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Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies

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Background. Emergence agitation (EA) in children is increased after sevoflurane anaesthesia. The efficacy of prophylactic treatment is controversial. The aim of this study was to provide a meta-analysis of the studies of the pharmacological prevention of EA in children.

Methods. A comprehensive literature search was conducted to identify clinical trials that focused on the prevention of EA in children anaesthetized with sevoflurane, desflurane, or both. The data from each trial were combined using the Mantel–Haenszel model to calculate the pooled odds ratio (OR) and 95% confidence interval. I^2 statistics were used to assess statistics heterogeneity and the funnel plot and the Begg–Mazumdar test to assess bias.

Results. Thirty-seven articles were found which included a total of 1695 patients in the intervention groups and 1477 in the control ones. Midazolam and $5HT_3$ inhibitors were not found to have a protective effect against EA [OR=0.88 (0.44, 1.76); OR=0.39 (0.12, 1.31), respectively], whereas propofol [OR=0.21 (0.16, 0.28)], ketamine [OR=0.28 (0.13, 0.60)], α_2-adrenoceptors [OR=0.23 (0.17, 0.33)], fentanyl [OR=0.31 (0.18, 0.56)], and peroperative analgesia [OR=0.15 (0.07, 0.34)] were all found to have a preventive effect. Subgroup analysis according to the peroperative analgesia given does not affect the results.

Conclusions. This meta-analysis found that propofol, ketamine, fentanyl, and preoperative analgesia had a prophylactic effect in preventing EA. The analgesic properties of these drugs do not seem to have a role in this effect.

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The increased use of sevoflurane and desflurane in developing countries has been accompanied by an increase in emergence agitation (EA), a postoperative behavioural disorder. First described in the early 1960s,[1] EA is characterized by a variety of presentations including crying, excitation, agitation, and delirium occurring during the early stage of emergence from anaesthesia in children.[2]

With sevoflurane or desflurane anaesthesia, the incidence of EA varies widely between 2% and 80% depending on the scoring system and the anaesthetic technique used, and is more frequently observed in preschool children.[3–5] Despite its spontaneous resolution, EA is still considered as a potentially serious complication because of the risks of self-injury, and because of the stress caused to both caregivers and families.

The incidence of EA has led many authors to propose prophylactic treatment to reduce its incidence. These have included propofol, α_2-adrenoceptor (AR) agonists, midazolam, and ketamine.[6–8] However, their efficacy remains the subject of debate.

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Meta-analysis is a statistical method allowing aggregation and quantification of the therapeutic effects from multiple studies. The aim of this study was to perform a meta-analysis of the efficacy of pharmacological prophylactic interventions currently proposed to reduce the incidence of EA.

Methods

The bibliographic search and analysis for this meta-analysis was conducted according to the guidelines of the Cochrane Handbook for systematic reviews of intervention and the QUORUM statements.[9]

The databases searched included Pubmed, Embase, and the Cochrane Database for Systemic Review. As descriptions of EA including agitation, behavioural problems, and delirium, the following search terms were used: 'agitation, and sevoflurane or desflurane, and children or infant, behavior, and sevoflurane or desflurane, and children or infant, delirium, and sevoflurane or desflurane, and children and infant'. Only articles published in English were considered. Where the full text could not be found, authors were contacted to provide a copy of the original article.

The articles obtained were independently analysed by two senior anaesthetists and those meeting the following criteria were included in the analysis: randomized controlled trial, double-blinded (articles in whom the evaluation was blinded were included), sevoflurane or desflurane anaesthesia, absence of neurological disease, standardized anaesthesia protocols, agitation or delirium or behavioural disturbances as one of the study endpoints, a control group, and a standardized definition of EA between the control and intervention groups in each study.

We excluded from analysis all studies comparing two prophylactic agents or interventions, and those exploring curative treatments for EA. In addition, a manual search of references cited in the selected articles (including reviews and meta-analyses) was performed. The most recent search date was February 2009.

Two independent readers assessed article quality and extracted data. Retained data included the age of patients, type of surgery, sedative premedication (dose, timing, and route of administration), dose, timing, and route of administration of prophylactic agent or technique, hypnotic agents, intraoperative opioids used, peroperative analgesia, and the percentage of patients experiencing agitation in each group based on the criteria chosen by the authors. When conflicting results were found, the article was rechecked by both anaesthetists.

