Review paper

The effect of different anesthetic drugs on the incidence of emergence delirium or agitation in pediatric surgeries

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Submitted: August 18, 2024, Revised: version 1, September 28, 2024, version 2, October 1, 2024, version 2, October 3, 2024, version 4, October 4, 2024
Accepted: October 26, 2024

Abstract

Emergence delirium (ED) and emergence agitation (EA) are induced perturbations to the mental state of an individual after anesthesia. The phenomenon and presentation can vary widely, as they are associated with several symptoms such as restlessness, confusion, and hyperactivity. Patients undergoing tonsillectomy and adenoidectomy often require the use of anesthetics and can experience EA and/or ED. Various practices have been implemented to prevent the development of this condition through different regimens of anesthetics for such procedures. However, inconsistencies exist within the literature, thus precluding a consensus on the optimal approach to mitigating the effects of EA and ED. The objective of this work was to provide a comprehensive review of the literature evaluating different anesthetic drugs and their effectiveness in lowering the postoperative EA and ED risks in pediatric patients after undergoing tonsillectomies and/or adenoidectomies. A systematic review of the literature was performed using PRISMA guidelines. The 13 studies that were selected were partitioned into different groups: single anesthetic (n=2) and combination anesthetic (n=11). Furthermore, the combination group was divided into combinations with sevoflurane (n=8), combinations with propofol (n=2), and multiple administrations of dexmedetomidine (n=1). Analysis of the data from these selected studies found that the use of a combination of anesthetic drugs decreased ED/EA when compared with solo administration. Propofol, ketamine and remimazolam were the most effective at reducing the incidence of ED/EA when combined with sevoflurane. The mechanism of action of these three drugs was similar, suggesting that combinations of GABA agonists and NMDA antagonists when combined with sevoflurane may be the most efficacious at decreasing the psycho-pathological symptoms of ED and EA. The results also suggested that; contrary to conventional wisdom; a deeper level of anesthesia achieved when combining these drugs may lead to greater alleviation of ED/EA symptoms.

Keywords

Anesthesia, Delirium, Emergence delirium, Agitation, Adenoidectomy, Tonsillectomy, Pediatric surgery, Sevoflurane, Propofol, Ketamine

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Introduction

The effect of anesthetics on pediatric Emergence Delirium and Agitation

Postoperative awakening from anesthesia may present with side effects including Emergence Delirium (ED) and Emergence Agitation (EA) which are psycho-pathological symptoms. ED is an abnormal mental state which appears at the time the patient wakes up from unconsciousness after anesthesia has been administered while EA is also an abnormal mental state. The signs of 'energy dispersion' can be excessive physical activity, increased motor activity, confusion and aimless movement (1). Children between the age of two to six are the most vulnerable to the foregoing propensity, the incidence of ED is reported to range between 10 - 80% (2). Both, ED and EA are viewed as problems which should be prevented because the patient may further harm themselves or their immediate environment or may cause further challenges in postoperative care.

This study assumed that different anesthetics would have different effects on postoperative emergence delirium and agitation. In the1960's Eckenhoff and coworkers found higher rates of emergence excitation in healthy children undergoing tonsillectomy or thyroidectomy surgery while under cyclopropane or ketamine anesthesia (3). A later study compared the effects of sevoflurane to halothane anesthetic regimens, in patients who were undergoing bilateral myringotomy. The study found that the children administered sevoflurane had a higher incidence of EA (4). Tonsillectomy and adenoidectomy have been found to be related to a higher occurrence of ED and EA in children compared with other pediatric surgeries.

Consequently, it was suggested that further evaluation be performed regarding the effect of different anesthetics used for preventing postoperative delirium (3, 5). In the past decade, multiple high-quality randomized controlled trials have been performed comparing the effects of different anesthetic drugs on the incidence of ED and EA. These drugs include, propofol, desflurane, and ketamine (6 - 8). However, there seems to be no comprehensive review that has evaluated all of the existing literature to date. Furthermore, the heterogeneity across studies ranging from factors such as patient demographics, dosage of anesthetic drugs, and methods of assessing and defining ED and EA contributes to the inconclusiveness of the findings in the literature. The purpose of this review was to provide a comprehensive understanding of the literature to evaluate which anesthetic drug(s) are most effective at reducing the risk of postoperative emergence agitation and delirium in children who receive tonsillectomy and adenoidectomy.

Global utilization of anesthetics for Tonsillectomy or Adenoidectomy

Currently, the optimum use of anesthetics in children, especially during tonsillectomy and adenoidectomy operations, remains a topic of discussion among medical practitioners, with its practice in different countries depending on the available practices, resources, and cultural values (9). Surprisingly, there is an unprecedented similarity regarding the types of anesthetics, however, the differences lie in the various methods, mixed formation and different surgical procedures utilized. This plurality highlights the need for considering regional practices when comparing outcomes associated with the use of various anesthetics on their effectiveness in decreasing ED and EA.

