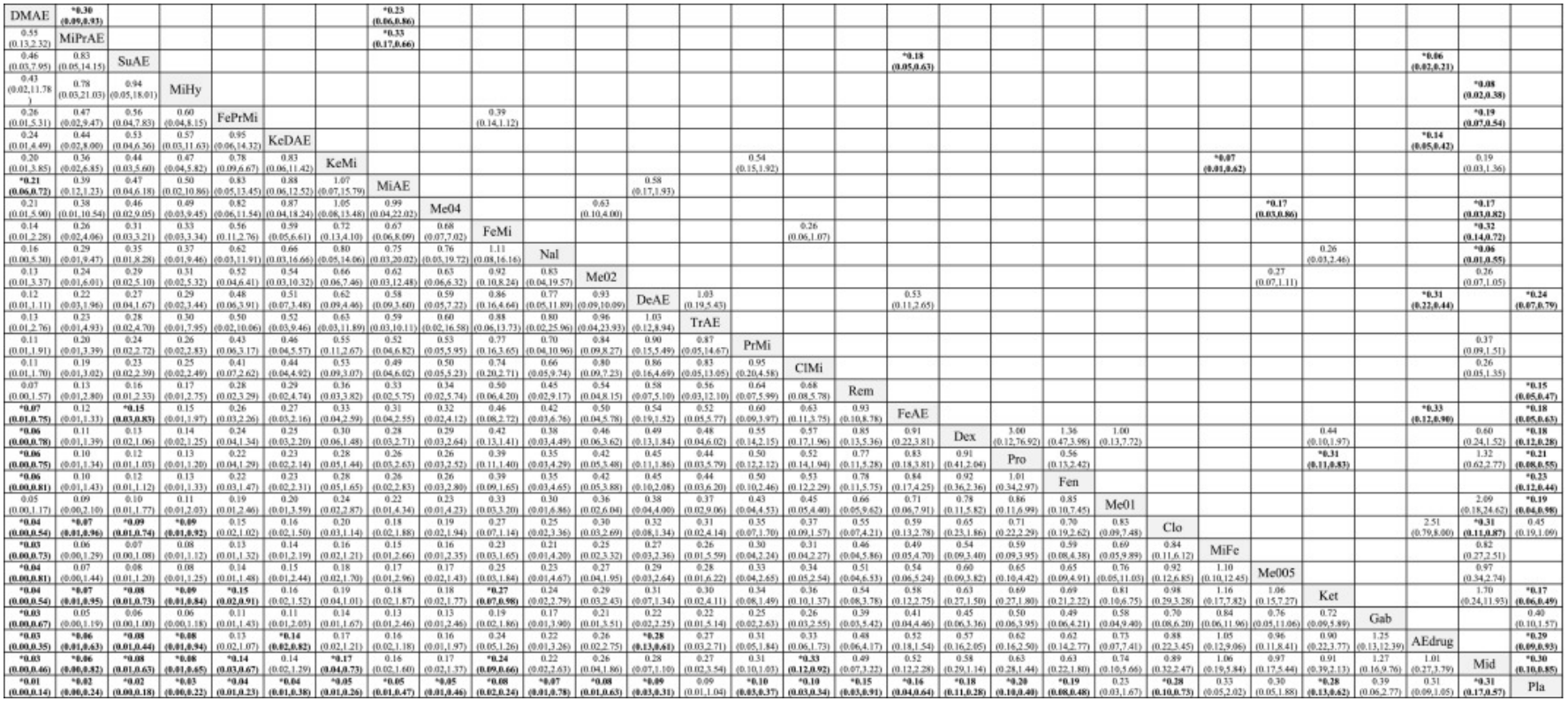


Abbreviations: AEdrug: antiemetic drug; CI: confidence interval; ClMi: clonidine + midazolam; Clo: clonidine; DeAE: dexmedetomidine + antiemetic drug; DeMi: dexmedetomidine + midazolam; Dex: dexmedetomidine; DMAE: dexmedetomidine + midazolam + antiemetic drug; ES: effect size; FeAE: fentanyl + antiemetic drug; FeMi: fentanyl + midazolam; Fen: fentanyl; FePrMi: fentanyl + propofol + midazolam; Gab: gabapentin; KeDAE: ketamine + dexmedetomidine + antiemetic drug; KeMi: midazolam + ketamine; Ket: ketamine; Me005: Melatonin 0.05 mg/kg; Me01: melatonin 0.1mg/kg; Me02: Melatonin 0.2 mg/kg; Me04: Melatonin 0.4 mg/kg; MiAE: antiemetic drug + midazolam; Mid: midazolam; MiFe: midazolam +

alfentanil; MiHy: midazolam + hydroxyzine; MiKeto: ketorolac + midazolam; MiPrAE: midazolam + propofol + antiemetic drug; NA: not available; Nal: Nalbuphine; NMA: network meta-analysis; pedED: postoperative emergence delirium in pediatric population; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; PrMi: midazolam + propofol; Pro: propofol; RCT: randomized control trial; Rem: remifentanil; MD: mean difference; SuAE: sufentanil + antiemetic drug; SUCRA: surface under the cumulative ranking curve; TrAE: tramadol + antiemetic drug

Table 1

League table of the prophylactic effects of intraoperative pharmacological interventions against postoperative emergence delirium in pediatric population following sevoflurane anesthesia: Incidence rate of postoperative emergence delirium.



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

Abbreviation: AEdrug: antiemetic drug; CI: confidence interval; ClMi: clonidine + midazolam; Clo: clonidine; DeAE: dexmedetomidine + antiemetic drug; DeMi: dexmedetomidine + midazolam; Dex: dexmedetomidine; DMAE: dexmedetomidine + midazolam + antiemetic drug; ES: effect size; FeAE: fentanyl + antiemetic drug; FeMi: fentanyl + midazolam; Fen: fentanyl; FePrMi: fentanyl + propofol + midazolam; Gab: gabapentin; KeDAE: ketamine + dexmedetomidine + antiemetic drug; KeMi: midazolam + ketamine; Ket: ketamine; Me005: Melatonin 0.05 mg/kg; Me01: melatonin 0.1 mg/kg; Me02: Melatonin 0.2 mg/kg; Me04: Melatonin 0.4 mg/kg; MiAE: antiemetic drug + midazolam; Mid: midazolam; MiFe: midazolam + alfentanil; MiHy: midazolam + hydroxyzine; MiKeto: ketorolac + midazolam; MiPrAE: midazolam + propofol + antiemetic drug; NA: not available; Nal: Nalbuphine; NMA: network meta-analysis; OR: odds ratio; pedED: postoperative emergence delirium in pediatric population; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; PrMi: midazolam +

propofol; Pro: propofol; RCT: randomized control trial; Rem: remifentanil; SMD: standardized mean difference; SuAE: sufentanil + antiemetic drug; SUCRA: surface under the cumulative ranking curve; TrAE: tramadol + antiemetic drug.

Supplementary Tables

eTable 1: PRISMA 2020 checklist of current network meta-analysis

Section and Topic	Item #	Checklist item	Page where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	5-6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	7-8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	7-8
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	9-10
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	9-10
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	9-10
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	9-10
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	10-11
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	10-11
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	10-11
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	10-11
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	11-12

Section and Topic	Item #	Checklist item	Page where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	11-12
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	11-12
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	12-13
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	12-13
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	12-13
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	13-14
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	13-14
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	13-14
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	15-17, Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	15-17, eTab 2
Study characteristics	17	Cite each included study and present its characteristics.	15-17, eTab 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	16-17, eFig 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	17-18, eTab 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	17-18, eFig 3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	17-18, Fig 3, eFig 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	17-18, eTab 6-7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	18-19

Section and Topic	Item #	Checklist item	Page where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	18-19, eFig 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	18-19, eTab 6-7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	20-23
	23b	Discuss any limitations of the evidence included in the review.	23-24
	23c	Discuss any limitations of the review processes used.	23-24
	23d	Discuss implications of the results for practice, policy, and future research.	24
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Conflict of interest form
Competing interests	26	Declare any competing interests of review authors.	Conflict of interest form
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Conflict of interest form

The current checklist followed the latest PRISMA 2020 guideline [1].

Reference

[1] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj 2021;372:n71.

eTable 2: Excluded studies and reasons:

Reason	Numbers	References
Compare different anesthesia method but not different pharmacologic intervention	6	[1-6]
Development of emergence delirium evaluation scale but not report of outcome of emergence delirium	1	[7]
Lack of adequate control	1	[8]
Lack of sufficient data	4	[9-12]
Meta-analysis	5	[13-17]
Not compare specific medication intervention	2	[18,19]
Not investigate the emergent delirium associated outcome	3	[20-22]
Not pediatric patients	16	[23-38]
Not randomized controlled trial	4	[39-42]
Not related to pharmacological treatment	2	[43,44]
Not related to sevoflurane anesthesia	21	[45-65]
Regional anesthesia but not general anesthesia	2	[66,67]
Review article	5	[68-72]
Treat but not prevention to pediatric delirium	1	[73]

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eTable 3: characteristics of the included studies

Study	Patient characteristics	Comparison	Subject	Intraoperative analgesic drugs	Intraoperative antiemetic drugs	Time of prescription	Emergence delirium scale	Country	Follow up
Shi, M. (2019)[1]	Aged 2-7 years with ASA physical status I or II, scheduled for tonsillecton with/without adenoidectomy	Dexmedetomidine + antiemetic drug Placebo + antiemetic drug	45 45	Paracetamol 15 mg/kg, remifentanil	Dexamethasone + dolasetron	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	China	30 min
Chai, D.D. (2018)[2]	Aged 1-3 years with ASA physical status I or II, scheduled for oral surgery	Dexmedetomidine + midazolam Placebo + midazolam	60 60	None	None	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	China	NA
Lin, L. (2017)[3]	Pediatric patients with ASA physical status I or II, scheduled for oral surgery	Dexmedetomidine + antiemetic drug Placebo + antiemetic drug	40 40	Sufentanil	Tropisetron	During anesthesia in the operation	Four-point agitation scale	China	120 min
Chen, F. (2018)[4]	Aged 3-7 years with ASA physical status I or II, scheduled for elective surgery	Dexmedetomidine Placebo	80 20	Ilioinguinal/ Iliohypogastric nerve block	None	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	China	NA
Kain, ZN. (2009)[5]	Aged 2-8 years with ASA physical status I or II, scheduled for outpatient elective surgery	IV Melatonin 0.05 mg/kg IV Melatonin 0.2 mg/kg IV Melatonin 0.4 mg/kg Oral midazolam premedication	36 36 37 39	Not mention	None	Approximately 45 minutes before the start of anesthesia and operation in the holding area	Emergence Behavior scales	USA	15 min
Bong, C.L. (2015)[6]	Aged 2-7 years with ASA physical status I or II, scheduled to undergo magnetic resonance imaging	Dexmedetomidine IV Propofol IV Placebo	40 39 41	None (Not surgery)	None	10 minutes after induction of anaesthesia	Pediatric Anesthesia Emergence Delirium scale	Singapore	30 min
Kim, K.M. (2016)[7]	Aged 2-6 years with ASA physical status I or II, scheduled to undergo elective ophthalmic surgery	IV midazolam IV ketamine	34 33	None	None	One hour before the start of anesthesia and operation in the waiting area	Aono's four-point scale score	Korea	30 min
Kim, M.S. (2013)[8]	Aged 1.5-6 years with ASA physical status I or II, who were undergoing ambulatory inguinal hernia repair	IV propofol IV fentanyl Placebo	69 66 70	Caudal block	None	10 minutes before the end of surgery	Pediatric Anesthesia Emergence Delirium scale	Korea	NA
Byon, H.J. (2012)[9]	Aged 4-12 years ASA physical status I or II, to undergo strabismus surgery	Antiemetic drug Antiemetic drug + midazolam IV premedication	202 203	None	Ramosetron	Before the start of anesthesia and operation	Pediatric Anesthesia Emergence Delirium scale	Korea	30 min