Statistical analysis was performed using the Review Manager 5 software (RevMan 5, The Cochrane Collaboration, Oxford, UK). The analysis of the incidence of EA was performed using the odds ratio (OR) computed using the Mantel–Haenszel method (fixed or random models). The OR represents the odds of EA occurring in the prophylactic group compared with the control group. A confidence interval for the OR of <1 indicates efficacy in EA prevention. In order to minimize the publication bias, some data transformations were necessary. Secondly, OR computation requires the results to be expressed as percentages. Where outcomes were given as mixed percentages and continuous results, a standardized mean ratio was first computed, then transformed as partial OR using the formula of Chinn:[10] Ln OR$=1.814\times$SMR (Ln: logarithm). The data were then entered as Ln(OR) and SD(LnOR). Overall OR (and 95% confidence interval) was finally computed with the inverse variance method [http://www.cochrane-handbook.org/ (Section 9.4.6)].

To assess the impact of study heterogeneity on the results of the meta-analysis, the differences of study design regarding premedication, anaesthetic agent used (sevoflurane or desflurane), modalities of pain treatment, and parental presence during induction and recovery from anaesthesia, an I^2 test was performed. According to the Cochrane review guidelines, an $I^2 >40\%$ and a P-value of <0.1 are considered as the threshold for heterogeneity and indicate the use of a random effect in OR calculation.

Each prophylactic agent was tested grouping all administration routes and timing modalities. Then, for each drug, EA prevention was analysed according to timing of administration, route of administration, anaesthesia agent used, concurrent preoperative analgesia, and pain expected as a result of the intervention (anaesthesia for MRI *vs* surgery). In addition, if statistical heterogeneity was present, analysis was carried out by removing studies one by one according to the route and timing of drug administration. Studies displaying statistical heterogeneity were then further analysed for differences in design and results. Results are expressed as OR (95% confidence interval), I^2, and P-value for heterogeneity.

In the case of studies with more than one intervention group, each group was considered as a study in the meta-analysis and compared with the control group. Finally, to avoid calculation problems related to zero effectives, 1 was added to all groups in these cases. Bias related to unpublished studies was assessed for analysis by aggregating at least 10 studies. The bias was assessed using the funnel plot and the Begg–Mazumdar test.

Results

A total of 324 articles were identified using the search criteria, and 58 relevant articles identified for meta-analysis. The details of the selection process are summarized in Figure 1. Articles examining the efficacy of physostigmine,[11] remifentanil[12] (in addition, the full text for this article was not found), desflurane,[13] delayed emergence,[14] and N_2O administration during sevoflurane washout[15] were discarded after applying selection criteria. When full text could not be found, the authors were contacted twice (without response in all cases).

The meta-analysis included 37 articles (1695 patients in the intervention groups and 1477 in the control groups). The pharmacological treatments studied for prevention of EA were: midazolam[16–20] (four articles), propofol[16 21–32] as single bolus or continuous administration (13), fentanyl[33–37] (five), ketamine[29 38–40] (four), α_2-AR agonists[41–50] clonidine or dexmedetomidine, given orally, by i.v. or caudal route (10), peroperative local anaesthetics,[39 51 52] caudal analgesia, and peroperative parenteral local anaesthetics (three), and $5HT_3$ inhibitors[45 53] either ondansetron or tropisotron (two) (Supplementary Table S1).

