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Meta-analysis

Effect of Dexmedetomidine on emergence agitation in pediatric patients undergoing surgery with sevoflurane-based general anaesthesia: A systematic review and meta-analysis

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Abstract

Background: Emergence agitation (EA) is a common adverse event in pediatric patients following surgeries performed under sevoflurane-based general anesthesia. This condition is characterized by confusion, restlessness, and aggressive behavior as patients emerge from anesthesia. Dexmedetomidine (Dex) is an α-2 adrenergic agonist that has been shown to effectively reduce the incidence of EA due to its sedative and anxiolytic properties, which are similar to natural sleep. Dexmedetomidine has minimal effects on respiration, making it a favorable option for pediatric anesthesia. Despite its potential, the extent of its effectiveness in mitigating EA in various pediatric surgical populations requires further investigation.

Aims: The objective of this systematic review and meta-analysis was to evaluate the efficacy of Dexmedetomidine in reducing the incidence of emergence agitation in pediatric patients undergoing surgeries under sevoflurane anesthesia. We aimed to assess the impact of Dexmedetomidine across a range of pediatric surgeries, including those for conditions such as cleft palate, adenotonsillectomy, and cataract surgery, among others

Materials and Methods: A comprehensive search of PubMed and Google Scholar was conducted for randomized controlled trials (RCTs) from 2002 to 2024 that investigated the use of Dexmedetomidine in paediatric patients. The analysis was performed using RevMan 5.4. The effectiveness of Dexmedetomidine in preventing emergence agitation was examined across various surgical procedures, including cleft palate surgery, elective cardiac surgery, palatoplasty, adenotonsillectomy, elective strabismus surgery, cataract surgery, ambulatory surgery, paediatric liver surgery, laryngeal mask insertion, vitreoretinal surgery, outpatient surgery, spinal dysraphism surgery, and inguinal hernia repair. The risk of bias (ROB) was assessed using the Cochrane ROB-1 tool.

Results: A total of 370 research articles were identified from English-language databases. Following the application of inclusion and exclusion criteria, 15 studies were included in the review. Ten of these were selected for meta-analysis, involving 1,091 children aged between 8 months and 12 years. The results revealed that the 1 mcg/kg Dexmedetomidine group experienced a statistically significant reduction in the incidence of postoperative emergence agitation compared to the control group (OR = 0.30, 95% CI: 0.24, 0.39, P < 0.00001). Significant decreases in agitation were also observed in the tonsillectomy group (OR = 0.20, 95% CI: 0.09, 0.44, P < 0.0001) and the ophthalmic group (OR = 0.21, 95% CI: 0.13, 0.36, P < 0.00001). All studies indicated a low risk of bias.

Conclusions: Dexmedetomidine is highly effective in significantly reducing the incidence of emergence agitation in children undergoing a variety of surgeries, particularly those under sevoflurane-based anesthesia.

Keywords: Dexmedetomidine, Sevoflurane, Emergency agitation.

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1. Introduction

With the advancement in anaesthesia practice and the introduction of novel anaesthetic medications, the available anaesthetics have become more diverse in recent years. Inhalational anaesthetic induction is a technique commonly used by paediatric anaesthesiologists, particularly when venous injection is not available.[1] Sevoflurane, an inhaled anaesthetic with a quick onset and recovery, has gained increasing interest due to its comfort and safety for young patients. Sevoflurane can improve the anaesthesia experience for paediatric patients by reducing the risk of postoperative aspiration, vomiting, and other unpleasant effects in addition to producing a stable anaesthetic state.[2,3]

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However, more than 80% of children who received sevoflurane have emergence agitation (EA) or delirium (ED). In paediatrics, EA typically has no lasting effects. Nevertheless, it is a problematic psychomotor excitation that can cause harm to the patient or the surgical site and even it can cause concern and discontent among the parents, and necessitate more nursing care. The primary clinical signs of EA in children are confusion, nonsensical speech, sobbing, wiggling, groaning, restlessness, and the inability to distinguish or identify people or objects. As a result, it is critical to select appropriate and targeted drugs based on the patient's individual condition to prevent the EA occurrence effectively.[4-6]