Study	Patient characteristics	Comparison	Subject	Intraoperative analgesic drugs	Intraoperative antiemetic drugs	Time of prescription	Emergence delirium scale	Country	Follow up
Cho, E.J. (2014)[10]	Aged 1-13 years with ASA physical status I or II, for elective strabismus surgery	IV midazolam Placebo	60 30	Paracetamol 10 mg/kg iv	None	Just before the end of surgery	Pediatric Anesthesia Emergence Delirium scale	Korea	30 min
Chen, J.Y. (2013)[11]	Aged 2-7 years with ASA physical status I or II, undergoing elective strabismus surgery	Dexmedetomidine IV IV ketamine Placebo	27 27 24	Topical anesthesia	None	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	China	NA
Hauber, J.A. (2015)[12]	Aged 4-10 years with ASA physical status I, II or III, scheduled to undergo tonsillectomy	Dexmedetomidine IV + antiemetic drug Placebo + antiemetic drug	195 198	Morphine	Dexamethasone	5 minutes before the end of surgery	Pediatric Anesthesia Emergence Delirium scale	USA	30 min
Isik, B. (2006)[13]	Aged 1.5-10 years with ASA physical status I or II, scheduled to undergo cranial MRI scanning	Dexmedetomidine IV premedication Placebo	21 21	None (Not surgery)	None	Just after the induction	Cole's five point scale	Turkey	30 min
Patel, A. (2010)[14]	Aged 2-10 years with ASA physical status II-III with baseline obstructive sleep apnea, undergoing elective adenotonsillectomy	Dexmedetomidine IV + antiemetic drug Fentanyl IV + antiemetic drug	61 61	Fentanyl (If HR changed), rectal acetaminophen 30-40 mg/kg	Dexamethasone	During anesthesia in the operation	Cole's five point scale	USA	120 min
Shukry, M. (2005)[15]	Aged 1-10 years with ASA physical status I-II, scheduled for elective outpatient surgical procedures	Dexmedetomidine IV Placebo	23 23	Fentanyl if needed	None	During anesthesia in the operation	Watcha scale	USA	60 min
Bilgen, S. (2014)[16]	Aged 1-8 years with ASA physical status I or II, for urological surgical procedures	Oral midazolam premedication + IV ketamine Oral midazolam premedication + alfentanil IV Oral midazolam premedication	26 25 27	Caudal block	None	8-10 min before the induction of anaesthesia	Pediatric Anesthesia Emergence Delirium scale	Turkey	30 min
Abu-Shahwan, I. (2008)[17]	Aged 2-7 years with ASA physical status I-III, for magnetic resonance imaging as an outpatient procedure	IV subhypnotic dose propofol Placebo	42 41	None (Not surgery)	None	Just before the end of diagnostic procedure	Pediatric Anesthesia Emergence Delirium scale	Canada	30 min
Boku, A. (2016)[18]	Aged 0.8-1.2 years with ASA physical status I, planed for palatoplasty	Dexmedetomidine IV Placebo	35 35	Fentanyl	None	10 minutes before the end of surgery	Cole's five point scale	Japan	120 min
Koner, O. (2011)[19]	Aged 1-7 years with ASA physical status I or II, undergoing infraumbilical daycase surgery	Oral midazolam + hydroxyzine premedication Oral midazolam premedication	42 42	Caudal epidural block	None	30 minutes before the start of anesthesia and operation	Pediatric Anesthesia Emergence Delirium scale	Turkey	30 min

Study	Patient characteristics	Comparison	Subject	Intraoperative analgesic drugs	Intraoperative antiemetic drugs	Time of prescription	Emergence delirium scale	Country	Follow up
Ozturk, T. (2016)[20]	Aged 1-8 years, scheduled for elective diagnostic fiberoptic bronchoscopy for bronchoalveolar lavage	Oral midazolam premedication + IV ketamine Oral midazolam premedication + IV low dose propofol Oral midazolam premedication + placebo	23 22 23	Remifentanil (all)	None	Just before the end of procedure	Pediatric Anesthesia Emergence Delirium scale	Turkey	20 min
Lin, Y. (2016)[21]	Aged 1-8 years with ASA physical status I or II, undergoing cataract surgeries	Premedication dexmedetomidine (intra-nasal) Placebo	60 30	Topical anesthesia	None	45 minutes before the start of anesthesia	Pediatric Anesthesia Emergence Delirium scale	China	40 min
Chen, J. (2010)[22]	Aged 1-7 years with ASA physical status I or II, underwent cataract surgery	IV ketamine IV propofol IV midazolam	40 40 40	Remifentanil, fentanyl	None	Just before the end of anesthesia	Pediatric Anesthesia Emergence Delirium scale	China	30 min
Salman, A.E. (2013)[23]	Aged 3-12 years with ASA physical status I or II, undergoing elective tonsillectomy and adenoidectomy	Oral gabapentin premedication Placebo	23 23	Metamizol 15 mg/kg	None	Before the start of anesthesia	Cole's five point scale	Turkey	30 min
Yao, Y. (2015)[24]	Aged 3-7 years with ASA physical status I, underwent elective unilateral strabismus surgery	Premedication dexmedetomidine (intra-nasal) Placebo	60 30	Paracetamol 15 mg/kg iv	None	45 minutes before the start of anesthesia	Pediatric Anesthesia Emergence Delirium scale	China	NA
Abu-Shahwan, I. (2007)[25]	Aged 4-7 years with ASA physical status I-III, undergoing dental repair with no extraction	Oral midazolam premedication + IV ketamine Oral midazolam premedication	42 38	Acetaminophen 30 mg/kg	None	10 minutes before the end of anesthesia	Pediatric Anesthesia Emergence Delirium scale	Canada	NA
Bortone, L. (2014)[26]	Aged 2-11 years with ASA physical status I or II, undergoing elective subumbilical surgery suitable for regional anesthesia	IV fentanyl + oral midazolam premedication Oral midazolam premedication + IV clonidine Oral midazolam premedication + placebo	29 29 29	Acetaminophen 40 mg/kg iv + caudal block	None	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	Canada	60 min
Hadi, S.M. (2015)[27]	Aged 3-7 years with ASA physical status I or II, scheduled for adenotonsillectomy	IV ketamine + dexmedetomidine + antiemetic drug Placebo + antiemetic drug	45 47	None	Dexamethasone	10 minutes before the end of anesthesia	Pediatric Anesthesia Emergence Delirium scale	China	60 min

Study	Patient characteristics	Comparison	Subject	Intraoperative analgesic drugs	Intraoperative antiemetic drugs	Time of prescription	Emergence delirium scale	Country	Follow up
Dong, Y.X. (2010)[28]	Aged 3-7 years with ASA physical status I or II	Remifentanil Placebo	30 30	Noe	None	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	China	NA
Di, M. (2017)[29]	Aged 3-7 years with ASA physical status I or II, scheduled to undergo an adenotonsillectomy	Premedication dexmedetomidine + antiemetic drug Placebo + antiemetic drug	50 25	Fentanyl + local anesthesia	Dexamethasone + ondansetron	10 minutes before the start of anesthesia	Pediatric Anesthesia Emergence Delirium scale	China	NA
Bedirli, N. (2017)[30]	Aged 2-12 years with ASA physical status I or II, undergoing adenotonsillectomy	Dexmedetomidine + antiemetic drug Tramadol + antiemetic drug	38 39	Fentanyl	Dexamethasone+ ondansetron	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	Turkey	60 min
Costi, D. (2015)[31]	Aged 1-12 years with ASA physical status I or II, undergoing magnetic resonance imaging (MRI)	Oral midazolam premedication + propofol Oral midazolam premedication + placebo	109 109	None (Not surgery)	None	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	Australia	30 min
Cho, E.A. (2019)[32]	Aged 2-12 years with ASA physical status I or II, scheduled for elective tonsillectomy	Single dexmedetomidine Intravenous midazolam	34 32	Ketorolac 0.5 mg/kg iv	None	5 minutes before the end of anesthesia	Pediatric Anesthesia Emergence Delirium scale	Korea	20 min
Abbas, M.S. (2019)[33]	Aged 1-12 years with ASA physical status I or II, assigned for elective inguinal hernia repair	Propofol Placebo	32 32	Caudal epidural block + paracetamol 15 mg/kg	None	3 minutes before the end of anesthesia	Pediatric Anesthesia Emergence Delirium scale	Egypt	30 min
Aouad, M.T. (2007)[34]	Aged 2-6 years with ASA physical status I or II, scheduled to undergo strabismus surgery	Oral midazolam premedication + propofol + antiemetic drug Oral midazolam premedication + placebo + antiemetic drug	41 36	Paracetamol 15 mg/kg	Dexamethasone	Just before the end of anesthesia	Pediatric Anesthesia Emergence Delirium scale	USA	30 min
Tazeroualti, N. (2007)[35]	Aged 1-6 years with ASA physical status I or II, undergoing circumcision	Oral midazolam Clonidine premedication	20 40	Penile block + paracetamol 30 mg/kg rectal	None	30 minutes before the start of anesthesia and operation	Three item scale (movement, tears, and behavior)	Belgium	60 min
Galinkin, J.L. (2000)[36]	Aged 0.75-6 years with ASA physical status I or II, scheduled for bilateral myringotomy and tympanostomy tube placement procedures	Intranasal fentanyl + midazolam premedication Placebo + midazolam premedication	64 69	Oral acetaminophen 10 mg/kg	None	Just before the start of surgery	Aono's four-point scale score	USA	120 min

Study	Patient characteristics	Comparison	Subject	Intraoperative analgesic drugs	Intraoperative antiemetic drugs	Time of prescription	Emergence delirium scale	Country	Follow up
Lankinen, U. (2006)[37]	Aged 1-7 years with ASA physical status I or II, undergoing elective outpatient adenoidectomy	Antiemetic drug Clonidine Placebo	25 24 26	Alfentanil 20 g/kg	Tropisetron	During anesthesia in the operation	Pain discomfort scale	Finland	120 min
Tesoro, S. (2005)[38]	Children with ASA physical status I or II, elected for pediatric day-surgery	Clonidine + oral midazolam premedication Oral midazolam	91 78	Nerve block + acetaminophen 30 mg/kg rectal	None	Just before the start of surgery	Pain Discomfort Score	Italy	120 min
Kulka, P.J. (2001)[39]	Aged 2-7 years with ASA physical status I or II, undergoing circumcision	Clonidine + oral midazolam premedication Oral midazolam	20 20	Paracetamol 15 mg/kg + penile block	None	During anesthesia in the operation	Pain Discomfort Score	Germany	120 min
Bakhamees, H.S. (2009)[40]	Aged 2-6 years with ASA physical status I, scheduled for adenoidectomy and/or bilateral myringotomy	IV fentanyl + oral midazolam premedication IV fentanyl + propofol + oral midazolam premedication Oral midazolam + placebo	40 40 40	Rectal paracetamol 40 mg/kg	None	During anesthesia in the operation	Ten-point agitation scale	Saudi Arabia	60 min
Tsai, P.S. (2008)[41]	Aged 1-9.2 years with ASA physical status I or II, scheduled for elective outpatient surgeries	Oral midazolam premedication + IV ketamine Oral midazolam premedication + IV propofol Oral midazolam premedication	20 20 20	None	None	During anesthesia in the operation	Ten-point agitation scale	Taiwan	45 min
Viitanen, H. (1999)[42]	Aged 1-3 years with ASA physical status I or II, scheduled for ambulatory adenoidectomy	Oral midazolam Placebo	30 30	Acetaminophen 20 mg/kg iv	None	30 minutes before the start of anesthesia and operation	Pain Discomfort Score	Finland	30 min
Demirbilek, S. (2004)[43]	Aged 2-7 years with ASA physical status I, scheduled for adenoidectomy and/or tonsillectomy	IV fentanyl + oral midazolam premedication Oral midazolam + placebo	30 30	Paracetamol 30 mg/kg	None	During anesthesia in the operation	Objective Pain Scale	Turkey	30 min
Almenrader, N. (2007)[44]	Aged 1-6 years with ASA physical status I or II, scheduled for inguinal herniorrhaphy, hydrocele repair, circumcision, or orchidopexy	Clonidine premedication Oral midazolam premedication	30 34	Caudal block + rectal paracetamol 30–40 mg/kg	None	Before the start of anesthesia and operation	Three point scale for agitation	Italy	30 min