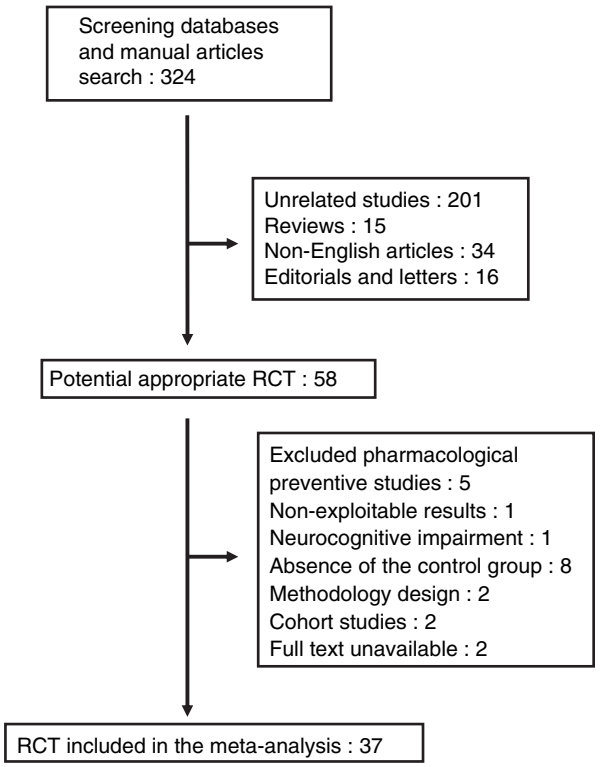

Fig 1 Meta analysis flowchart. RCT, randomized controlled trials.

Midazolam, given as either premedication 30 min before induction of anaesthesia or after induction, does not have a prophylactic effect against EA [OR=0.88 (0.44, 1.76); I^2=47%, P=0.11, Supplementary Fig. S1). The heterogeneity identified was explored by analysing studies by the timing of midazolam administration. Removing one study[16] in which midazolam was given after induction did not correct heterogeneity. When subgroup analysis was performed using the preoperative analgesia given, heterogeneity was within acceptable values. Analysis including studies with or without preoperative analgesia decreased heterogeneity, but midazolam was still found to be ineffective in preventing EA [OR=1.88 (0.85, 4.13), I^2=0%, P=0.79; OR=0.58 (0.31, 1.09), I^2=9%, P=0.33, respectively]. Finally, excluding the study using desflurane[16] had no effect on the results [OR=0.96 (0.46, 2.01), I^2=55%, P=0.09].

Propofol showed an overall protective effect against EA [OR=0.21 (0.16, 0.28), I^2=52%, P=0.01, Fig. 2]. Subgroup analysis of studies by the timing of administration (continuous, bolus after induction, or bolus at the end of anaesthesia) demonstrated that continuous administration and a bolus dose at the end of anaesthesia were protective [OR=0.17 (0.11, 0.27), I^2=36%, P=0.13; OR=0.21 (0.09, 0.50), I^2=0, P=0.47, respectively], whereas bolus at induction was ineffective in preventing EA [OR=0.46 (0.20, 1.06), I^2=40%, P=0.19]. Subgroup analysis of the studies showing efficacy, that is, those using an end of surgery bolus or continuous administration, by administration of peroperative analgesia found no effect of this on propofol efficacy [OR=0.15 (0.06, 0.36), I^2=0%, P=0.46; OR=0.19 (0.13, 0.28), I^2=0%,