Anesthetic utilization in North America

In North America, particularly in America and Canada, there is continued use of inhalation anesthetics, such as sevoflurane (10) in children who undergo tonsillectomy and adenoidectomy operations. It is easier to use sevoflurane because of its fast induction and emergence, and because it has a less unpleasant smell compared to the other agents, thus making it better for use for children during the surgical process. The increasing use of intravenous anesthetics, such as propofol in Total Intravenous Anesthesia (TIVA) techniques or alongside inhalation agents, is partly driven by efforts to minimize incidents of ED associated with volatile anesthetic agents. Also, various regional anesthesia techniques are being used to supplement other forms of anesthesia such as general anesthesia to optimize pain relief during the period of the surgery as well as immediately following it.

Anesthetic utilization in Asia

In Asian nations, rather than having a standard care plan for pediatric tonsillectomy and adenoidectomy, diverse methods exist. Sevoflurane is preferred in both Japan and South Korea, as these two countries prefer inhalation anesthetic agents. Nevertheless, there is a growing concern about investigating methods that may help minimize ED, and therefore, the practice of propofol-based TIVA in some institutions is gaining acceptance (11). The selection of chosen anesthetics in China and India is still vulnerable to economic considerations, as it is felt necessary to utilize both the old and the innovative agents depending on their availability and effectiveness. Despite the fact that ketamine can be used alone or in combination with other anesthetic agents, its use has been reported to be used more often in some areas of Asia compared to that in the western world, especially where there is limitation in the availability of resources.

Anesthetic utilization in Europe

The current practice of pediatric anesthesia in Europe for tonsillectomy and adenoidectomy incorporates both traditional as well as newer practices. Most countries across Europe prefer the balanced approach of using both inhalation agents and intravenous drugs. Sevoflurane and desflurane are the two primary volatile inhalation anesthetics, with short-acting opioids such as remifentanil or fentanyl added to prolong the effect (12). Other countries such as Germany prefer to use propofol, specifically for ED and EA management for pediatric surgeries (13). There is increasing awareness of TIVA, especially in the U.K. and some Scandinavian countries, due to the neurocognitive effects of the inhaled anesthetic agents on the developing brain in children. Of these countries, there are a number that are on the forefront of discovering additional, new agents and or methodologies.

Heterogeneity of anesthetic use

Variability in anesthetic management for pediatric tonsillectomy and adenoidectomy is quite evident, providing further evidence that the decision-making process regarding which anesthetic to use is not straightforward. Some factors involved may include the circumstantial access to drugs and equipment, cost factors, the training and academic discretion of the practitioner, and the local as well as national protocols (14). The existence of such diverse practices does make research in this area both difficult but at the same time exposed to possibilities. It makes the comparison of the studies performed in different settings more challenging but helps to consider various factors that can influence ED and EA associated with the choice of anesthetic. Understanding this diversity is important for interpreting the outcomes of various studies and developing clear recommendations that can be applied in a variety of clinical settings.

Methods

Search strategy and criteria

To improve the rigor of this review, some aspects of a systematic review were adapted using the PRISMA guidelines. Existing literature was reviewed using the free online database “PubMed.” The following search terms were entered in the database to search for the relevant articles - “anesthesia,” “emergence delirium,” “emergence agitation,” “children,” “tonsillectomy,” and “adenoidectomy.” The search was performed on articles published between January 2010 and December 2023. Articles before 2010 were not included due to significant advancements in anesthetic technique, drug formulation, and pediatric care protocols made during the last decade. In addition, combination anesthetic use has shown to be more effective than single anesthetic use and studies published before 2010 typically evaluated single use anesthetics, rather than their use in combination.

Study selection and evaluation

A total of 82 search results were returned from PubMed. Studies that were randomized control trials that presented data in quantitative form, evaluated only EA and/or ED, and utilized intravenous and intramuscular anesthesia for the drug being tested were included. Additionally, the articles reviewed also had to have been written in English. Literature reviews, systematic reviews or clinical trials, and randomized control trials that used spray or topical anesthetics were excluded. Upon applying these inclusion and exclusion criteria, 13 articles remained. The final articles selected for this review were assessed based on the anesthetic drug or combination anesthetics tested, the methodological rigor, and the quality of data presented.

Results

The reviewed literature included in the study is summarized in Tables 1 and 2. The results were partitioned by the regimen of anesthetic studied, including single anesthetic studies (n=2) and combination anesthetic studies (n=11). The combination group was further subdivided into categories for multi-drug regimens including sevoflurane (n=8) and propofol (n=2). One study analyzed the use of multiple administrations of dexmedetomidine (n=1). Overall, a review of 13 studies was performed.