Study	Patient characteristics	Comparison	Subject	Intraoperative analgesic drugs	Intraoperative antiemetic drugs	Time of prescription	Emergence delirium scale	Country	Follow up
Ibacache, M.E. (2004)[45]	Aged 1-10 years with ASA physical status I, scheduled to undergo inguinal hernia repair, orchiopexy, or circumcision	Single dexmedetomidine Placebo	60 30	Caudal block	None	During anesthesia in the operation	Aono's four-point scale score	Chile	NA
Dalens, B.J. (2006)[46]	Aged 0.5-8 years with ASA physical status I-III, scheduled for cerebral MRI procedure	IV ketamine IV Nalbuphine Placebo	33 29 28	None	None	Just before the end of anesthesia	5-step Emergence Agitation Scale	Canada	30 min
Guler, G. (2005)[47]	Aged 3-7 years with ASA physical status I, scheduled to undergo adenotonsillectomy	Single dexmedetomidine Placebo	30 30	Acetaminophen 15 mg/kg orally	None	5 min before the end of anesthesia	Cole's five point scale	Turkey	NA
Cravero, J.P. (2003)[48]	Aged 1.5-10 years with ASA physical status I or II, scheduled to undergo magnetic resonance imaging (MRI) scanning	IV fentanyl Placebo	16 16	None	None	Just before the end of anesthesia	5-step Emergence Agitation Scale	USA	NA
Akin, A. (2012)[49]	Aged 2-9 years with ASA physical status I, scheduled to undergo an elective adenotonsillectomy	Intranasal midazolam + antiemetic drug Dexmedetomidine (intra-nasal) premedication + antiemetic drug	45 45	None	Metoclopramide + dexamethasone	45-60 minutes before the start of anesthesia and operation	Three point scale for agitation	Turkey	NA
Meng, Q.T. (2012)[50]	Aged 5-14 years with ASA physical status I or II, scheduled for tonsillectomy operation	IV dexmedetomidine + midazolam premedication + antiemetic drug Oral midazolam + antiemetic drug	80 40	Remifentanil (all)	Tropisetron	During anesthesia in the operation	Four-point scale score	China	60 min
Kim, N.Y. (2014)[51]	Aged 1-5 years with ASA physical status I, undergoing ambulatory hernioplasty or orchiopexy	Dexmedetomidine Placebo	20 20	Caudal block	None	During anesthesia in the operation	Watcha scale	Korea	30 min
Kim, Y.H. (2011)[52]	Aged 1-13 years with ASA physical status I or II, scheduled to undergo strabismus surgery	Propofol IV IV midazolam Placebo	31 35 35	Paracetamol 10 mg/kg iv	None	5 minutes before the end of anesthesia	Four-point scale score	Korea	60 min
Li, J. (2011)[53]	Aged 3-11 years with ASA physical status I or II, scheduled for adenotonsillectomy	IV fentanyl + antiemetic drug IV sufentanil + antiemetic drug Placebo + antiemetic drug	34 32 34	Tramadol 2 mg/kg iv	Dexamethasone	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	China	NA
Lili, X. (2012)[54]	Aged 3-7 years with ASA physical status I or II, undergoing vitreoretinal surgery	Dexmedetomidine Placebo	30 30	Remifentanil (all)	None	During anesthesia in the operation	Aono's four-point scale score	China	NA

Study	Patient characteristics	Comparison	Subject	Intraoperative analgesic drugs	Intraoperative antiemetic drugs	Time of prescription	Emergence delirium scale	Country	Follow up
Lee, Y.S. (2010)[55]	Aged 2-14 years with ASA physical status I or II, scheduled to undergo an adenotonsillectomy (or adenoidectomy)	IV ketamine Placebo	60 30	None	None	10 minutes before the end of anesthesia	Four-point scale score	Korea	NA
Lee, C.J. (2010)[56]	Aged 3-8 years with ASA physical status I, scheduled to undergo adenotonsillectomy without myringotomy	Propofol Placebo	44 44	Ketorolac 1 mg/kg iv	None	Just before the end of anesthesia	Pediatric Anesthesia Emergence Delirium scale	Korea	30 min
Erdil, F. (2009)[57]	Aged 2-7 years with ASA physical status I, undergoing adenoidectomy with or without bilateral myringotomy and insertion of tubes	Single dexmedetomidine + antiemetic drug IV fentanyl + antiemetic drug Placebo	29 30 30	Rectal paracetamol 40 mg/kg	Dexamethasone	During anesthesia in the operation	Cole's five point scale	Turkey	30 min
Rampersad, S. (2010)[58]	Aged 1-5 years with ASA physical status I or II, scheduled for bilateral myringotomies with tube placement surgery	Oral midazolam Fentanyl + oral midazolam premedication Ketorolac + oral midazolam premedication	77 75 76	Acetaminophen 40 mg/kg rectal	None	During anesthesia in the operation	Watcha scale	USA	NA
Gupta, N. (2013)[59]	Aged 8-12 years with ASA physical status I or II, undergoing elective surgery for spinal dysraphism	IV dexmedetomidine Placebo	18 18	Fentanyl (If HR changed)	None	During anesthesia in the operation	Cole's five point scale	India	120 min
Sato, M. (2010)[60]	Aged 1-9 years with ASA physical status I or II, scheduled to receive same-day surgery or overnight stay surgery	Single dexmedetomidine Placebo	39 42	Acetaminophen 40 mg/kg rectal	None	During anesthesia in the operation	Aono's four-point scale score	Japan	NA
He, L. (2013)[61]	Aged 3-7 years with ASA physical status I or II, undergoing elective minor surface surgery	IV dexmedetomidine Placebo	61 26	Regional block	None	During anesthesia in the operation	Cole's five point scale	China	NA
Inomata, S. (2010)[62]	Aged 2-6 years with ASA physical status I or II, undergoing elective minor surface surgery	IV fentanyl Placebo	93 46	Fentanyl	None	During anesthesia in the operation	Pediatric Anesthesia Emergence Delirium scale	Japan	15 min
Ali, M.A. (2013)[63]	Aged 2-6 years with ASA physical status I or II, scheduled to undergo adenotonsillectomy	IV dexmedetomidine + midazolam premedication + antiemetic drug Oral midazolam premedication + IV low dose propofol + antiemetic drug Oral midazolam + antiemetic drug	40 40 40	Paracetamol 15 mg/kg	Dexamethasone	5 minutes before the end of anesthesia	Pediatric Anesthesia Emergence Delirium scale	Egypt	30 min

Study	Patient characteristics	Comparison	Subject	Intraoperative analgesic drugs	Intraoperative antiemetic drugs	Time of prescription	Emergence delirium scale	Country	Follow up
Ozcengiz, D. (2011)[64]	Aged 3-9 years with ASA physical status I or II, scheduled for esophageal dilatation procedures	Dexmedetomidine premedication Melatonin premedication 0.1 mg/kg Oral midazolam Placebo	25 25 25 25	Paracetamol 2–2.5 mg/kg oral	None	40-45 minutes before the start of anesthesia and operation	Emergence agitation scale	Turkey	60 min
Sheta, S.A. (2014)[65]	Aged 3-6 years with ASA physical status I or II, for complete dental rehabilitation	Dexmedetomidine (intra-nasal premedication) Intranasal midazolam premedication	36 36	Rectal paracetamol 30-40 mg/kg	None	45-60 minutes before the start of anesthesia and operation	Aono's four-point scale score	Saudi Arabia	NA
Ko, Y.P. (2001)[66]	Aged 1-9.2 years with ASA physical status I or II, for elective outpatient surgery, including herniorrhaphy, hydrocelectomy, orchiopexy, simple excision of a mass, and simple fistulectomy	IV midazolam premedication Placebo	66 22	None	None	10 minutes before the start of anesthesia and operation	Taiwan 10 point scoring system	Taiwan	45 min
Pestieau, S.R. (2011)[67]	Aged 0.5-6 years with ASA physical status I or II, scheduled for elective bilateral myringotomy with insertion of pressure equalizing tubes	Dexmedetomidine (intra-nasal) Fentanyl (intra-nasal) Placebo	53 23 27	None	None	During anesthesia in the operation	Watcha scale	USA	NA
Asaad, O.M. (2011)[68]	Aged 5-10 years with ASA physical status I, for elective surgery (e.g. inguinal hernia repair, hydrocele, or circumcision)	IV fentanyl IV dexmedetomidine Placebo	30 30 30	Caudal block	None	During anesthesia in the operation	Four-point scale score	Egypt	NA
Ghosh, S.M. (2011)[69]	Aged 1-5 years with ASA physical status I or II, undergoing elective urogenital and lower limb surgery	Caudal clonidine Placebo	60 30	Caudal epidural block	None	During anesthesia in the operation	Pain and Discomfort Scale agitation	India	60 min
Al-Zaben, K.R. (2010)[70]	Aged 1-12 years with ASA physical status I, scheduled for hypospadias surgical repair	Dexmedetomidine Placebo	24 24	Fentanyl 1 μg/kg boluses if required	None	During anesthesia in the operation	Watcha scale	Jordan	120 min

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eTable 4A. Dosage of dexmedetomidine and incidence of delirium

Study	Dexmedetomidine dosage	Incidence (%)
Shi, M. (2019)[1]	0.5 μg/kg bolus	31.1
Lin, L. (2017)[2]	1.0 μg·kg-1 bolus	15.0
Chen, F. (2018)[3]	0.25-1 μg/kg bolus	2.5
Bong, C.L. (2015)[4]	0.3 μg/kg bolus	2.5
Chen, J.Y. (2013)[5]	1 μg/kg iv followed 1 μg/kg/hour	11.1
Hauber, J.A. (2015)[6]	0.5 μg/kg bolus	35.4
Isik, B. (2006)[7]	1.0 μg·kg-1 bolus	4.8
Patel, A. (2010)[8]	2 μg/kg iv followed 0.7 μg/kg/hour	18.0
Shukry, M. (2005)[9]	0.2 μg/kg /hour	26.1
Lin, Y. (2016)[10]	1 or 2 μg/kg	16.7
Yao, Y. (2015)[11]	1 or 2 μg/kg	10.0
Hadi, S.M. (2015)[12]	0.15 μg/kg iv followed 0.3 μg/kg/hour	11.1
Di, M. (2017)[13]	1 or 2 μg/kg	0.0
Bedirli, N. (2017)[14]	1 μg/kg	7.9
Cho, E.A. (2019)[15]	0.3 μg/kg	26.5
Ibacache, M.E. (2004)[16]	0.15 or 0.3 μg/kg	13.3
Guler, G. (2005)[17]	0.5 μg/kg	16.7
Meng, Q.T. (2012)[18]	0.5 or 0.1 μg/kg iv followed by 0.2 or 0.4 μg/kg/hour	10.0
Kim, N.Y. (2014)[19]	0.2 μg/kg/hour	5.0
Lili, X. (2012)[20]	0.5 μg/kg	10.0
Erdil, F. (2009)[21]	0.5 μg/kg	17.2
Gupta, N. (2013)[22]	1 μg/kg iv followed 0.5 μg/kg/hour	0.0
Sato, M. (2010)[23]	0.3 μg/kg	28.2

He, L. (2013)[24]	0.5 or 1 μg/kg	11.5
Ali, M.A. (2013)[25]	0.3 μg/kg	12.5
Ozcengiz, D. (2011)[26]	2.5 μg/kg	8.0
Sheta, S.A. (2014)[27]	1 μg/kg	11.1
Pestieau, S.R. (2011)[28]	1 or 2 μg/kg	26.4

Iv: intravenous

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eTable 4B. Dosage and route of midazolam