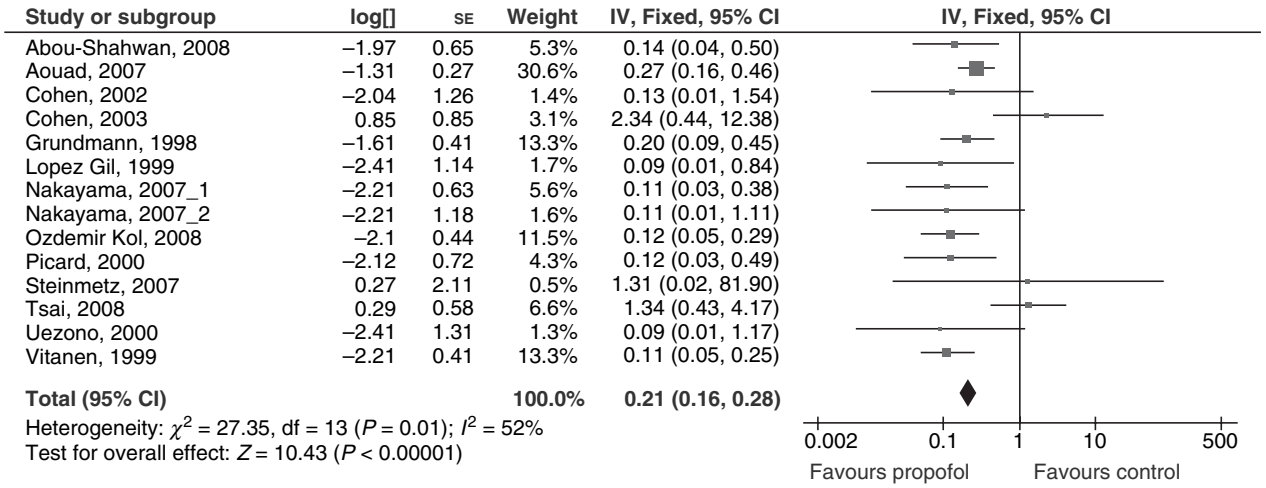

Fig 2 Forest plot of meta-analysis of propofol prevention in EA (propofol n=442, control n=450). The square shown for each study (first author and year of publication) is the OR for individual trials, and the corresponding horizontal line is the 95% confidence interval (CI). The diamond is the pooled OR with the 95% CI. Studies with more than one intervention group were numbered (author, year of publication_1) and (author, year of publication _2).

P=0.55, respectively]. Analysis of the studies using sevoflurane, by removing the one study that used desflurane,[21] still found propofol effective for EA [0.21 (0.12, 0.37), I^2=56%, P=0.007].

Ketamine administration was found to prevent EA [OR=0.28 (0.13, 0.60), I^2=0%, P=0.68, Supplementary Fig. S2]. Subgroup analysis found no effect of the absence of peroperative analgesia on the preventive effect of ketamine [OR=0.34 (0.14, 0.86), I^2=0%, P=0.84]. One study[38] used preoperative fentanyl and found that ketamine had a preventative effect [OR=0.17 (0.04, 0.70)]. After removing the desflurane study[38] from the analysis, ketamine still had a preventive effect against EA [OR=0.34 (0.14, 0.86), I^2=0%, P=0.84].

α_2-AR agonists were also found to be protective [OR=0.23 (0.17, 0.33), I^2=24%, P=0.2, Fig. 3]. Subgroup analysis of the route of administration (i.v. or caudal), the α_2-AR agonist used (dexmedetomidine or clonidine), and concurrent peroperative analgesia (none, preoperative analgesia, and locoregional analgesia) found no effect of these factors on the efficacy of α_2-AR agonists against ER (Supplementary Table S2).

Peroperative fentanyl was also found to protect against EA [OR=0.31 (0.18, 0.56), I^2=47%, P=0.06, Fig. 4]. Subgroup analysis of the route of administration decreased heterogeneity but found intranasal fentanyl to exhibit a preventive effect against EA [OR=0.23 (0.13, 0.43), I^2=28%, P=0.24] whereas i.v. fentanyl did not [OR=0.35 (0.12, 1.06), I^2=20%, P=0.29]. Analysing studies in which sevoflurane was used showed fentanyl to still be preventative against EA [OR=0.29 (0.15, 0.54), I^2=52%, P=0.05].

Peroperative analgesia was also found to protect against EA [OR=0.15 (0.07, 0.34), I^2=8%, P=0.36, Supplementary Fig. S3]. For the i.v. route, homogeneity