Table 1. Description of studies using single anesthetic anesthetics for Tonsillectomy or Adenoidectomy in children

Author	Year	Title of Study	Study Population (Country)	Drug(s) Used and Dosage	Key Findings
He et al.	2022	Nalbuphine reduces the incidence of emergence agitation in children undergoing Adenotonsillectomy: A prospective, randomized, double-blind, multicenter study	800 children (3-9 years old) in China	Nalbuphine 0.1 mg/kg intravenously	Nalbuphine significantly reduced EA incidence (10.28% vs 28.39%) and pain scores in children after adenotonsillectomy
Hauberet al.	2015	Dexmedetomidine as a Rapid Bolus for Treatment and Prophylactic Prevention of Emergence Agitation in Anesthetized Children	400 children aged 4-10 years in the United States	Dexmedetomidine 0.5 μg/kg IV bolus injection	Incidence of EA was 36% for the dexmedetomidine group versus 66% for the saline (control) group

Table 2. Description of studies using combination anesthetics for Tonsillectomy or Adenoidectomy in children

Author	Year	Title of Study	Study Population (Country)	Drug(s) Used and Dosage	Key Findings
Bedirli et al.	2017	Tramadol vs dexmedetomidine for emergence agitation control in pediatric patients undergoing adenotonsillectomy with sevoflurane anesthesia: prospective randomized controlled clinical study	77 children aged 2-12 years in Turkey	Tramadol 2 mg/kg intravenous with sevoflurane, Dexmedetomidine 1 μg/kg intravenous with sevoflurane	Both tramadol and dexmedetomidine effectively controlled pain and incidence of EA. The dexmedetomidine group had an EA incidence of 15% while the tramadol group had an EA incidence of 45%
Yang et al.	2022	Remimazolam for the Prevention of Emergence Delirium in Children Following Tonsillectomy and Adenoidectomy Under Sevoflurane Anesthesia: A Randomized Controlled Study	104 children aged 3-7 years in China	Remimazolam 0.2 mg/kg at the end of surgery with 5% sevoflurane	Remimazolam significantly reduced ED incidence (12% vs 44%) and peak PAED scores in children under sevoflurane anesthesia
Shi et al.	2019	Dexmedetomidine for the prevention of emergence delirium and postoperative behavioral changes in pediatric patients with sevoflurane anesthesia: a double-blind, randomized trial	90 children aged 2-7 years in China	Dexmedetomidine 0.5 μg/kg injection with sevoflurane	Dexmedetomidine significantly reduced the incidence of ED (31.1% vs 53.3%) compared to the control group
Sousa-Júnior et al.	2020	Intraoperative clonidine to prevent postoperative emergence delirium following sevoflurane anesthesia in pediatric patients: a randomized clinical trial	62 children aged 2-12 years in Brazil	Clonidine 1 μg/kg intravenously during anesthesia induction with sevoflurane	Intraoperative clonidine significantly reduced the incidence of ED compared to control (17.2% vs 57.6%) in children undergoing tonsillectomy/adenotonsillectomy under sevoflurane anesthesia

Abdutalifet al.	2013	The effect of magnesium sulphate infusion on the incidence and severity of emergence agitation in children undergoing adenotonsillectomy using sevoflurane anaesthesia	70 children aged 4-7 years in Egypt	Magnesium sulphate 30 mg/kg bolus followed by 10 mg/kg/h infusion with 8% sevoflurane	Intraoperative magnesium sulphate significantly reduced the incidence of EA compared to control (36% vs 72%) in children under sevoflurane anesthesia
Ali et al.	2020	Ketofol performance to reduce postoperative emergence agitation in children undergoing adenotonsillectomy	120 children aged 3-15 years in China	Ketofol (1:3 ratio) - ketamine 0.15 mg/kg followed by propofol 0.45 mg/kg intravenously, about 10 minutes before the end of surgery	Ketofol significantly reduced the incidence (13.33% vs 48.33%) and severity (8% vs 15%) of EA compared to control
Cao et al.	2016	Effects of intraoperative dexmedetomidine with intravenous anesthesia on postoperative emergence agitation/delirium in pediatric patients undergoing tonsillectomy with or without adenoidectomy: A CONSORT-prospective, randomized, controlled clinical trial	60 children aged 2-8 years in China	Dexmedetomidine 1 µg/kg IV over 10 minutes, followed by 0.5 µg/kg/h continuous infusion	No significant difference in incidence of ED between the dexmedetomidine group (27%) and the control group (30%)
Dong et al.	2010	The effect of remifentanil on the incidence of agitation on emergence from sevoflurane anaesthesia in children undergoing adenotonsillectomy	60 children aged 3-7 years in China	Remifentanil 1 µg/kg/minute intraoperatively with 8% sevoflurane anesthesia	EA incidence for the remifentanil group was 23.3%, which is lower compared to the sevoflurane group, which had an EA incidence of 66.7%
Tsiotouet al.	2018	Dexmedetomidine for the reduction of emergence delirium in children undergoing tonsillectomy with propofol anesthesia: A double-blind, randomized study	Children 3-14 years old in Greece	Dexmedetomidine 1 mcg/kg with propofol	Dexmedetomidine significantly reduced ED incidence (12.9%) with propofol anesthesia compared to the control (41.4%)
Hadi et al.	2015	The effect of KETODEX on the incidence and severity of emergence agitation in children undergoing adenotonsillectomy using sevoflurane based-anesthesia	Children aged 3-7 years in China	Ketamine 0.15 mg/kg followed by dexmedetomidine 0.3 µg/kg intravenously. (KETODEX) with sevoflurane	KETODEX significantly reduced EA incidence (11% vs 47%) and severity (2% vs 13%) compared to control
Na et al.	2012	Emergence agitation in children undergoing adenotonsillectomy: a comparison of sevoflurane vs. sevoflurane-remifentanil administration	84 preschool children in South Korea	Remifentanil group: 1% sevoflurane + remifentanil infusion. Sevoflurane group: 2-3% sevoflurane	Combining lower concentration sevoflurane with remifentanil reduced EA incidence compared to higher concentration sevoflurane alone (26.1% vs. 50%)