Studies	Dosage	Time of administration	Route
Akin, A. (2012)[1]	0.2 mg/kg	Premedication	Nasal
Ali, M.A. (2013)[2]	0.5 mg/kg	Premedication	Oral
Almenrader, N. (2007)[3]	0.5 mg/kg	Premedication	Oral
Aouad, M.T. (2007)[4]	0.5 mg/kg	Premedication	Oral
Bakhamees, H.S. (2009)[5]	0.5 mg/kg	Premedication	Oral
Bilgen, S. (2014)[6]	0.5 mg/kg	Premedication	Oral
Bortone, L. (2014)[7]	0.5 mg/kg	Premedication	Oral
Chen, J. (2010)[8]	0.05 mg/kg	Before end of surgery	Intravenous
Cho, E.A. (2019)[9]	0.03 mg/kg	Before end of surgery	Intravenous
Cho, E.J. (2014)[10]	0.03-0.05 mg/kg	Before end of surgery	Intravenous
Costi, D. (2015)[11]	0.5 mg/kg	Premedication	Oral
Demirbilek, S. (2004)[12]	0.5 mg/kg	Premedication	Oral
Galinkin, J.L. (2000)[13]	0.5 mg/kg	Premedication	Oral
Kain, ZN. (2009)[14]	0.5 mg/kg	Premedication	Oral
Kim, K.M. (2016)[15]	0.1 mg/kg	Premedication	Intravenous
Kim, Y.H. (2011)[16]	0.05 mg/kg	Before end of surgery	Intravenous

Ko, Y.P. (2001)[17]	0.2 mg/kg	Premedication	Oral
Koner, O. (2011)[18]	0.5 mg/kg	Premedication	Oral
Kulka, P.J. (2001)[19]	0.5 mg/kg	Premedication	Oral
Meng, Q.T. (2012)[20]	0.04 mg/kg	Premedication	Intravenous
Ozcengiz, D. (2011)[21]	0.5 mg/kg	Premedication	Oral
Sheta, S.A. (2014)[22]	0.2 mg/kg	Premedication	Nasal
Tazeroualti, N. (2007)[23]	0.5 mg/kg	Premedication	Oral
Tesoro, S. (2005)[24]	0.5 mg/kg	Premedication	Oral
Tsai, P.S. (2008)[25]	0.2 mg/kg	Premedication	Oral
Viitanen, H. (1999)[26]	0.5 mg/kg	Premedication	Oral

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eTable 5A: SUCRA analysis of the prophylactic effect of pharmacological interventions on postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of postoperative emergence delirium incidence rate

Treatment	SUCRA
DMAE	92.3
MiPrAE	85.1
SuAE	83.3
MiHy	81.0
FePrMi	75.4
KeDAE	72.5
KeMi	70.5
MiAE	68.6
Me04	67.3
FeMi	63.8
Nal	62.7
Me02	59.1
DeAE	59.0
TrAE	56.5
PrMi	55.7
ClMi	54.9
Rem	43.7
FeAE	40.6
Dex	38.7

Pro	35.9
Fen	35.5
Me01	33.8
Clo	24.8
MiFe	24.6
Me005	24.5
Ket	24.0
Gab	22.1
AEdrug	21.9
Mid	20.0
Pla	2.0

Sorted by order of preventive effect (the former, the less incidence rate)

Supplement Table 5B: SUCRA analysis of the prophylactic effect of pharmacological interventions on postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of postoperative emergence delirium incidence rate (subgroup of population with age ≤ 7 years old)

Treatment	SUCRA
ClMi	93.8
KeDAE	83.6
MiHy	80.3
FePrMi	68.1
DeAE	65.3
FeAE	61.7
Fen	54.1
Dex	53.3
Pro	50.7
FeMi	47.8
AEdrug	32.8
Clo	29.5
Ket	13.6
Mid	11.8
Pla	3.4

Sorted by order of preventive effect (the former, the less incidence rate)

Supplement Table 5C: SUCRA analysis of the prophylactic effect of pharmacological interventions on postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of postoperative emergence delirium incidence rate (subgroup of population in whom Pediatric Anesthesia Emergence Delirium was used as diagnostic criteria)

Treatment	SUCRA
KeMi	93.4
MiHy	92.0
PrMi	81.7
FeMi	73.1
MiFe	51.1
Mid	45.5
Pro	45.2
Dex	39.6
ClMi	39.5
Rem	27.5
Ket	11.4
Pla	0.0

Sorted by order of preventive effect (the former, the less incidence rate)

Supplement Table 5D: SUCRA analysis of the prophylactic effect of pharmacological interventions on postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of postoperative emergence delirium incidence rate (subgroup of population with (a) age ≤ 7 years old, (b) use of the Pediatric Anesthesia Emergence Delirium as diagnostic criteria, and (c) specific intraoperative analgesic information available)

Treatment	SUCRA
MiHy	99.9
Mid	74.1
Pro	62.0
Dex	54.7
Fen	38.2
Ket	21.0
Pla	0.1

Sorted by order of preventive effect (the former, the less incidence rate)
Abbreviation: AEdrug: antiemetic drug; CI: confidence interval; ClMi: clonidine + midazolam; Clo: clonidine; DeAE: dexmedetomidine + antiemetic drug; DeMi: dexmedetomidine + midazolam; Dex: dexmedetomidine; DMAE: dexmedetomidine + midazolam + antiemetic drug; ES: effect size; FeAE: fentanyl + antiemetic drug; FeMi: fentanyl + midazolam; Fen: fentanyl; FePrMi: fentanyl + propofol + midazolam; Gab: gabapentin; KeDAE: ketamine + dexmedetomidine + antiemetic drug; KeMi: midazolam + ketamine; Ket: ketamine; Me005: Melatonin 0.05 mg/kg; Me01: melatonin 0.1mg/kg; Me02: Melatonin 0.2 mg/kg; Me04: Melatonin 0.4 mg/kg; MiAE: antiemetic drug + midazolam; Mid: midazolam; MiFe: midazolam + alfentanil; MiHy: midazolam + hydroxyzine; MiKeto: ketorolac + midazolam; MiPrAE: midazolam + propofol + antiemetic drug; NA: not available; Nal: Nalbuphine; NMA: network meta-analysis; OR: odds ratio; pedED: postoperative emergence delirium in pediatric population; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; PrMi: midazolam + propofol; Pro: propofol; RCT: randomized control trial; Rem: remifentanil; SMD: standardized mean difference; SuAE: sufentanil + antiemetic drug; SUCRA: surface under the cumulative ranking curve; TrAE: tramadol + antiemetic drug

eTable 6A: League table of the prophylactic effect of pharmacological interventions on postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of postoperative emergence delirium incidence rate (subgroup of patients with age ≤ 7 years old)

ClMi													***0.03 (0.00,0.17)**	
0.41 (0.02,8.25)	KeDAE									***0.14 (0.05,0.42)**				
0.34 (0.02,6.00)	0.82 (0.05,13.97)	MiHy											***0.08 (0.02,0.38)**	
0.18 (0.01,2.39)	0.44 (0.03,5.56)	0.53 (0.05,5.80)	FePrMi						0.39 (0.14,1.12)				***0.19 (0.07,0.54)**	
0.16 (0.01,2.08)	0.38 (0.06,2.56)	0.46 (0.04,5.04)	0.86 (0.11,6.64)	DeAE	1.36 (0.32,5.65)					0.16 (0.01,1.80)				***0.24 (0.07,0.79)**
0.15 (0.01,2.41)	0.35 (0.03,3.92)	0.43 (0.03,5.94)	0.80 (0.08,8.10)	0.94 (0.17,5.16)	FeAE									***0.18 (0.05,0.63)**
0.11 (0.01,1.33)	0.26 (0.03,2.47)	0.32 (0.03,3.22)	0.59 (0.08,4.19)	0.69 (0.13,3.67)	0.74 (0.10,5.28)	Fen	0.42 (0.11,1.63)	1.80 (0.41,7.87)						***0.21 (0.09,0.49)**
0.10 (0.01,1.06)	0.25 (0.03,1.95)	0.31 (0.04,2.51)	0.58 (0.11,3.11)	0.67 (0.17,2.65)	0.72 (0.13,4.02)	0.97 (0.30,3.10)	Dex	3.00 (0.12,76.92)				0.44 (0.10,1.97)	***0.28 (0.08,1.00)**	***0.18 (0.10,0.30)**
0.10 (0.01,1.06)	0.24 (0.03,2.07)	0.29 (0.03,2.53)	0.54 (0.09,3.20)	0.63 (0.13,2.99)	0.67 (0.10,4.39)	0.91 (0.24,3.42)	0.94 (0.33,2.65)	Pro				***0.31 (0.11,0.83)**	1.42 (0.44,4.52)	***0.14 (0.05,0.36)**
***0.09 (0.01,0.99)**	0.22 (0.02,2.30)	0.27 (0.03,2.36)	0.50 (0.12,2.12)	0.58 (0.10,3.53)	0.62 (0.08,5.05)	0.84 (0.15,4.60)	0.87 (0.22,3.47)	0.93 (0.21,4.14)	FeMi				***0.29 (0.84,0.97)**	
***0.06 (0.00,0.76)**	***0.14 (0.03,0.67)**	0.17 (0.02,1.83)	0.32 (0.04,2.41)	0.38 (0.12,1.16)	0.40 (0.06,2.52)	0.55 (0.11,2.76)	0.56 (0.15,2.11)	0.60 (0.13,2.74)	0.65 (0.11,3.78)	AEdrug	0.40 (0.13,1.27)			***0.29 (0.09,0.93)**
***0.05 (0.00,0.55)**	***0.13 (0.02,0.96)**	0.15 (0.02,1.32)	0.29 (0.05,1.66)	0.34 (0.08,1.40)	0.36 (0.06,2.22)	0.48 (0.12,1.97)	0.50 (0.18,1.40)	0.54 (0.15,1.86)	0.58 (0.13,2.48)	0.89 (0.24,3.28)	Clo		***0.31 (0.11,0.87)**	0.45 (0.19,1.09)
***0.03 (0.00,0.30)**	***0.07 (0.01,0.62)**	***0.09 (0.01,0.71)**	***0.16 (0.03,0.88)**	***0.19 (0.04,0.90)**	0.20 (0.03,1.33)	0.27 (0.07,1.11)	***0.28 (0.10,0.78)**	***0.30 (0.10,0.90)**	0.32 (0.08,1.31)	0.50 (0.11,2.26)	0.56 (0.17,1.88)	Ket	1.70 (0.24,11.93)	0.34 (0.10,1.13)
***0.03 (0.00,0.24)**	***0.07 (0.01,0.54)**	***0.08 (0.01,0.55)**	***0.15 (0.04,0.64)**	***0.18 (0.04,0.77)**	0.19 (0.03,1.16)	***0.26 (0.07,0.96)**	***0.27 (0.11,0.64)**	***0.28 (0.10,0.81)**	***0.31 (0.11,0.89)**	0.47 (0.12,1.90)	0.53 (0.20,1.43)	0.95 (0.38,2.34)	Mid	1.71 (0.62,4.77)
***0.02 (0.00,0.19)**	***0.05 (0.01,0.34)**	***0.06 (0.01,0.46)**	***0.11 (0.02,0.56)**	***0.13 (0.04,0.44)**	***0.13 (0.03,0.69)**	***0.18 (0.06,0.55)**	***0.19 (0.11,0.33)**	***0.20 (0.08,0.52)**	***0.22 (0.06,0.83)**	0.33 (0.10,1.11)	***0.38 (0.15,0.92)**	0.67 (0.26,1.75)	0.71 (0.31,1.59)	Pla

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

eTable 6B: League table of the prophylactic effect of pharmacological interventions on postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of postoperative emergence delirium incidence rate (subgroup of population in whom Pediatric Anesthesia Emergence Delirium was used as diagnostic criteria)