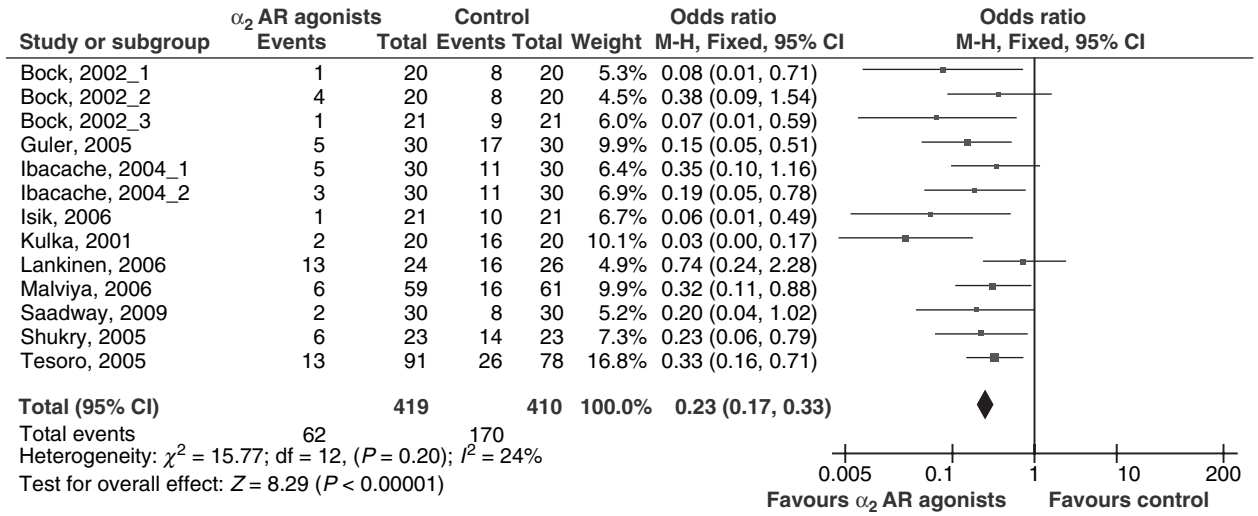

Fig 3 Forest plot of meta-analysis of α_2-AR agonists prevention in EA (α_2-AR n=418, control n=339). The square shown for each study (first author and year of publication) is the OR for individual trials, and the corresponding horizontal line is the 95% CI. The diamond is the pooled OR with the CI. Studies with more than one intervention group were numbered (author, year of publication_1) and (author, year of publication _2).

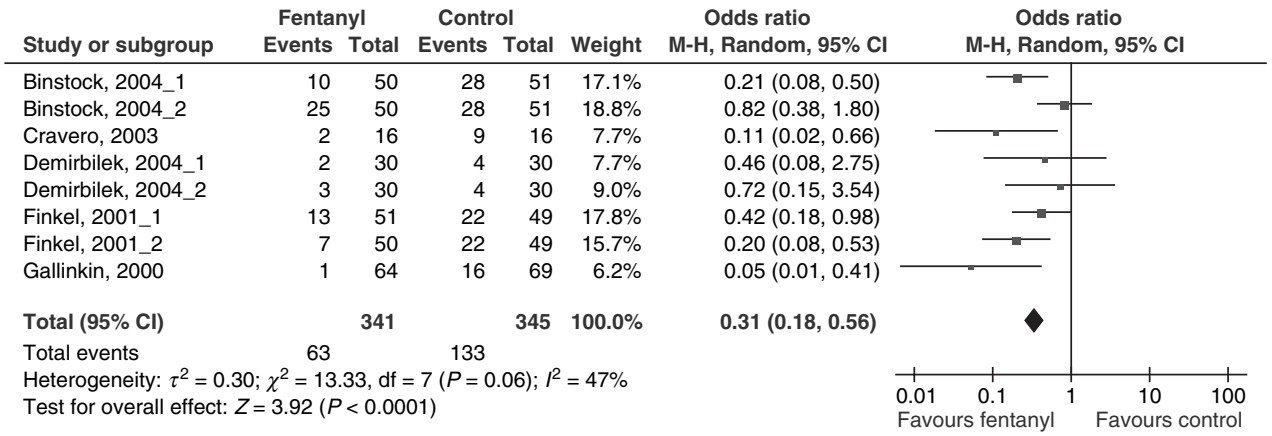

Fig 4 Forest plot of meta-analysis of fentanyl prevention in EA (fentanyl n=341, control n=215). The square shown for each study (first author and year of publication) is the OR for individual trials, and the corresponding horizontal line is the 95% CI. The diamond is the pooled OR with the 95% CI. Studies with more than one intervention group were numbered (author, year of publication_1) and (author, year of publication _2).