Effectiveness of single anesthetic use

The analysis of the literature provided evidence that certain single anesthetic agents are capable of lowering the rate of ED and/or EA in children who are subjected to tonsillectomy and/or adenoidectomy. For instance, He and colleagues' study in China (2022) investigated the effects of nalbuphine and its effect on EA. The study was a double-blinded, RCT conducted across several centers. The authors concluded that, EA incidence reduced significantly in patients who received nalbuphine alone to 10.28% compared to 28.39% in the saline control group when the treatment was given at 0.1 mg/kg IV for adenotonsillectomy performed in combination with other procedures (15). The study also found that pain scores decreased in this regimen. Similarly, in a U. S study by Hauber and colleagues (2015), dexmedetomidine; administered at 0.5 µg/kg as a rapid IV bolus alone also showed a significant decrease in EA with an incidence of 36% compared with 66% in the control group (16).

These findings suggested that single anesthetic agents like nalbuphine and dexmedetomidine were effective in reducing EA in pediatric patients (15,16). These agents can be considered as primary options in settings where single-use anesthetic and efficacy are desired. However, the varying efficacy across different studies indicates the need for further research to identify the most effective single agents and their optimal dosages. In part, the differences in outcomes from these drugs may result from their mechanism of action. However, additional research and studies are required to determine the causes of variability.

Other considerations for additional studies may consider cost to the patient, longer-term side effects, and an analysis on the age groups that may benefit the most from different agents/dosages. With such evidence, a more targeted approach can be formulated when selecting agents for anesthesia in children undergoing adenotonsillectomy. As a result of this research, specified protocols can be formulated to implement in the clinical setting, which can possibly guide providers on the best anesthetic choice based on the target population being treated, which can vary by age, medical condition, weight, and/or the type of surgical procedure.

Effectiveness of combination anesthetic use

The total utilization of different anesthetic agents simultaneously presented with a lesser occurrence of ED and EA compared to the single component cases. For example, a tramadol-dexmedetomidine mix was observed to be effective (17). Bedirli et al. (2017) performed a study using a prospective, randomized, placebo-controlled study design in Turkey on patients after adenotonsillectomy. The authors found that with the use of 2 mg/kg IV tramadol and sevoflurane, 45% of patients developed EA. In contrast, in a study by Shapiro et al., the co-administration of dexmedetomidine with 1 µg/kg IV, and sevoflurane resulted in 15% of the patients displayed EA (17). An RCT by Yang et al. (2022) assessed the effect of 0.3 mg. kg of remimazolam together with 5% sevoflurane in the postoperative period. The authors found that this combination of drug use lowered the rate of ED from 44% to 12% (18).

Ali et al. divided the patients into three groups in which a ‘ketofol’ at a ratio of 1:3 of ketamine and propofol was administered, and a reduction in EA incidence was observed from 48.33% to 13.33% (19). Sousa-Junior et al. (2021) performed an RCT on a sample of the Brazilian population with sevoflurane combined with other agents. These authors investigated the effect of a bolus dose of 1 µg/kg IV clonidine during induction of anesthesia with sevoflurane. They found that this combination anesthetic use was effective in lowering the incidence of ED to 17.2% compared to the control group of children undergoing surgery (20).