KeMi				***0.07 (0.01,0.62)**	***0.06 (0.01,0.50)**						
0.72 (0.05,10.07)	MiHy				***0.08 (0.02,0.38)**						
0.31 (0.03,3.03)	0.43 (0.07,2.47)	PrMi			***0.19 (0.08,0.44)**						
0.19 (0.01,2.54)	0.27 (0.03,2.24)	0.63 (0.12,3.33)	FeMi		0.30 (0.07,1.29)			0.26 (0.06,1.07)			
***0.07 (0.01,0.62)**	***0.10 (0.01,0.67)**	***0.23 (0.06,0.94)**	0.37 (0.06,2.31)	MiFe	0.82 (0.27,2.51)						
***0.06 (0.01,0.50)**	***0.08 (0.02,0.38)**	***0.19 (0.08,0.44)**	0.30 (0.07,1.29)	0.82 (0.27,2.51)	Mid	0.71 (0.22,2.26)		0.85 (0.27,2.63)		***0.22 (0.07,0.63)**	***0.14 (0.03,0.66)**
***0.06 (0.01,0.59)**	***0.08 (0.01,0.49)**	***0.18 (0.05,0.66)**	0.29 (0.05,1.67)	0.79 (0.18,3.47)	0.96 (0.36,2.55)	Pro	0.33 (0.01,8.43)			***0.31 (0.11,0.83)**	***0.09 (0.03,0.34)**
***0.05 (0.00,0.53)**	***0.07 (0.01,0.44)**	***0.15 (0.04,0.62)**	0.25 (0.04,1.52)	0.66 (0.14,3.22)	0.81 (0.27,2.47)	0.84 (0.33,2.17)	Dex			0.44 (0.10,1.97)	***0.11 (0.05,0.26)**
***0.05 (0.00,0.56)**	***0.07 (0.01,0.47)**	***0.16 (0.04,0.66)**	0.26 (0.06,1.07)	0.69 (0.14,3.41)	0.85 (0.27,2.63)	0.88 (0.20,3.92)	1.04 (0.21,5.09)	ClMi			
***0.03 (0.00,0.42)**	***0.04 (0.01,0.37)**	***0.10 (0.02,0.56)**	0.16 (0.02,1.29)	0.44 (0.07,2.82)	0.53 (0.12,2.37)	0.55 (0.14,2.19)	0.66 (0.18,2.40)	0.63 (0.10,4.10)	Rem		***0.15 (0.05,0.47)**
***0.02 (0.00,0.16)**	***0.02 (0.00,0.13)**	***0.05 (0.01,0.17)**	***0.08 (0.01,0.44)**	***0.21 (0.05,0.92)**	***0.26 (0.10,0.66)**	***0.27 (0.12,0.62)**	***0.32 (0.12,0.84)**	0.31 (0.07,1.34)	0.49 (0.12,2.00)	Ket	0.34 (0.10,1.13)
***0.00 (0.00,0.05)**	***0.01 (0.00,0.04)**	***0.02 (0.00,0.06)**	***0.02 (0.00,0.14)**	***0.07 (0.02,0.29)**	***0.08 (0.03,0.21)**	***0.08 (0.04,0.18)**	***0.10 (0.05,0.19)**	***0.10 (0.02,0.42)**	***0.15 (0.05,0.47)**	***0.31 (0.14,0.71)**	Pla

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

eTable 6C: League table of the prophylactic effect of pharmacological interventions on postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of postoperative emergence delirium incidence rate: aspect of postoperative emergence delirium incidence rate (subgroup of population with (a) age ≤ 7 years old, (b) use of the Pediatric Anesthesia Emergence Delirium as diagnostic criteria, and (c) specific intraoperative analgesic information available)

MiHy	***0.08 (0.02,0.38)**					
***0.08 (0.02,0.38)**	Mid	0.71 (0.22,2.26)			***0.22 (0.07,0.63)**	
***0.06 (0.01,0.37)**	0.68 (0.22,2.08)	Pro	0.33 (0.01,8.40)	0.55 (0.13,2.42)	***0.31 (0.11,0.83)**	***0.14 (0.05,0.36)**
***0.05 (0.01,0.37)**	0.57 (0.14,2.25)	0.83 (0.30,2.31)	Dex		0.44 (0.10,1.97)	***0.15 (0.05,0.40)**
***0.03 (0.00,0.28)**	0.38 (0.08,1.83)	0.56 (0.16,1.90)	0.67 (0.19,2.39)	Fen		***0.21 (0.07,0.59)**
***0.02 (0.00,0.12)**	***0.22 (0.08,0.63)**	***0.32 (0.14,0.74)**	0.39 (0.14,1.11)	0.58 (0.16,2.16)	Ket	0.34 (0.10,1.13)
***0.01 (0.00,0.05)**	***0.08 (0.02,0.27)**	***0.11 (0.05,0.26)**	***0.14 (0.07,0.29)**	***0.21 (0.07,0.58)**	***0.35 (0.15,0.86)**	Pla

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

Abbreviation: AEdrug: antiemetic drug; CI: confidence interval; ClMi: clonidine + midazolam; Clo: clonidine; DeAE: dexmedetomidine + antiemetic drug; DeMi: dexmedetomidine + midazolam; Dex: dexmedetomidine; DMAE: dexmedetomidine + midazolam + antiemetic drug; ES: effect size; FeAE: fentanyl + antiemetic drug; FeMi: fentanyl + midazolam; Fen: fentanyl; FePrMi: fentanyl + propofol + midazolam; Gab: gabapentin; KeDAE: ketamine + dexmedetomidine + antiemetic drug; KeMi: midazolam + ketamine; Ket: ketamine; Me005: Melatonin 0.05 mg/kg; Me01: melatonin 0.1mg/kg; Me02: Melatonin 0.2 mg/kg; Me04: Melatonin 0.4 mg/kg; MiAE: antiemetic drug + midazolam; Mid:

midazolam; MiFe: midazolam + alfentanil; MiHy: midazolam + hydroxyzine; MiKeto: ketorolac + midazolam; MiPrAE: midazolam + propofol + antiemetic drug; NA: not available; Nal: Nalbuphine; NMA: network meta-analysis; OR: odds ratio; pedED: postoperative emergence delirium in pediatric population; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; PrMi: midazolam + propofol; Pro: propofol; RCT: randomized control trial; Rem: remifentanil; SMD: standardized mean difference; SuAE: sufentanil + antiemetic drug; SUCRA: surface under the cumulative ranking curve; TrAE: tramadol + antiemetic drug

eTable 7A: SUCRA analysis of the post-operation nausea and vomiting by different interventions

Treatment	SUCRA
ClMi	98.0
Dex	83.0
Mid	77.0
DeAE	58.6
KeDAE	58.1
MiFe	55.9
FeMi	55.6
KeMi	51.1
Pla	50.4
Ket	50.0
Pro	47.1
AEdrug	43.0
MiAE	42.6
TrAE	41.6
Clo	40.2
DMAE	34.8
MiPrAE	29.2
FeAE	24.4
Fen	9.2

Sorted by efficacy order (the former, the less post-operation nausea and vomiting incidence rate)

Supplement Table 7B: SUCRA analysis of the prophylactic effect of pharmacological interventions on postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of time to leave post-anesthesia care unit based on Aldrete-score criteria

Treatment	SUCRA
TrAE	1.1
FeAE	21.9
SuAE	24.5
AEdrug	27.9
KeDAE	31.7
DeAE	40.2
Pla	42.0
Pro	44.3
Fen	53.1
PrMi	60.7
Ket	62.7
Mid	67.4
KeMi	69.0
Clo	72.8
FeMi	72.9
Dex	75.1
FePrMi	82.7

Sorted by order of preventive effect (the former, the shorter time to leave post-anesthesia care unit)

eTable 7C: SUCRA analysis of the prophylactic effect of pharmacological interventions on postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of time to extubation

Treatment	SUCRA
TrAE	2.9
AEdrug	18.4
DeAE	33.7
Pla	36.9
MiAE	40.4
Rem	40.7
SuAE	45.1
Ket	48.4
DMAE	50.1
KeDAE	53.1
Mid	54.1
FeAE	56.7
Pro	61.7
FeMi	63.0
MiPrAE	63.2
Dex	63.9
Gab	74.5
DeMi	93.5

Sorted by order of preventive effect (the former, the shorter time to extubation)

Abbreviation: AEdrug: antiemetic drug; CI: confidence interval; ClMi: clonidine + midazolam; Clo: clonidine; DeAE: dexmedetomidine + antiemetic drug; DeMi: dexmedetomidine + midazolam; Dex: dexmedetomidine; DMAE: dexmedetomidine + midazolam + antiemetic drug; ES: effect size; FeAE: fentanyl + antiemetic drug; FeMi: fentanyl + midazolam; Fen: fentanyl; FePrMi: fentanyl + propofol + midazolam; Gab: gabapentin; KeDAE: ketamine + dexmedetomidine + antiemetic drug; KeMi: midazolam + ketamine; Ket: ketamine; Me005: Melatonin 0.05 mg/kg; Me01: melatonin 0.1mg/kg; Me02: Melatonin 0.2 mg/kg; Me04: Melatonin 0.4 mg/kg; MiAE: antiemetic drug + midazolam; Mid: midazolam; MiFe: midazolam + alfentanil; MiHy: midazolam + hydroxyzine; MiKeto: ketorolac + midazolam; MiPrAE: midazolam + propofol + antiemetic drug; NA: not available; Nal: Nalbuphine; NMA: network meta-analysis; OR: odds ratio; pedED: postoperative emergence delirium in pediatric population; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; PrMi: midazolam + propofol; Pro: propofol; RCT: randomized control trial; Rem: remifentanil; SMD: standardized mean difference; SuAE: sufentanil + antiemetic drug; SUCRA: surface under the cumulative ranking curve; TrAE: tramadol + antiemetic drug

eTable 8A: League table of association between individual intervention and post-operation nausea and vomiting incidence rate