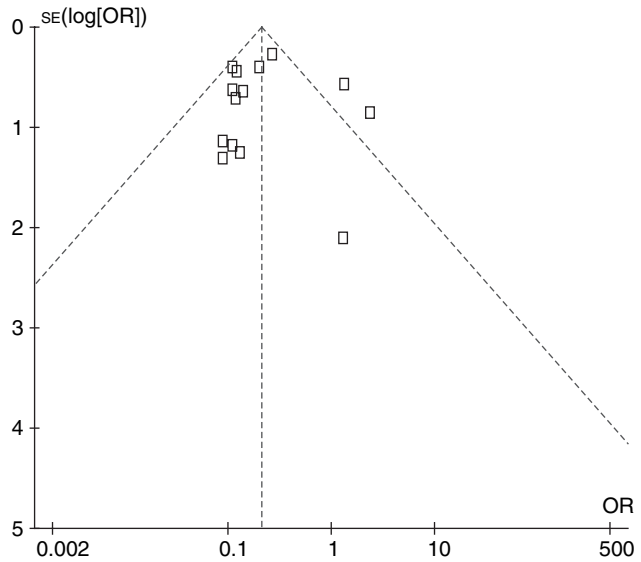

Fig 5 Funnel plot of the studies included in propofol meta-analysis.

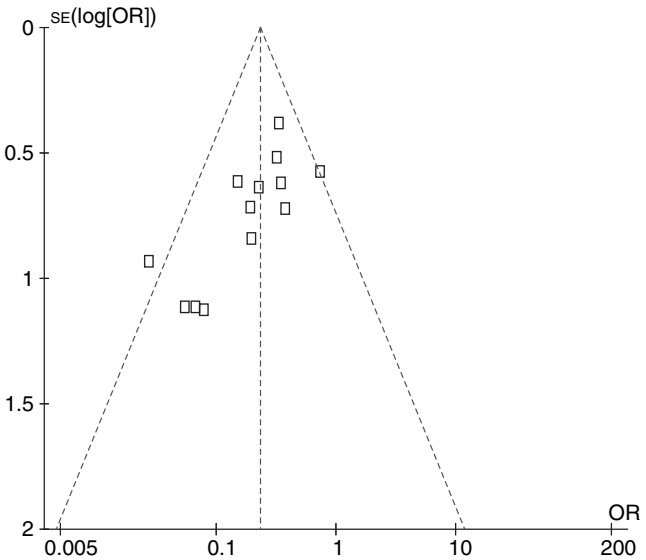

Fig 6 Funnel plot of the studies included in α_2-AR agonists meta-analysis.

was acceptable [OR=0.19; 95% confidence interval 0.06–0.6; I^2=30%, P=0.23]. As there was only one study of caudal analgesia,[1] meta-analysis was not indicated.

Finally, meta-analysis of the two studies examining the preventive effects of $5HT_3$ antagonists on EA found these drugs to be ineffective (OR=0.39, 95% confidence interval 0.12–1.31; I^2=0%, P=0.56, Supplementary Fig. S4).

Bias was assessed for propofol (13 studies) and α_2-AR agonists (12 studies). The results for propofol were a symmetric funnel plot (Fig. 5) and a Begg–Mazumdar Kendall's τ=0.15 (P=0.47), indicating the absence of bias. However, for α_2-AR agonists, analysis indicates the possibility of bias (asymmetric funnel plot, Fig. 6; Begg–Mazumdar Kendall's τ=−0.56, P=0.004).

Discussion

The main findings of this meta-analysis are that midazolam, classically considered as the 'ideal' drug for premedication appears to be ineffective in the prevention of EA, propofol seems to be effective, but is dependent upon the timing of administration, and that ketamine, α_2-AR agonists, fentanyl, and peroperative analgesia were all effective methods of EA prevention.

The aetiology of EA is currently unknown. Recent hypotheses emphasize rapid emergence associated with new anaesthetic agents such as sevoflurane and desflurane. This may create a dissociative state, that is, children awaken with altered cognitive perception.[2 6 8 54] The efficacy of $5HT_3$ serotonin receptor antagonists, reported in one study, suggests the involvement of the serotoninergic system processes in the aetiology of EA.[45] Other factors have been proposed as contributing to or exacerbating this problem, including postoperative pain and preoperative anxiety.[39 55] EA has been shown to be associated with preoperative anxiety, and to be prevented by parental presence and pain prevention.[56]

On this basis, midazolam, an anxiolytic agent widely used as premedication, would appear to be a logical candidate for preventing EA. However, our meta-analysis does not support this. In addition, statistical heterogeneity was decreased when subgroup analysis was performed taking into account peroperative analgesia. Two studies[18 19] in which patients were given alfentanil and acetaminophen peroperatively found no preventative effect, whereas studies without preoperative analgesia found midazolam to be efficient in preventing EA. Thus, analgesia, sedation, or both produced by opioids may blunt any effect of midazolam.