In an Egyptian study by Abdulatif and colleagues (2013), 30 mg/kg IV bolus magnesium sulfate followed by 10 mg/kg/h of 8% sevoflurane was successful at reducing the incidence of EA from 72% to 36% with intraoperative administration of the drug in children undergoing adenotonsillectomy (21). Another study, performed in China by Hadi et al. (2015), examined the incidence and severity of EA following the use of 0.15 mg/kg ketamine with 0.3 μg/kg IV dexmedetomidine. This study found that the combination drug use group experienced a greater reduction in EA incidence and severity compared to the control group; The incidence of EA was 47% in the control group compared to 11% in the intervention group and the severity of EA was 13% (control) and 2% (intervention) (22).

Combination therapies generally yielded lower incidence and severity of EA and ED when compared to single agents. The synergistic effects of combining agents such as tramadol, dexmedetomidine, and remimazolam with each other or with other anesthetics significantly reduced ED and EA (17, 19). Other agents, including clonidine and magnesium sulphate, were also studied in combination with sevoflurane (20, 21).

These drugs and anesthetics for the prevention of EA and ED can be administered in addition to other medications, such as dexmedetomidine or remimazolam. The reason for such an outcome indicating the benefit of applying combined anesthetics may stem from the following: there could be an accumulation of the effect resulting from the physiological action of each drug in the mixture based on their separate mechanisms of action. Further research is required concerning enhancing the best synergistic relationships and the correct proportional share of combined drug doses. The significantly lesser EA and ED symptoms resulting from combination anesthetics underline the need to consider a varied combination of anesthetics to improve the patient's psycho-pathological symptoms after surgery. Subsequent codes of practice should, therefore, incorporate combination therapies as the standard of care, especially among children undergoing high risk surgery.

Effectiveness of anesthetic combined with sevoflurane

When anesthetics were combined with sevoflurane, the outcomes in terms of reducing ED and EA were significantly improved as exemplified in the study conducted by Bedirli and colleagues (2017) in Turkey. The study found that the combination of dexmedetomidine and sevoflurane resulted in a lower incidence of EA (15%) compared to the use of sevoflurane alone or with other agent combinations, such as with tramadol (45%) (17). Another study that was a double-blind randomized trial, performed by Shi and colleagues (2019) in China, analyzed dexmedetomidine 0.5 μg/kg IV with sevoflurane compared to the control, finding a reduced incidence of ED of 31.3% (intervention) compared 53.5% (control) (23). This suggests that the combination of sevoflurane with agents like dexmedetomidine or tramadol, was effective in mitigating postoperative agitation in children, though the secondary drug used with sevoflurane could cause variable results in reduction of EA or ED incidence.

Additionally, two studies investigated the use of remifentanil with sevoflurane. One comparison study, performed in South Korea by Na and colleagues (2013), examined the use of low-dose sevoflurane in combination with remifentanil compared to high-dose sevoflurane alone, demonstrating that 1% sevoflurane with remifentanil provided a better outcome than 2-3% sevoflurane alone, with an incidence of EA being 26.1% *vs*. 50%, respectively (24). Another study, by Dong and colleagues (2010) performed in China, examined a similar combination, demonstrating EA incidence reduction to 23.3% for a remifentanil 1 μg/kg/minute intraoperative IV administration with 8% sevoflurane, compared to sevoflurane alone, with respective incidences of 23.3% and 66.7% (25).

Sevoflurane, when combined with other agents, demonstrated a marked reduction in ED and EA, suggesting its potential as a core component of pediatric anesthesia protocols. The combination with dexmedetomidine was particularly effective, indicating a robust synergistic effect that warrants further exploration (17, 23). This combination could be recommended for routine use, especially in cases where ED and EA are of significant concern. Additionally, remifentanil also proved to be an effective combination with sevoflurane, since multiple studies demonstrated reduced incidences of EA when comparing the combination to sevoflurane use alone (24). While the benefits of these combinations have been outlined, other possible considerations for the use of combined anesthetics may include an analysis of side effect profiles other than EA or ED that may occur due to increased drug administration to better characterize the safety of use.