ClMi		***0.13 (0.02,0.80)**				***0.03 (0.00,0.57)**												
0.16 (0.02,1.16)	Dex	0.77 (0.27,2.21)						***0.37 (0.19,0.74)**	***0.22 (0.06,0.80)**									
***0.13 (0.02,0.77)**	0.80 (0.34,1.87)	Mid			0.40 (0.09,1.79)	0.56 (0.29,1.08)	0.46 (0.17,1.25)	0.48 (0.09,2.53)		0.29 (0.01,7.30)					0.26 (0.01,5.31)			
0.06 (0.00,1.80)	0.35 (0.02,6.28)	0.44 (0.02,8.55)	DeAE					1.04 (0.06,17.38)			0.64 (0.19,2.18)	0.69 (0.26,1.84)	0.65 (0.17,2.50)				0.32 (0.03,3.29)	
0.06 (0.00,2.32)	0.36 (0.02,8.43)	0.45 (0.02,11.39)	1.03 (0.29,3.64)	KeDAE							0.65 (0.25,1.73)							
***0.07 (0.01,0.66)**	0.44 (0.09,2.14)	0.55 (0.15,2.08)	1.27 (0.05,32.79)	1.23 (0.04,40.26)	MiFe		0.71 (0.21,2.45)											
***0.07 (0.01,0.45)**	0.44 (0.15,1.27)	0.55 (0.29,1.05)	1.25 (0.06,26.21)	1.21 (0.04,32.68)	0.99 (0.23,4.33)	FeMi												
***0.06 (0.01,0.46)**	0.37 (0.10,1.36)	0.46 (0.17,1.25)	1.06 (0.05,24.25)	1.02 (0.03,30.03)	0.83 (0.25,2.74)	0.85 (0.26,2.77)	KeMi											
***0.06 (0.01,0.44)**	***0.36 (0.20,0.67)**	0.45 (0.18,1.16)	1.04 (0.06,17.38)	1.00 (0.05,22.06)	0.82 (0.16,4.16)	0.83 (0.26,2.60)	0.98 (0.25,3.84)	Pla	1.09 (0.50,2.38)	0.89 (0.33,2.44)							0.31 (0.03,3.16)	***0.08 (0.02,0.38)**
***0.06 (0.01,0.47)**	***0.35 (0.14,0.85)**	0.44 (0.14,1.39)	1.00 (0.05,18.49)	0.97 (0.04,23.28)	0.79 (0.14,4.59)	0.80 (0.21,3.01)	0.95 (0.21,4.34)	0.96 (0.46,2.04)	Ket									
***0.05 (0.01,0.47)**	0.32 (0.10,1.01)	0.40 (0.11,1.49)	0.92 (0.05,18.25)	0.89 (0.03,22.85)	0.73 (0.11,4.70)	0.74 (0.17,3.18)	0.87 (0.17,4.51)	0.89 (0.33,2.37)	0.92 (0.27,3.16)	Pro								***0.18 (0.06,0.56)**
0.04 (0.00,1.33)	0.24 (0.01,4.73)	0.29 (0.01,6.42)	0.67 (0.30,1.51)	0.65 (0.25,1.73)	0.53 (0.02,15.24)	0.54 (0.02,12.56)	0.64 (0.03,16.22)	0.65 (0.03,12.23)	0.67 (0.03,13.93)	0.73 (0.03,16.14)	AEdrug	0.98 (0.64,1.51)						
0.04 (0.00,1.31)	0.23 (0.01,4.65)	0.29 (0.01,6.31)	0.67 (0.30,1.46)	0.65 (0.22,1.86)	0.53 (0.02,14.98)	0.53 (0.02,12.34)	0.63 (0.02,15.95)	0.64 (0.03,12.02)	0.67 (0.03,13.69)	0.72 (0.03,15.86)	0.99 (0.65,1.50)	MiAE			0.73 (0.15,3.50)	0.57 (0.13,2.55)		
0.04 (0.00,1.50)	0.23 (0.01,5.49)	0.28 (0.01,7.41)	0.65 (0.17,2.50)	0.63 (0.10,3.99)	0.51 (0.02,17.36)	0.52 (0.02,14.46)	0.61 (0.02,18.59)	0.62 (0.03,14.26)	0.65 (0.03,16.15)	0.70 (0.03,18.63)	0.96 (0.20,4.64)	0.97 (0.20,4.63)	TrAE					
0.03 (0.00,1.11)	0.21 (0.01,4.78)	0.26 (0.01,5.31)	0.60 (0.01,41.12)	0.58 (0.01,47.93)	0.47 (0.02,12.68)	0.48 (0.02,10.41)	0.57 (0.02,13.47)	0.58 (0.02,13.53)	0.60 (0.02,15.05)	0.65 (0.02,17.32)	0.89 (0.01,65.81)	0.90 (0.01,66.28)	0.92 (0.01,78.48)	Clo				
0.03 (0.00,1.33)	0.17 (0.01,4.98)	0.21 (0.01,6.70)	0.49 (0.08,2.80)	0.47 (0.07,3.12)	0.38 (0.01,15.48)	0.39 (0.01,13.02)	0.46 (0.01,16.67)	0.47 (0.02,12.98)	0.49 (0.02,14.63)	0.53 (0.02,16.83)	0.72 (0.14,3.65)	0.73 (0.15,3.49)	0.75 (0.08,6.87)	0.81 (0.01,79.35)	DMAE	0.78 (0.19,3.13)		
0.02 (0.00,1.01)	0.13 (0.00,3.77)	0.17 (0.01,5.07)	0.38 (0.07,2.06)	0.37 (0.06,2.31)	0.30 (0.01,11.74)	0.30 (0.01,9.86)	0.36 (0.01,12.63)	0.37 (0.01,9.81)	0.38 (0.01,11.07)	0.41 (0.01,12.74)	0.56 (0.12,2.67)	0.57 (0.13,2.55)	0.58 (0.07,5.12)	0.63 (0.01,60.45)	0.78 (0.19,3.14)	MiPrAE		
***0.02 (0.00,0.39)**	0.11 (0.01,1.24)	0.14 (0.01,1.72)	0.32 (0.03,3.28)	0.31 (0.02,4.39)	0.25 (0.01,4.33)	0.26 (0.02,3.42)	0.30 (0.02,4.50)	0.31 (0.03,3.17)	0.32 (0.03,3.69)	0.35 (0.03,4.35)	0.48 (0.04,5.58)	0.48 (0.04,5.60)	0.50 (0.03,7.31)	0.54 (0.01,27.06)	0.66 (0.04,12.13)	0.85 (0.05,15.09)	FeAE	
***0.01 (0.00,0.08)**	***0.05 (0.01,0.17)**	***0.06 (0.01,0.25)**	0.13 (0.01,2.81)	0.13 (0.00,3.50)	***0.10 (0.01,0.76)**	***0.11 (0.02,0.53)**	***0.13 (0.02,0.74)**	***0.13 (0.04,0.42)**	***0.13 (0.03,0.54)**	***0.14 (0.05,0.41)**	0.20 (0.01,4.63)	0.20 (0.01,4.66)	0.20 (0.01,5.79)	0.22 (0.01,6.35)	0.27 (0.01,9.22)	0.35 (0.01,11.54)	0.41 (0.03,5.58)	Fen

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimate effect sizes for the outcome of post-operation nausea and vomiting incidence rate. Interventions are reported in order of mean ranking of safety profile, and outcomes are expressed as odds ratio (OR) (95% confidence intervals). For the pairwise meta-analyses, OR of less than 1 indicate that the treatment specified in the row got better safety profile than that specified in the column. For the network meta-analysis (NMA), OR of less than 1 indicate that the treatment specified in the column got better safety profile than that specified in the row. Bold results marked with * indicate statistical significance.

eTable 8B: League table of the prophylactic effect of postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of time to leave post-anesthesia care unit

TrAE					***-22.40 (-24.66,-20.14)**											
-16.34 (-34.98,2.31)	FeAE	-1.10 (-4.03,1.83)	-2.80 (-5.78,0.18)													
-17.44 (-36.11,1.24)	-1.10 (-13.52,11.32)	SuAE	-1.70 (-4.89,1.49)													
***-19.14 (-33.03,-5.25)**	-2.80 (-15.23,9.63)	-1.70 (-14.18,10.78)	AEdrug	-0.90 (-7.79,5.99)	-3.11 (-10.59,4.37)	-9.00 (-27.39,9.39)							-19.00 (-44.18,6.18)			
***-20.04 (-39.68,-0.39)**	-3.70 (-22.35,14.95)	-2.60 (-21.28,16.08)	-0.90 (-14.80,13.00)	KeDAE												
***-22.40 (-34.68,-10.12)**	-6.06 (-20.09,7.96)	-4.96 (-19.03,9.11)	-3.26 (-9.75,3.23)	-2.36 (-17.70,12.97)	DeAE											
***-28.13 (-54.15,-2.12)**	-11.80 (-37.06,13.47)	-10.70 (-35.99,14.59)	-9.00 (-30.99,13.00)	-8.10 (-34.11,17.92)	-5.73 (-28.67,17.20)	Pla	1.43 (-0.29,3.15)	***-2.00 (-3.19,-0.81)**		-4.15 (-12.50,4.19)	-10.00 (-21.64,1.64)		-10.00 (-35.25,15.25)		-7.22 (-14.46,0.02)	
***-28.15 (-55.12,-1.18)**	-11.82 (-38.07,14.43)	-10.72 (-36.99,15.56)	-9.02 (-32.13,14.10)	-8.12 (-35.09,18.86)	-5.75 (-29.76,18.26)	-0.02 (-7.14,7.10)	Pro			***-3.10 (-4.93,-1.27)**	-2.00 (-4.45,0.45)					
***-30.13 (-58.83,-1.43)**	-13.80 (-41.82,14.23)	-12.70 (-40.75,15.35)	-11.00 (-36.11,14.12)	-10.10 (-38.80,18.61)	-7.73 (-33.67,18.21)	-2.00 (-14.13,10.13)	-1.98 (-16.04,12.08)	Fen								
***-32.09 (-61.32,-2.87)**	-15.76 (-44.32,12.80)	-14.66 (-43.24,13.93)	-12.96 (-38.67,12.76)	-12.06 (-41.29,17.17)	-9.69 (-36.22,16.83)	-3.96 (-17.28,9.36)	-3.94 (-18.13,10.25)	-1.96 (-19.98,16.06)	PrMi		0.00 (-1.52,1.52)	***-3.75 (-7.32,-0.18)**				
***-32.43 (-59.29,-5.57)**	-16.09 (-42.23,10.04)	-14.99 (-41.15,11.16)	-13.29 (-36.28,9.69)	-12.39 (-39.25,14.47)	-10.03 (-33.92,13.86)	-4.30 (-10.98,2.39)	-4.28 (-12.59,4.03)	-2.30 (-16.14,11.55)	-0.34 (-13.81,13.13)	Ket	0.93 (-1.11,2.97)				-1.90 (-4.25,0.45)	
***-33.51 (-60.41,-6.60)**	-17.17 (-43.35,9.01)	-16.07 (-42.28,10.13)	-14.37 (-37.41,8.67)	-13.47 (-40.38,13.43)	-11.11 (-35.05,12.83)	-5.38 (-12.24,1.49)	-5.36 (-13.77,3.06)	-3.38 (-17.31,10.56)	-1.42 (-12.83,10.00)	-1.08 (-8.23,6.07)	Mid	-0.65 (-6.47,5.18)		-2.00 (-4.50,0.50)	-0.17 (-2.14,1.79)	***-5.00 (-7.77,-2.23)**
***-34.23 (-62.54,-5.91)**	-17.89 (-45.52,9.73)	-16.79 (-44.44,10.86)	-15.09 (-39.76,9.58)	-14.19 (-42.50,14.12)	-11.83 (-37.34,13.68)	-6.09 (-17.27,5.08)	-6.07 (-18.26,6.11)	-4.09 (-20.58,12.40)	-2.13 (-13.78,9.51)	-1.80 (-13.15,9.55)	-0.72 (-9.53,8.10)	KeMi				
***-38.13 (-69.32,-6.95)**	-21.80 (-52.37,8.77)	-20.70 (-51.29,9.89)	-19.00 (-46.92,8.92)	-18.10 (-49.29,13.09)	-15.74 (-44.40,12.93)	-10.00 (-37.99,17.98)	-9.98 (-38.86,18.90)	-8.00 (-38.50,22.50)	-6.04 (-37.04,24.95)	-5.71 (-34.48,23.07)	-4.63 (-33.44,24.19)	-3.91 (-34.04,26.23)	Clo			
***-35.51 (-65.10,-5.92)**	-19.17 (-48.11,9.76)	-18.07 (-47.03,10.88)	-16.37 (-42.50,9.76)	-15.47 (-45.07,14.12)	-13.11 (-40.04,13.82)	-7.38 (-21.48,6.73)	-7.36 (-22.28,7.57)	-5.38 (-23.98,13.23)	-3.42 (-20.22,13.39)	-3.08 (-17.33,11.17)	-2.00 (-14.33,10.33)	-1.28 (-16.43,13.87)	2.63 (-28.71,33.97)	FeMi		-3.00 (-6.29,0.29)
***-34.81 (-61.31,-8.32)**	-18.48 (-44.24,7.28)	-17.38 (-43.16,8.41)	-15.68 (-38.24,6.88)	-14.78 (-41.28,11.72)	-12.41 (-35.89,11.06)	***-6.68 (-11.71,-1.65)**	-6.66 (-14.81,1.49)	-4.68 (-17.81,8.45)	-2.72 (-15.92,10.48)	-2.38 (-9.53,4.77)	-1.30 (-7.92,5.32)	-0.59 (-11.61,10.44)	3.32 (-25.11,31.76)	0.70 (-13.29,14.69)	Dex	
***-38.51 (-68.13,-8.89)**	-22.17 (-51.13,6.79)	-21.07 (-50.06,7.91)	-19.37 (-45.53,6.78)	-18.47 (-48.09,11.15)	-16.11 (-43.06,10.84)	-10.38 (-24.53,3.78)	-10.36 (-25.33,4.62)	-8.38 (-27.02,10.27)	-6.42 (-23.26,10.43)	-6.08 (-20.38,8.22)	-5.00 (-17.38,7.38)	-4.28 (-19.48,10.92)	-0.37 (-31.74,30.99)	-3.00 (-15.51,9.51)	-3.70 (-17.74,10.35)	FePrMi