Currently, a variety of medications, including non-opioid and opioid analgesics,[7] intravenous anesthetics,[8] benzodiazepines[9] and α2 agonists,[10] are used to minimize emerging agitation following sevoflurane anaesthesia in paediatric patients. Dexmedetomidine (Dex) is an FDA-approved medication that selectively activates the α2 adrenergic receptor, thereby blocking norepinephrine release, transmission of pain signals and agitation-induced pain stimulation.[11] In the spinal cord, it can bind to the α2 receptor to provide sedative and analgesic effects. It can also lower blood pressure and heart rate and maintain hemodynamic stability.[12] The half-life of Dex in children is approximately 120 minutes and had a very low inhibitory effect on the respiratory system.[13] Dexmedetomidine has been shown to prevent paediatric EA during sevoflurane anaesthesia at a dosage range of 0.15 to 2.0 μg/kg, while the ideal dosage is unknown.[14]

Dex is a well-known drug since 1999. Although prior studies have been conducted, not many discussed Dex's positive as well as adverse effects on children. The present systematic review and meta-analysis aims to examine and summarize the most recent data on the use of Dexmedetomidine to prevent ED caused due to sevoflurane anaesthesia and also examine its potentiality to decrease postoperative nausea and vomiting in paediatric patients undergoing various surgeries. Further, adverse effects caused by Dex were also reviewed.

2. Materials and Methods

A systematic review and meta-analysis were conducted as per PRISMA guidelines. PubMed and Google Scholar databases were searched for randomized controlled trials (RCTs) from 2002 to 2024 involving paediatric patients undergoing surgery administered with sevoflurane-based general anesthesia[15]**.** The exclusive criteria include non-randomized studies, observational studies, review articles, case reports, and laboratory reports. For PubMed the main keywords used are paediatrics, sevoflurane anaesthesia, Dexmedetomidine, and emergency agitation. The pertinent medical subject headings (MeSH) used are ("Dexmedetomidine" [MeSH Terms] OR "Dexmedetomidine"[All Fields] OR "Dexmedetomidine "[All Fields]) AND ("emergence delirium"[MeSH Terms] OR ("emergence"[All Fields] AND "delirium"[All Fields]) OR "emergence delirium"[All Fields] OR ("emergence delirium"[MeSH Terms] OR ("emergence"[All Fields] AND "delirium"[All Fields]) OR "emergence delirium"[All Fields] OR ("emergence"[All Fields] AND "agitation"[All Fields]) OR "emergence agitation"[All Fields])). For Google scholar, the main keywords used are "Dexmedetomidine", "emergence delirium" or "emergence agitation", "sevoflurane" and "paediatrics ". To find other related studies, we thoroughly reviewed our options, selected the study with the greatest sample size or the most recent publication for our research samples, and then looked further into the publications' references to find comparable studies.

2.1. Selection and screening

The screening approach consists of three steps of screening performed separately by two researchers. The title and abstract were screened first as part of the screening process. The second step involved thoroughly reviewing relevant research documents to determine the inclusion and exclusion criteria. The research paper was excluded if a study was not pertinent to paediatric anaesthesia and Dexmedetomidine. Finally, the researcher independently retrieved pertinent data from the included studies using a pre-designed data-collecting form. Any differences in the data collected were sorted out through discussion. The primary contents of the data collection form include the title of the research article, author name, year of publication, aim, study design, sample size, inclusion and exclusion criteria, surgery type, general anaesthesia, intervention given, comparative analysis, method, result and outcomes of each study**.**

2.2. Risk of bias analysis

The cochrane risk of bias (RoB 2) tool was used to evaluate the quality of the selected research articles[16]. The RoB evaluated randomized trials on domains including research article selection criteria bias, performance bias, detection bias, attrition bias, and reporting bias. To assist the authors in assessing the likelihood of bias signalling questions were added. The answers were rated as Yes (high risk) and No (low risk) **(Table 1)**.