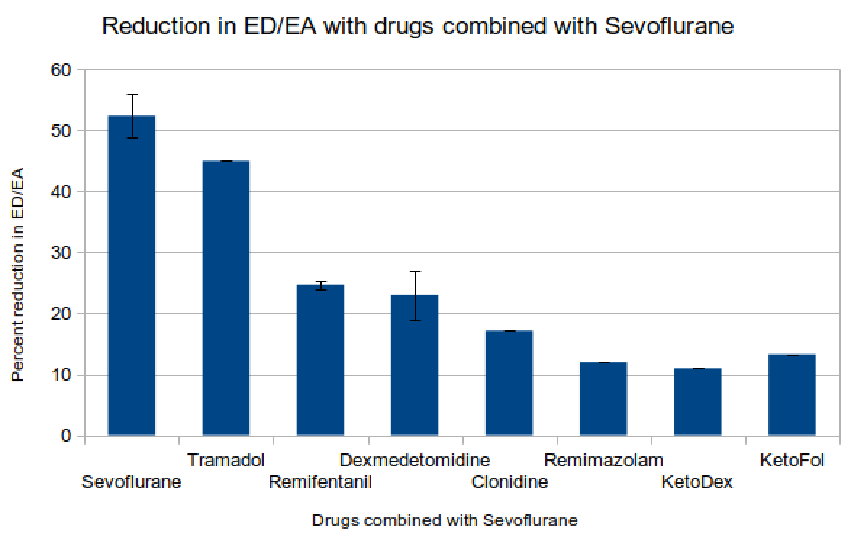

Figure 1. Relative reduction in ED/EA symptoms using drugs combined with Sevoflurane. Note that the data are from different studies (from Table 2) which used different Sevoflurane concentrations; among other different factors. The first column is Sevoflurane administered without any other drugs. KetoDex is a combination of Ketamine and Dexmedetomidine, while KetoFol is a combination of Ketamine and Propofol.

Figure 1 shows the drugs that were used with sevoflurane to minimize EDA. Quantitative analysis of the data is not possible due to the fact that different Sevoflurane concentrations were used, protocols were different and the data were derived from different clinical studies. However, certain relevant observations can be made. Combining Sevoflurane with other drugs resulted in a reduction in ED/EA symptoms. The greatest reduction in symptoms was obtained with Remimazolam, Ketodex and KetoFol when combined with Sevoflurane. Interestingly, Remimazolam, Ketamine and Propofol, all possess either GABA agonist activity or NMDA antagonistic activity (Table 3), which are subsets of the mechanisms of action of Sevoflurane; i.e. their mechanism of action is congruent with that of Sevoflurane.

Effectiveness of anesthetics combined with propofol

The combination of propofol with other anesthetic agents also demonstrated favorable results. For instance, in a study by Ali and colleagues (2020) in China, 'ketofol' (ketamine and propofol) was particularly effective, reducing the incidence of EA from 48.33% to 13.33% (19). Accordingly, a double-blind, randomized study by Tsiotou and colleagues (2018) in Greece showed that the use of dexmedetomidine 1 μg/kg with propofol demonstrated similar outcomes, with the intervention group resulting in a 12.9% incidence of emergence delirium, compared with the control group with an incidence of 41.4% (26). This suggesed that propofol, when used in combination with other anesthetics like ketamine or dexmedetomidine, could significantly lower the rates of ED and EA, making it a viable option for pediatric anesthesia, especially in the setting of tonsillectomy and/or adenotonsillectomy.

Propofol combinations, such as 'ketofol', demonstrated significant reductions in ED and EA (19). Dexmedetomidine demonstrated similar results, demonstrating a positive benefit in reducing EA and ED (26). The findings support the use of propofol in combination with other agents like ketamine to achieve better postoperative outcomes. This combination not only reduced agitation but also provided the benefits of rapid recovery and minimal side effects, making it a preferred choice in pediatric anesthesia. A more descriptive profile on the use of propofol in conjunction with other anesthetics may be warranted, as this would allow for titration of dosages based on weight and/or age for children undergoing tonsillectomy and/or adenotonsillectomy.

Table 3. Drug classes based on mechanisms of action

Drug(s)	Class, Mechanism of action
Sevoflurane	GABA agonist, NMDA antagonist
Clonidine, Dexmedetomidine	α2 agonist
Tramodol, Remifentanil	Opiods
Propofol	GABA agonist
Remimazolam	Benzodiazepene, GABA agonist
Ketamine	NMDA antagonist

Figure 2 categorizes drugs into their classes and mechanisms of actions to identify possible interactions and the ability to reduce EDA with different sevoflurane concentrations. The mechanism of action of the individual drugs in the studies are presented in Table 3. The results indicate that NMDA antagonists and GABA agonists, either alone or in combination, are more effective when used in combination with sevoflurane, which may – again - be attributable to the similar mechanisms of action of the combined drugs. Conversely, it may be speculated that α2 agonists and opioids by themselves in combination with sevoflurane are not as effective in ED/EA reduction due to their mechanisms of action being dissimilar to those of sevoflurane; which is a GABA agonist and NMDA antagonist. Assuming non-saturation of receptors at the doses administered in these studies, drugs whose mechanism of action is similar to that of sevoflurane may be reasonably expected to deepen the mechanism-specific level of sevoflurane-induced anesthesia. This observation leads to the speculation that deepening the level of anesthesia using a higher concentration of sevoflurane alone may be more beneficial in attenuating EDA than at lighter levels of anesthesia, as may initially appear and be intuitively assumed.