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of the time to leave post-anesthesia care unit. Interventions are reported in the order of mean ranking of the safety profile, and outcomes are expressed as mean difference (MD) (95% confidence intervals). For the pairwise meta-analyses, an MD of less than 0 indicated that the treatment specified in the row had a better safety profile than that specified in the column. For the network meta-analysis (NMA), an MD of less than 0 indicated that the treatment specified in the column had a better safety profile than that specified in the row. Bold results marked with * indicate statistical significance.

eTable8C: League table of the prophylactic effect of postoperative emergence delirium in pediatric population following sevoflurane anesthesia: aspect of time to extubation

TrAE		***-3.60 (-4.17,-3.03)**															
-2.55 (-6.03,0.93)	AEdrug	-3.88 (-11.48,3.72)				-0.60 (-2.31,1.11)			***-2.10 (-2.94,-1.26)**		-0.20 (-1.80,1.40)						
***-3.60 (-6.33,-0.87)**	-1.05 (-3.20,1.11)	DeAE	-1.00 (-2.89,0.89)	-0.40 (-1.41,0.61)							***-2.18 (-3.38,-0.98)**						
-3.86 (-7.92,0.20)	-1.31 (-4.79,2.17)	-0.26 (-3.26,2.75)	Pla		-0.07 (-1.31,1.17)		-0.33 (-0.76,0.10)			***-0.38 (-0.73,-0.03)**	-1.70 (-3.65,0.25)	-1.50 (-3.15,0.15)			***-1.33 (-2.30,-0.36)**	-4.50 (-16.56,7.56)	
***-4.00 (-7.95,-0.05)**	-1.45 (-5.03,2.13)	-0.40 (-3.26,2.46)	-0.14 (-4.29,4.00)	MiAE				-0.37 (-1.30,0.56)						***-1.27 (-1.89,-0.65)**			
-3.93 (-8.94,1.09)	-1.38 (-5.94,3.18)	-0.33 (-4.54,3.88)	-0.07 (-3.01,2.87)	0.07 (-5.01,5.15)	Rem												
-4.13 (-8.39,0.13)	-1.58 (-4.59,1.43)	-0.53 (-3.80,2.74)	-0.27 (-4.41,3.87)	-0.13 (-4.47,4.21)	-0.20 (-5.28,4.88)	SuAE					0.40 (-1.41,2.21)						
-4.40 (-8.82,0.02)	-1.85 (-5.73,2.04)	-0.80 (-4.27,2.68)	-0.54 (-2.28,1.21)	-0.40 (-4.90,4.10)	-0.47 (-3.89,2.95)	-0.27 (-4.75,4.22)	Ket			-1.30 (-3.58,0.98)					0.10 (-0.46,0.66)		
***-4.60 (-9.16,-0.04)**	-2.05 (-6.32,2.22)	-1.00 (-4.65,2.65)	-0.74 (-5.47,3.99)	-0.60 (-2.88,1.67)	-0.67 (-6.25,4.90)	-0.47 (-5.39,4.45)	-0.20 (-5.25,4.85)	DMAE						***-1.13 (-2.14,-0.12)**			
***-4.65 (-9.11,-0.19)**	-2.10 (-4.90,0.70)	-1.05 (-4.58,2.48)	-0.79 (-5.26,3.67)	-0.65 (-5.19,3.89)	-0.72 (-6.07,4.63)	-0.52 (-4.63,3.59)	-0.25 (-5.04,4.53)	-0.05 (-5.16,5.05)	KeDAE								
***-4.78 (-9.41,-0.15)**	-2.23 (-6.39,1.93)	-1.18 (-4.92,2.56)	-0.92 (-3.16,1.32)	-0.78 (-5.48,3.93)	-0.85 (-4.55,2.85)	-0.65 (-5.36,4.06)	-0.38 (-2.79,2.03)	-0.18 (-5.40,5.05)	-0.13 (-5.14,4.89)	Mid			-0.70 (-1.71,0.31)				***-5.30 (-9.56,-1.04)**
***-4.79 (-8.15,-1.42)**	-2.23 (-4.55,0.08)	-1.19 (-3.15,0.78)	-0.93 (-3.94,2.09)	-0.79 (-4.25,2.68)	-0.86 (-5.07,3.36)	-0.66 (-3.70,2.38)	-0.39 (-3.87,3.10)	-0.19 (-4.34,3.97)	-0.13 (-3.77,3.50)	-0.01 (-3.77,3.75)	FeAE						
***-5.36 (-10.49,-0.23)**	-2.81 (-7.50,1.88)	-1.76 (-6.10,2.59)	-1.50 (-4.64,1.64)	-1.36 (-6.56,3.84)	-1.43 (-5.73,2.87)	-1.23 (-6.42,3.96)	-0.96 (-4.55,2.63)	-0.76 (-6.44,4.92)	-0.71 (-6.17,4.75)	-0.58 (-4.43,3.27)	-0.57 (-4.93,3.78)	Pro					
***-5.48 (-10.92,-0.04)**	-2.93 (-7.97,2.12)	-1.88 (-6.58,2.83)	-1.62 (-5.25,2.01)	-1.48 (-6.98,4.03)	-1.55 (-6.22,3.12)	-1.35 (-6.86,4.16)	-1.08 (-4.82,2.66)	-0.88 (-6.83,5.08)	-0.83 (-6.60,4.94)	-0.70 (-3.55,2.15)	-0.69 (-5.41,4.03)	-0.12 (-4.92,4.68)	FeMi				
***-5.40 (-9.81,-0.99)**	-2.85 (-6.94,1.24)	-1.80 (-5.27,1.66)	-1.54 (-6.13,3.04)	-1.40 (-3.36,0.56)	-1.47 (-6.92,3.97)	-1.28 (-6.04,3.49)	-1.01 (-5.92,3.90)	-0.80 (-3.27,1.67)	-0.75 (-5.71,4.20)	-0.63 (-5.72,4.47)	-0.62 (-4.60,3.36)	-0.04 (-5.60,5.51)	0.07 (-5.77,5.92)	MiPrAE			
***-5.13 (-9.34,-0.93)**	-2.58 (-6.21,1.04)	-1.53 (-4.73,1.66)	***-1.28 (-2.34,-0.21)**	-1.14 (-5.42,3.15)	-1.21 (-4.34,1.93)	-1.01 (-5.27,3.26)	-0.74 (-2.63,1.15)	-0.53 (-5.39,4.32)	-0.48 (-5.06,4.10)	-0.36 (-2.80,2.08)	-0.35 (-3.55,2.85)	0.22 (-3.09,3.54)	0.34 (-3.41,4.10)	0.27 (-4.44,4.98)	Dex		
-8.36 (-21.36,4.64)	-5.81 (-18.64,7.02)	-4.76 (-17.47,7.95)	-4.50 (-16.85,7.85)	-4.36 (-17.39,8.67)	-4.43 (-17.13,8.27)	-4.23 (-17.25,8.79)	-3.96 (-16.43,8.51)	-3.76 (-16.98,9.47)	-3.71 (-16.84,9.42)	-3.58 (-16.13,8.97)	-3.57 (-16.29,9.14)	-3.00 (-15.74,9.74)	-2.88 (-15.75,9.99)	-2.96 (-16.13,10.22)	-3.22 (-15.62,9.17)	Gab	
***-10.08 (-16.91,-3.24)**	***-7.53 (-14.05,-1.00)**	***-6.48 (-12.75,-0.21)**	***-6.22 (-11.72,-0.72)**	-6.08 (-12.96,0.81)	-6.15 (-12.39,0.09)	-5.95 (-12.84,0.94)	***-5.68 (-11.26,-0.10)**	-5.48 (-12.73,1.77)	-5.43 (-12.53,1.67)	***-5.30 (-10.33,-0.27)**	-5.29 (-11.57,0.99)	-4.72 (-11.05,1.62)	-4.60 (-10.38,1.18)	-4.67 (-11.83,2.49)	-4.94 (-10.53,0.65)	-1.72 (-15.24,11.80)	DeMi

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of the time to extubation. Interventions are reported in the order of mean ranking of the safety profile, and outcomes are expressed as mean difference (MD) (95% confidence intervals). For the pairwise meta-analyses, an MD of less than 0 indicated that the treatment specified in the row had a better safety profile than that specified in the column. For the network meta-analysis (NMA), an MD of less than 0 indicated that the treatment specified in the column had a better safety profile than that specified in the row. Bold results marked with * indicate statistical significance.

Abbreviation: AEdrug: antiemetic drug; CI: confidence interval; ClMi: clonidine + midazolam; Clo: clonidine; DeAE: dexmedetomidine + antiemetic drug; DeMi: dexmedetomidine + midazolam; Dex: dexmedetomidine; DMAE: dexmedetomidine + midazolam + antiemetic drug; ES:

effect size; FeAE: fentanyl + antiemetic drug; FeMi: fentanyl + midazolam; Fen: fentanyl; FePrMi: fentanyl + propofol + midazolam; Gab: gabapentin; KeDAE: ketamine + dexmedetomidine + antiemetic drug; KeMi: midazolam + ketamine; Ket: ketamine; Me005: Melatonin 0.05 mg/kg; Me01: melatonin 0.1mg/kg; Me02: Melatonin 0.2 mg/kg; Me04: Melatonin 0.4 mg/kg; MiAE: antiemetic drug + midazolam; Mid: midazolam; MiFe: midazolam + alfentanil; MiHy: midazolam + hydroxyzine; MiKeto: ketorolac + midazolam; MiPrAE: midazolam + propofol + antiemetic drug; NA: not available; Nal: Nalbuphine; NMA: network meta-analysis; OR: odds ratio; pedED: postoperative emergence delirium in pediatric population; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; PrMi: midazolam + propofol; Pro: propofol; RCT: randomized control trial; Rem: remifentanil; SMD: standardized mean difference; SuAE: sufentanil + antiemetic drug; SUCRA: surface under the cumulative ranking curve; TrAE: tramadol + antiemetic drug

eTable 9: Inconsistency of different intervention

Part 1: design-by-treatment and loop inconsistency model

Inconsistency model	chi^2	$Prob>chi^2$
	changes in postoperative emergence delirium severity	
design-by-treatment	1.86	1.0000
loop inconsistency	0.12	1.0000
	postoperative emergence delirium incidence rate	
design-by-treatment	26.16	0.6169
loop inconsistency	7.51	0.4832
	post-operation nausea and vomiting incidence rate	
design-by-treatment	4.17	0.9392
loop inconsistency	0.10	0.9915
	time to leave post-anesthesia care unit	
design-by-treatment	1.39	0.9860
loop inconsistency	0.99	0.9119
	time to extubation	
design-by-treatment	3.38	0.8482
loop inconsistency	3.73	0.2926

Part 2: side-splitting inconsistency model:

Part of postoperative emergence delirium incidence rate

Side	symmetric		nosymmetric		Treatments used	
	P>z	tau	P>z	tau		
AA AC	0.184	0.699137	0.064	0.681596	AA (reference):	Pla
AA AD	0.934	0.716525	0.774	0.716729	AB:	MiAE

AA AE	0.148	0.695001	0.16	0.694199	AC:	Clo
AA AI	0.459	0.707861	.	.	AD:	Dex
AA AK	0.788	0.71648	0.593	0.712896	AE:	DeAE
AA AL	0.971	0.716652	0.711	0.717706	AF:	ClMi
AA AN	0.13	0.677811	0.166	0.682587	AG:	Me04
AA AP	0.72	0.717113	0.883	0.716351	AH:	DMAE
AA AS	0.881	0.715715	.	.	AI:	Fen
AA AU	0.626	0.711069	.	.	AJ:	FeMi
AA AV	.	.	.	.	AK:	FeAE
AA AY	.	.	.	.	AL:	Mid
AA BC	0.938	0.717612	0.283	0.706123	AM:	FePrMi
AB AE	0.928	0.703261	0.928	0.703261	AN:	Ket
AB AH	0.58	0.714803	.	.	AO:	KeDAE
AB BB	0.247	0.698609	.	.	AP:	Pro
AC AL	0.064	0.681598	0.064	0.681597	AQ:	Me005
AC BC	0.076	0.684127	0.283	0.706123	AR:	Me02
AD AI	0.355	0.702142	0.951	0.71539	AS:	Nal
AD AL	0.892	0.716491	0.759	0.716123	AT:	SuAE
AD AN	0.696	0.713351	0.736	0.715608	AU:	Me01
AD AP	0.324	0.70174	0.834	0.705953	AV:	Gab
AD AU	0.737	0.712755	.	.	AW:	TrAE
AE AK	0.855	0.716817	0.5	0.70778	AX:	MiFe
AE AW	0.983	0.703247	.	.	AY:	Rem