2.3. Statistical analysis

A meta-analysis was conducted utilizing RevMan version 7.13.0. Statistical heterogeneity was evaluated using the $\chi 2$ test and the I2 test for the size of heterogeneity. A subgroup analysis was conducted based on the origin of heterogeneity. A fixed effect model was utilized when no statistical heterogeneity was present among the studies ($p>0.1$ or $I2<50\%$). If statistical heterogeneity was detected among the studies, a random effects model ($p<0.1$ or $I2>50\%$) was utilized, followed by a subgroup analysis to identify the source of the heterogeneity. The analysed data were categorical and expressed as risk ratio with a 95% confidence interval. We analysed publication bias by developing a funnel

plot and testing for asymmetry using Egger's test[17], which corresponds to linear regression (R version 4.3.2).

3. Results

3.1. Literature search

A summary of the systematic literature review and article selection process was shown in flowchart **(Figure 1).** Initially, 370 research articles were selected from English databases. 11 duplicate documents were removed and the remaining 359 research documents were selected for further screening based on title and abstract. For full text analysis, 300 documents not meeting the inclusion criteria were excluded and 52 documents were selected. Finally, 15 research papers were included for the review based on inclusion and exclusion criteria. Out of 15 articles, 10 research articles were selected for meta-analysis.

3.2. Study characteristics

In 15 included randomized controlled studies, a total of 1091 children aged between 8 months to 12 years from various geographical locations were assessed. Surgeries including cleft palate surgery[18], elective cardiac surgery,[19] palatoplasty,[20], adenotonsillectomy[21-23], elective strabismus surgery,[24] cataract surgery,[25] ambulatory surgery,[26] paediatric liver surgery,[27] laryngeal mask insertion,[28] vitreoretinal surgery,[29] elective outpatient surgery,[30] spinal dysraphism surgery[13] and inguinal hernia repair[10] were performed. Characteristics of the study are given in **Table 1**.

3.3. Sevoflurane anesthesia and Dexmedetomidine administration

Preoperatively, children from all the selected studies were subjected to sevoflurane-based general anaesthesia in a dosage range of 8% in 7 studies,[13,22-24,26,29,30] 5% in one study,[28] 4% in one study,[20] 3% in one study[10] and 2% in one study.[21]

Dexmedetomidine was administered preoperatively in 10 studies preoperatively and intraoperatively in 1 study[19] intraoperatively in 1 study and both preoperatively and continued postoperatively in 1 study and postoperatively in 2 studies. Dexmedetomidine was administered intranasally in 2 studies[25,28] and intravenously in 13 studies.[10,13,18,20,23,26,27,29,30]