Propofol delays or modifies emergence and could decrease the incidence of EA. However, the rapid pharmacokinetics of this agent and the relatively low doses given in selected studies (1 mg kg^{-1}) could explain the failure of bolus doses to prevent EA when given during and after induction. This argument is supported by the efficacy of both end-intervention boluses and continuous administration of propofol during maintenance of anaesthesia, as propofol concentration at emergence would be more effective in preventing EA.

Ketamine, α_2-agonists, fentanyl, and peroperative analgesia were effective in preventing EA. Ketamine, an *N*-methyl-D-aspartate receptor antagonist, produces both analgesic- and opioid-sparing effects when used at low doses.[57 58] Dexmedetomidine and clonidine are also considered as potent analgesics and are used both pareneterally and in loco-regional anaesthesia (caudal and epidural).[59 60] Finally, fentanyl is a potent opioid receptor agonist routinely used in the peroperative period. Together with the high efficacy of peroperative analgesia in the prevention of EA, these results suggest, as previously stated, a relationship between postoperative pain and agitation.[39]

However, subgroup analysis of peroperative analgesia found no influence of this factor on the efficacy of ketamine, propofol, and α_2-agonists on EA. In addition, i.v. peroperative fentanyl failed to prevent EA. Finally, the greater efficacy of ketamine, α_2-agonists, and fentanyl in postoperative pain relief was not a constant finding in the analysed articles and was not always a study endpoint. These results suggest that the analgesic properties of these compounds are unlikely to be involved in their preventive effects. Other mechanisms such as potentiation of anaesthesia or sedation might be involved. This is particularly pertinent for α_2-AR agonists. They have been found to decrease anaesthetic requirements and to induce emergence sedation[61] which could explain their preventive effect on EA. Finally, studies performed during anaesthesia for imaging found EA to occur,[31 35 39 42] despite the non-painful character of this procedure. Excluding them from analysis did not impact upon the efficacy of any of these drugs.

It has been proposed that $5HT_3$ antagonists administered for prevention of postoperative nausea and vomiting may also prevent EA. Our results do not support this proposition, but this is based on only two studies and further work is needed before any solid conclusion.

Bias analysis found both funnel plots and Begg–Mazumdar testing suggestive of publication bias in α_2-AR agonists meta-analysis. Consequently, meta-analysis results for these drugs must be interpreted cautiously, because of the risk of unpublished negative results.

The quality of a meta-analysis relies upon two important factors: the quality of selected studies, and their heterogeneity and bias detection. Concerning article quality, the articles included met strict selection criteria as described above. All studies were randomized and double-blinded, and anaesthesia protocols and postoperative evaluation were standardized in the intervention and control groups. Concerning heterogeneity and bias, the articles included were heterogeneous because of their anaesthesia and analgesia protocols. Study design varied in terms of: premedication given, administration of peroperative analgesics, the route and timing of administration of the studied agent, and the evaluation tools used to quantify EA. This could explain the wide variability in the incidence of EA observed. However, all statistical analyses were performed after assessment of statistical heterogeneity, and subgroup analyses examined study design variations, resulting in acceptable statistical heterogeneity. The quality of EA evaluation was of great concern, and particular attention was paid to quantification. In all cases, EA quantification was standardized between the control and intervention groups, but the large number of unvalidated evaluation scales, along with individual scale EA threshold definitions may well impact upon EA incidence measurement, and furthermore, postoperative pain can *per se* induce agitation. However, only one included study used the validated paediatric anaesthesia emergence delirium (PAED) scale.[62] Ideally, new studies on EA prevention should be based upon the use of a standardized tool. Finally, bias was assessed following the recommendations of the Cochrane collaboration.

In summary, this meta-analysis evaluating EA prevention demonstrates that propofol, pain prevention, ketamine, and α_2-AR agonists appear to be effective. This is of interest because of the potential use of combinations of these different agents and their various routes of administration. Future studies should focus on associations of these drugs to study their effects in the prevention of EA and the use of the standardized PAED scale.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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