AE BC	0.79	0.72049	0.789	0.720492	AZ:	KeMi
AF AJ	0.114	0.686044	0.565	0.709651	BA:	PrMi
AF AL	0.565	0.709644	0.565	0.709644	BB:	MiPrAE
AG AL	0.984	0.703248	0.984	0.703248	BC:	AEdrug
AG AQ	.	.	.	.	BD:	MiHy
AG AR	.	.	.	.		
AH BB	0.278	0.701399	0.579	0.71481		
AI AP	0.509	0.709139	0.478	0.707576		
AJ AL	0.052	0.680568	0.052	0.680568		
AJ AM	0.3	0.704124	.	.		
AK AT	0.5	0.70778	.	.		
AK BC	0.5	0.707779	0.5	0.707777		
AL AM	0.3	0.704121	.	.		
AL AN	0.161	0.685587	0.166	0.682587		
AL AP	0.118	0.68559	0.519	0.715132		
AL AQ	0.984	0.703248	.	.		
AL AR	0.984	0.703248	.	.		
AL AU	0.296	0.702419	.	.		
AL AX	0.307	0.703876	.	.		
AL AZ	0.366	0.703797	.	.		
AL BA	0.308	0.70387	.	.		
AL BD	0.98	0.703248	.	.		
AN AP	0.215	0.687419	0.883	0.716352		

AN AS	0.881	0.715715	.	.
AO BC	0.978	0.703249	0.978	0.703249
AQ AR	.	.	.	.
AT BC	0.5	0.707777	0.5	0.707777
AX AZ	0.307	0.703878	0.307	0.703878
AZ BA	0.941	0.714856	0.365	0.703802

Part of changes in postoperative emergence delirium severity

Side	symmetric		nosymmetric		Treatments used	
	P>z	tau	P>z	tau		
A C	.	.	.	.	A (reference):	Pla
A D *	0.685	1.59965	0.959	1.603718	B:	MiAE
A E *	0.855	1.600222	0.834	1.602242	C:	Clo
A I *	0.377	1.5865	.	.	D:	Dex
A K *	0.809	1.60027	0.818	1.602281	E:	DeAE
A L *	0.941	1.603329	0.973	1.603541	F:	ClMi
A N	0.979	1.603828	0.895	1.60392	G:	DeMi
A P	0.855	1.604267	0.847	1.604094	H:	DMAE
A U *	0.365	1.58134	.	.	I:	Fen
A V	.	.	.	.	J:	FeMi
B H *	0.905	1.603366	.	.	K:	FeAE
B M *	0.937	1.574958	0.938	1.574962	L:	Mid
B W *	0.853	1.60294	.	.	M:	AEdrug

D I	0.756	1.601035	0.935	1.603911	N:	Ket
D L *	0.808	1.602121	0.523	1.592847	O:	KeDAE
D N	0.894	1.603347	0.972	1.603857	P:	Pro
D U *	0.807	1.602058	.	.	Q:	MiKeto
E K *	0.917	1.603698	0.908	1.603402	R:	TrAE
E M	0.922	1.603488	0.921	1.603475	S:	MiHy
E R *	0.972	1.57446	.	.	T:	SuAE
F J *	0.858	1.603043	0.858	1.603043	U:	Me01
F L *	0.861	1.603003	0.861	1.603003	V:	Gab
G L *	0.931	1.574421	0.931	1.574421	W:	MiPrAE
H W	0.846	1.602969	0.9	1.603573	X:	MiFe
I P	0.695	1.602114	0.529	1.597327	Y:	PrMi
J L *	0.909	1.574457	0.909	1.574457	Z:	KeMi
J Q *	0.75	1.601125	.	.		
K M *	0.909	1.603486	0.91	1.603473		
K T *	0.908	1.603402	.	.		
L N	0.972	1.60392	0.895	1.60392		
L P	0.885	1.604079	0.847	1.604094		
L Q *	0.753	1.601085	.	.		
L S *	0.947	1.574419	.	.		
L U *	0.487	1.590441	.	.		
L X *	0.722	1.599931	.	.		
L Y *	0.233	1.562735	.	.		

L Z *	0.749	1.60024	.	.
M O *	0.98	1.574487	.	.
M T *	0.91	1.603473	.	.
N P	0.848	1.604029	0.847	1.604094
X Z *	0.718	1.599961	0.718	1.599961
Y Z	0.303	1.573047	0.236	1.562855

Part of post-operation nausea and vomiting incidence rate

Side	symmetric		nosymmetric		Treatments used	
	P>z	tau	P>z	tau		
A D	0.762	4.41E-09	0.898	9.43E-08	A (reference):	Pla
A E *	0.999	1.06E-08	0.999	3.12E-08	B:	MiAE
A I *	0.393	3.11E-07	.	.	C:	Clo
A K *	0.999	4.95E-07	.	.	D:	Dex
A L	0.928	1.52E-07	0.898	6.24E-06	E:	DeAE
A N *	0.303	1.04E-07	.	.	F:	ClMi
A P *	0.973	3.30E-07	.	.	G:	AEdrug
B E	0.919	1.77E-08	0.919	9.37E-08	H:	DMAE
B G	0.919	1.85E-07	0.919	1.61E-07	I:	Fen
B H *	0.999	3.26E-06	.	.	J:	FeMi
B Q *	1	5.23E-06	.	.	K:	FeAE
C L *	1	1.26E-08	1	1.55E-07	L:	Mid
D L	0.898	2.08E-07	0.898	2.16E-07	M:	TrAE

D N	0.385	3.20E-07	0.73	1.57E-05	N:	Ket
E G	0.919	3.17E-08	0.919	2.64E-07	O:	KeDAE
E K *	0.999	6.90E-08	.	.	P:	Pro
E M *	1	9.94E-07	.	.	Q:	MiPrAE
F J	0.634	1.43E-05	0.783	6.50E-06	R:	KeMi
F L *	0.783	6.98E-06	0.783	6.36E-06	S:	MiFe
G O *	1	1.31E-08	.	.		
H Q	.	.	.	.		
I P *	0.393	1.57E-07	0.393	9.11E-08		
J L *	0.494	7.61E-08	0.494	5.84E-07		
L P	0.691	5.44E-08	0.536	1.89E-07		
L R *	1	1.25E-08	.	.		
L S *	0.364	1.44E-08	.	.		
R S *	0.364	3.31E-07	.	.		

Part of time to leave post-anesthesia care unit:

Side	symmetric		nosymmetric		Treatments used	
	P>z	tau	P>z	tau		
A B *	0.99	6.158225	.	.	A (reference):	Pla
A C	0.566	6.26402	0.764	6.352721	B:	Clo
A F	.	.	.	.	C:	Dex
A I	0.557	6.261567	0.557	6.261567	D:	DeAE
A K	0.95	6.399998	0.827	6.396823	E:	PrMi

A M	0.564	6.326263	0.564	6.326263	F:	Fen
A P *	0.99	6.158234	0.99	6.158234	G:	FeMi
B P *	0.99	6.158229	0.99	6.158234	H:	FeAE
C I	0.764	6.352721	0.764	6.352715	I:	Mid
C K	0.927	6.405412	0.628	6.343029	J:	FePrMi
D P *	0.99	6.158226	0.991	6.158224	K:	Ket
D Q *	0.991	6.158216	.	.	L:	KeDAE
E I *	0.517	6.30056	0.517	6.300564	M:	Pro
E O *	0.517	6.300562	0.517	6.300565	N:	SuAE
G I *	0.997	6.158208	0.997	6.158208	O:	KeMi
G J	.	.	.	.	P:	AEdrug
H N	.	.	.	.	Q:	TrAE
H P *	0.996	6.158193	0.996	6.158211		
I J *	0.997	6.158208	.	.		
I K	0.599	6.341436	0.827	6.396823		
I M	0.472	6.279358	0.564	6.326242		
I O *	0.996	6.158211	.	.		
K M	0.807	6.395171	0.564	6.326242		
L P *	0.999	6.158206	0.999	6.158206		
N P *	0.996	6.15821	0.996	6.158211		

Part of time to extubation:

Side	symmetric	nosymmetric	Treatments used

	P>z	tau	P>z	tau		
A D *	0.735	1.463699	.	.	A (reference):	Pla
A E *	0.268	1.387803	0.268	1.387835	B:	MiAE
A I	.	.	.	.	C:	AEdrug
A K *	0.268	1.387811	0.268	1.38784	D:	Dex
A L	0.495	1.414283	0.495	1.414283	E:	DeAE
A N	0.958	1.473266	0.495	1.414294	F:	TrAE
A P	.	.	.	.	G:	DeMi
A Q	.	.	.	.	H:	DMAE
B E *	0.998	1.361716	0.999	1.361726	I:	Rem
B H *	0.846	1.480379	.	.	J:	FeMi
B M *	0.591	1.41151	.	.	K:	FeAE
C E	0.068	1.319879	0.068	1.319877	L:	Mid
C K *	0.068	1.319872	0.068	1.319874	M:	MiPrAE
C O *	1	1.361722	.	.	N:	Ket
C R *	0.068	1.319878	.	.	O:	KeDAE
D N	0.415	1.380091	0.735	1.463713	P:	Pro
E F *	0.995	1.361723	.	.	Q:	Gab
E K *	0.068	1.319875	0.068	1.319876	R:	SuAE
G L *	0.999	1.36172	0.999	1.361721		
H M	0.66	1.446989	0.846	1.480379		
J L *	0.998	1.361721	0.998	1.361722		
K R *	0.068	1.319874	.	.		
L N	0.495	1.414285	0.495	1.414291		

eTable 10: Estimated between-studies standard deviation of different outcome

Outcome	Estimated between-studies standard deviation
Changes in postoperative emergence delirium severity	1.5743268
Postoperative emergence delirium incidence rate	0.70324536
Post-operation nausea and vomiting incidence rate	1.288e-07
Time to leave post-anesthesia care unit	6.1582046
Time to extubation	1.3617207

Supplementary material: PRISMA 2020 checklist of current network meta-analysis

Section and Topic	Item #	Checklist item	Page where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	5-6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	7-8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	7-8
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	9-10
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	9-10
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	9-10
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	9-10
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	10-11
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	10-11
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	10-11
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	10-11
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	11-12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	11-12

Section and Topic	Item #	Checklist item	Page where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	11-12
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	12-13
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	12-13
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	12-13
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	13-14
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	13-14
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	13-14
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	15-17, Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	15-17, eTab 2
Study characteristics	17	Cite each included study and present its characteristics.	15-17, eTab 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	16-17, eFig 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	17-18, eTab 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	17-18, eFig 3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	17-18, Fig 3, eFig 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	17-18, eTab 6-7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	18-19
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	18-19, eFig 3

Section and Topic	Item #	Checklist item	Page where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	18-19, eTab 6-7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	20-23
	23b	Discuss any limitations of the evidence included in the review.	23-24
	23c	Discuss any limitations of the review processes used.	23-24
	23d	Discuss implications of the results for practice, policy, and future research.	24
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Conflict of interest form
Competing interests	26	Declare any competing interests of review authors.	Conflict of interest form
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Conflict of interest form

The current checklist followed the latest PRISMA 2020 guideline [1].

Reference

[1] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj 2021;372:n71.