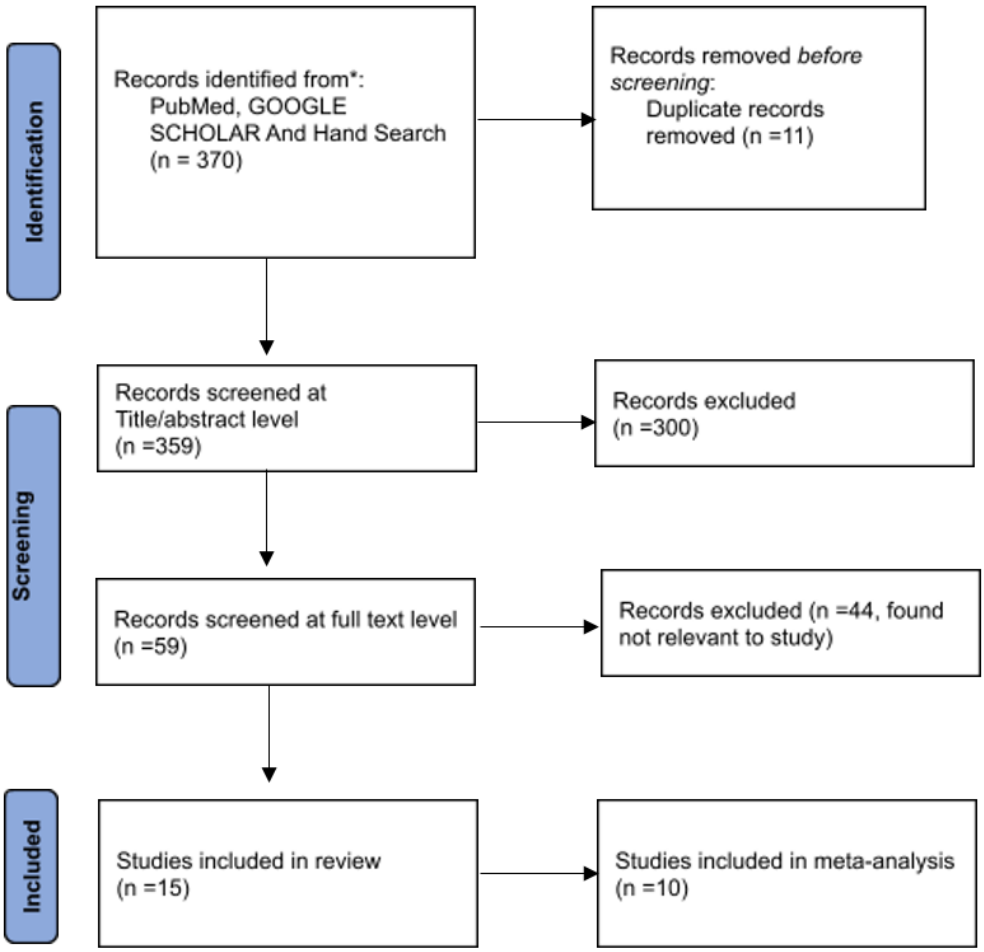

Figure 1: PRISMA flow diagram for the systematic review which included searches of databases

Table 1: Characteristics of the included articles

Aim	Study design	Sample size	Age	Surgery type	General anaesthesia	Intervention	Comparator	Scale	Results	Conclusion	Ref.
This study aimed to assess the effects of Dexmedetomidine and propofol on children's emerging delirium undergoing cleft palate surery	RCT	90	8 to 24 months	cleft palate surgery	Sevoflurane	IV 0.5 μg/kg/h Dexmedetomidine	Group C-IV 0.9% saline Group P- IV propofol 2 mg/kg/h	PAED scale and pain using FLACC score	The analysis included 86 patients in total. Among groups D, P, and C, the incidence of ED was 20.1%, 58.6%, and 85.7%, respectively ($P < 0.05$). Compared to groups P and C, group D had lower scores for face, legs, activity, crying, and consolability ($3.9 + 1.1$ vs 6.1 ± 0.9 and 7.1 ± 1.0, $P < 0.05$). Groups P and C had significantly greater heart rates and mean arterial pressures during emergence than group D (All $P < 0.05$).	According to these results, infants undergoing cleft palate surgery under sevoflurane-based anaesthesia saw fewer cases of emerging delirium when Dexmedetomidine was used instead of propofol.	18
To examine the impact of dexmedetomidine on ED in children having heart surgery.	RCT	50	1-6 years	Elective cardiac surgery	Sevoflurane	Dexmedetomidine was administered to group D (N = 25) at a rate of 0.5 μg/kg for 10 minutes, and then at a rate of 0.5 μg/kg/h till the procedure was completed.	Normal saline was given to Group S (N=25) as soon as anaesthesia was induced.	A 5-point scale was used to measure ED, and the PAED scale was used to determine its severity.	Group D's 5-point and PAED scale scores were considerably lower than group S. Furthermore, group D experienced noticeably less variation in melatonin levels. Both groups experienced increases in serum norepinephrine, TNF-α, IL-6, cortisol and glucose; however, group D experienced much smaller increases compared to group S. In group D, sevoflurane intake was considerably lower (P=0.0002). Group D used less fentanyl after surgery (P=0.04), but there was no significant difference in pain levels (P=0.502). Group D's extubation time was substantially longer than group S's (P=0.032), while the two groups' hospital stays and CICU stays were similar.	Children having heart surgery benefit from continual intraoperative administrations DEX because it lowers the need for sevoflurane and lowers the likelihood of ED, which is linked to lower plasma melatonin levels and less surgical stress.	19