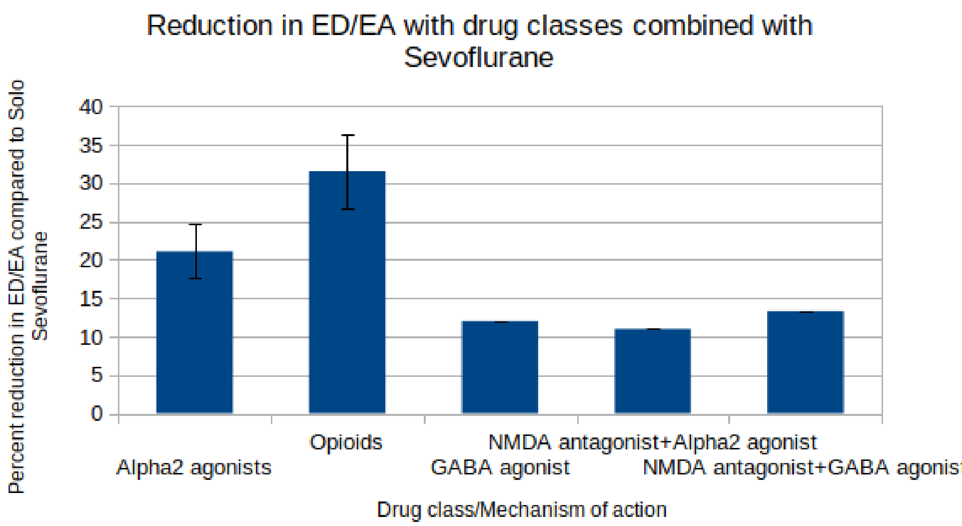

Figure 2. Relative reduction in ED/EA symptoms using drug classes combined with Sevoflurane. Note that the data are from different studies (from Table 2) which used different Sevoflurane concentrations; among other different factors.

Effectiveness of single-anesthetic, multi-dose combination

Another approach encountered in the literature involved multiple administrations of the same anesthetic at different dosages. A prospective, randomized control study analyzed this technique for the reduction of incidence of emergence agitation/delirium following tonsillectomy with or without adenoidectomy. Dexmedetomidine was administered IV at 1 µg/kg for 10 minutes, then followed by 0.5 µg/kg/h continuously. The results demonstrated no significant difference in the incidence of EA or ED between the dexmedetomidine group when compared to the control group, which demonstrated respective incidences of 27% and 30% at the conclusion of the study performed in China by Cao and colleagues (2016) (27).

The combination of dexmedetomidine at different dosages demonstrated no significant difference in outcomes for EA and/or ED incidence, suggesting this strategy was ineffective (27). However, additional research should be performed due to the scarce literature on this approach. Future studies may entail the same approach applied to different anesthetics, such as ketamine or propofol, or the use of additional dosing schemes for dexmedetomidine alone.

Depth of anesthesia and Bispectral Index

The depth of anesthesia as determined by tools such as the Bispectral Index (BIS) may be a factor for understanding the efficacy of anesthetic combinations in minimizing EDA. However, not all of the studies included in this review presented the BIS values that were used in the analysis. For those that did not, the BIS values were calculated using the reported sevoflurane percentages as shown in Table 4.

Table 4. Bispectral Index for different clinical studies

Study	Sevoflurane concentration	Drug combined with	Percent ED/EA reduction *versus* solo Sevoflurane	Bispectral Index calculated
Bedirli et al. (2017)	5	Tramadol Dexmedetomidine	45 15	34.0 34.0
Yang et al. (2022)	5	Remimazolam	12	34.0
Sousa-Junior et al. (2021)	8	Clonidine	17.2	30.6
Shi et al. (2019)	Unknown	Dexmedetomidine	31.1	40-60 reported
Na et al. (2013)	1	Remifentanil	26.1	53.5
Dong et al. (2010)	8	Remifentanil	23.3	30.6
Abdulatif et al. (2013)	8	Magnesium sulfate	36	30.6

BIS values were calculated using the power function $y=53.53*(x^{-0.26768})$, $R^2 > 0.92$, where y=BIS and x=sevoflurane concentration, from reference 28

As speculated in the section "*Effectiveness of anesthetics combined with propofol*" above, the effectiveness of ED/EA reduction may be greater under deeper anesthesia (lesser BIS). This does not appear to be the case from an examination of the values in Table 4. The drugs combined with sevoflurane in Table 4 however belong to the α2 agonists or opioid classes; which do not have the same mechanism of action as that of sevoflurane. Hence, while solo administration of sevoflurane under deeper anesthesia (lower BIS) may not achieve a greater reduction in ED/EA symptoms; the data from Table 4 does not rule out the possibility that such deeper levels of anesthesia when combined with drugs that are NMDA antagonists or GABA agonists will not.