Table 1 Continued….											
The study examined the impact of a continual perioperative infusion of 0.2 µ/kg/h Dexmedetomidine on the incidence of ED in children undergoing surgery	RCT	46	DEX group-59 ± 25.4 months Saline group-48 ± 33.4 months	Elective outpatient surgery	Sevoflurane	Group D-Dexmedetomidine 0.2 µg/kg/h	Group S-saline 0.2 µg/kg/h	ED and pain score	There was a statistically significant difference in the occurrence of ED between the two groups: 26% in Group D compared to Group S (60.8%) (P = 0.036). Furthermore, Group D experienced fewer ED episodes (P < 0.017). The durations for extubation and discharge from the PACU were identical, as were the pain levels.	After sevoflurane-based GA, children who get a perioperative 0.2 Dexmedetomidine infusion have a lower incidence and frequency of ED without needing more time to be extubated.	30
To investigate the possibility that giving Dex to infants having palatoplasty will lessen the quantity and intensity of EA following Sev-based anaesthesia	RCT	70	10 to 14 months	Palatoplasty	Sevoflurane	De group-Dex was given at a dosage of 6 µg/kg/h for 10 minutes prior to the completion of the procedure, and then 0.4 µg/kg/h for 5 minutes following extubation.	saline group: 6 µg/kg/h saline was given in a comparable way.	EA -5-point scale and pain scale-10-point scale were used.	The Dex group's EA and PS ratings were considerably lower than those of the saline group from the time of extubation until 120 minutes after they arrived in the PACU.	The study concludes that administering Dex include a lower EA and PS with no negative side effects. Dex helped infants undergoing palatoplasty recover satisfactorily.	20
To assess how a single intraoperative dosage of Dexmedetomidine and tramadol affects hemodynamics and the postoperative recovery, in pediatric patients having an adenotonsillectomy under general anesthesia-sevoflurane.	RCT	77		Adenotonsillectomy	Sevoflurane-based general anaesthesia	1 µg/kg Dexmedetomidine	2 mg/kg tramadol	Observational pain scores, PAED scores, and Ramsay sedation scores	Dexmedetomidine raised the RSS 15, 30, and 45 minutes after arrival at the PACU, while dramatically lowering the HR and MAP 10 and 15 minutes after induction. There was no discernible difference between the two groups' OPS and PAED scores or the proportion of subjects with OPS ≥ 4 or PAED score of 4 or 5 and having a score of 3 or 4. Group D's extubation and Alderete score > 9 times were noticeably longer.	Tramadol and Dexmedetomidine both worked well to reduce emergence agitation and discomfort. Administration of Dexmedetomidine was associated with bradycardia and extended sedation, as compared to intraoperative hypotension caused by tramadol.	21

Table 1 Continued….

To evaluate how intraoperative ketamine, Dexmedetomidine, and a placebo affected postoperative emergency agitation and postoperative vomiting.	RCT	84	2 to 7 years	Elective strabismus surgery	Sevoflurane	DEX group-Dexmedetomidine 1 µg/kg IV	Saline group-saline 1 µg/kg IV ketamine group- 1 µg/kg IV	PAED scale and POV score	Compared to the placebo group, the ketamine and Dexmedetomidine and ketamine groups had reduced peak PAED scores for EA. The Dexmedetomidine group (15%) had a lower incidence of POV than either the ketamine (44%) or placebo (45.8%) groups. Compared to the placebo group, the Dexmedetomidine and ketamine groups experienced less pain on the ward. Each group's time to LMA elimination was comparable. In comparison to the placebo group, the Dexmedetomidine and ketamine groups required more time to return to mental orientation and to be discharged from the PACU.	For paediatric strabismus surgery, Dexmedetomidine and ketamine seem to reduce postoperative pain and agitation following sevoflurane anaesthesia. Furthermore, Dexmedetomidine inhibits POV.	24
To investigate the possibility that giving children undergoing cataract surgery under sevoflurane anaesthesia a single dose of intranasal DEX as premedication could lessen their emerging agitation and preoperative anxiety.	RCT	90	1 to 8 years	Cataract surgeries	Sevoflurane	Group D1--1 µg/kg of DEX Group D2-2 µg/kg of DEX	Group C-normal saline	PAED scale	Compared to the D1 and D2 groups, the saline group's mask induction ratings were considerably greater (P<.001). Compared to the saline group, the D1 and D2 groups saw significantly fewer instances of emerging agitation (7/30 in group D1 and 3/30 in group D2 vs. 24/30 in group C, P<.001). All three groups had similar emergence and PACU stay times. When compared to the saline group, the DEX-treated groups' ED and PACU stay time did not change substantially; neither did the 1- nor 2-µg/kg groups. There were no serious clinical issues in any of the patients.	Without lengthening the emergency period or causing serious side effects, an intranasal DEX dose of 1 or 2 µg/kg independently increases the incidences of mask acceptance and reduces the occurrences of postoperative emergency agitation, primarily from sevoflurane.	25