Dosage of anesthetics and routes of administration

Another aspect that may be pertinent to dosing schemes and the prevention of emergence agitation or delirium involves the individual dosages of each anesthetic. The pharmacokinetics of each drug must be taken into consideration, and a dose-response effect would need to be optimized to demonstrate efficacy of each drug. For instance, a particular drug may need to reach a certain level in the blood before it attains the desired effect. Additionally, after a certain level, the drug may have no additional benefit and may only introduce the harmful risk of side effects. Creating this window of acceptable dosage ranges is crucial to treating EA and ED effectively and safely.

An example of this can be seen through the studies discussed in this review. For instance, in the U.S. study by Hauber and colleagues (2015), it was found that a 0.5 μg/kg as a rapid IV bolus of dexmedetomidine provided a reduction in EA to an incidence of 36% (16). Conversely, the study performed by Bedirli and colleagues (2017) in Turkey displayed similar results, utilizing dexmedetomidine at 1 μg/kg IV combined with another anesthetic (17). It would be beneficial to construct studies that compare the effectiveness of single anesthetics at graduated dosages. Such studies would provide more insight into the optimal dose range to be used. Furthermore, this can be stratified by a weight-based protocol to account for individual pharmacodynamics, that can vary widely in children of varying metabolism, ages, and weights.

An additional value that would be useful for such dosage profiling is the route of administration. While this study focused on the intravenous and intramuscular routes, other routes such as topical, intranasal, intrathecal, or even oral administration should be studied. Since the bioavailability of the anesthetic used would be different from each route, it would be essential to find the optimal dose through each method. In doing so, a wider variety of combinations and options could then be offered. This could also overcome socioeconomic barriers to use, as some drug preparations may be less costly when administered *via* one route than another. As a result, further research or studies should be performed in characterizing the difference in the efficacies of anesthetic drug route administrations.

Limitations

The limitations of this review are inherent to the need for significant, comprehensive meta-analyses or randomized control trials analyzing multiple uses of different anesthetics alone or in combined use. Additionally, the studies analyzed in this review occurred in different centers, institutions, and countries, while focusing on different subsets of ages in pediatric populations. The wide heterogeneity in this dataset renders even a random effects model for meta-analysis ineffective. This variability should be controlled in future research to standardize the results and limit the potential for bias. With such changes, the outcomes of the studies can be more generalizable to different populations, facilitating its implementation in practice. Additional aspects that were outside the scope of this study involve comparing more routes of administrations for each drug. The addition of such variables to this analysis would be able to further characterize unique treatment strategies in the prevention of EA and ED, offering a wider choice of options to patients and providers.

Perspective

The variability in anesthetic practices and outcomes suggests the need for tailored guidelines that consider regional preferences and available resources. The evidence supports the efficacy of combination therapies and the use of agents such as ketamine and propofol (17, 19, 26). Future research should focus on large-scale, multicenter trials to establish definitive guidelines and explore the long-term effects of these anesthetic combinations on pediatric patients' neurocognitive outcomes.

Other factors should also be included to account for socioeconomic factors in patient treatment approach and future study design. The incidence of EA and ED based on patient demographics, such as age, gender, and weight, may be significant in studying which anesthetics can be effective in certain groups. It can also provide insights into the potential costs that additional drugs may incur, which should be accounted for if studies demonstrate a disproportionate incidence of EA and/or ED in different demographics. Additionally, stratifying by these groups can help determine the best profile of anesthetics for different groups, thus allowing for targeted and personalized treatments, along with individualized safety profiles. The characterization of unique combinations of different dosages and agents can be further applied to not only specific patients but also different populations and regions that share similar characteristics. Therefore, such studies must be performed to find the optimal regimen for the use of pediatric anesthesia in EA and/or ED.

Conclusion

In conclusion, the review underscores the effectiveness of several drugs in combination with sevoflurane in reducing ED and/or EA in pediatric patients. Combining propofol, ketamine and remimazolam with sevoflurane found promising results, probably because the mechanism of action of all these drugs is similar and overlaps, highlighting the need for a multimodal approach in pediatric anesthesia. Emergent from this analysis and contrary to intuitive reasoning, a deeper level of anesthesia, achieved by combining drugs whose mechanisms of action are similar to sevoflurane, with sevoflurane, may decrease the symptoms of ED/EA in pediatric patients. Continued research may elucidate the mechanistic nuances underlying the synergistic effects of these drugs in the prevention of EA and/or ED. From such knowledge, tailored guidelines and personalized regimens can be created for different individuals, health systems, and regions. Thus, the information provided in this review highlights the foundation of anesthetic use for controlling and mitigating the symptoms of EA and ED. The development of further studies is essential to optimize patient outcomes and ensure safety in pediatric surgical care and anesthesia.

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