Table 1 Continued….											
To investigate how DEX affects recovery patterns, EA, and parental satisfaction following sevoflurane anaesthesia in paediatric ambulatory surgery	RCT	81	1 to 9 years	Ambulatory surgery	Sevoflurane	DEX 0.3 µg/ kg	Saline group	EA score- 1-4 point and pain score-0-10 point scale	The DEX group had a considerably reduced incidence of EA 3 or 4 (28%) compared to the saline group (64%), with a significant difference . During their stay in the post-anaesthesia care unit, the DEX group's mean pain scores were significantly lower than those of the saline group ($P < 0.01$). The two groups did not differ in terms of the frequency of adverse events, the amount of time spent in the PACU, the time until the first drinking and voiding occurred, or the degree of pleasure expressed by parents.	In paediatric ambulatory surgery, IV DEX 0.3 µg/kg dosage following anaesthetic induction decreased sevoflurane-associated EA and postoperative pain without raising the risk of adverse events or altering parents' satisfaction levels.	26
To evaluate the impact of remifentanil and dexmedetomidine (Dex) on emergence agitation (EA) during the recovery process following sevoflurane anesthesia for pediatric liver surgery.	RCT	60	1 to 6 years	Paediatric liver surgery	Sevoflurane	Group A-DEX 0.2-0.4 µg/kg·h	Group B-saline	Aono’s score, Craner’s PAED score, and Children’s and Infants’ Postoperative Pain Scale	Compared to children in group A, children in group B exhibited lower HR and MAP values both immediately following tracheal extubation and five minutes later. At 15 and 30 minutes after admission to the PACU, group B's Aono's scores, PAED agitation scores, and CHIPP scores were lower than those of group A. Compared to group A, group B experienced a reduced rate of agitation after postoperative anaesthesia waking. Group A and Group B did not significantly differ in their postoperative adverse responses.	Dex+remifentanil+sevoflurane anesthesia can relieve postoperative pain, regulate hemodynamic levels, and lower the frequency of EA following the awakening phase following pediatric liver surgery. It also has fewer postoperative side effects, which justifies clinical use.	27

Table 1 Continued….

To confirm the hypothesis that intranasal Dexmedetomidine premedication can lower the minimal alveolar concentration of sevoflurane for laryngeal mask airway installation in children,	RCT	90		Laryngeal mask insertion	Sevoflurane-based general anaesthesia	Group D1-DEX 1 g/kg Group D2-DEX 2g/kg	Group S-saline	PAED scale	The results indicate When 1 and 2 µg/kg of Dexmedetomidine were administered beforehand, sevoflurane decreased from 1.92% to 1.53% and 1.23%, which is equivalent to a 20% and 36% drop, respectively. In Group S, Group D1, and Group D2, the highest PAED scores 9, 5 and 3. Groups D1 and D2 had a significantly reduced prevalence of ED (≥ 10) than Group S. Concurrently, Groups D1 and D2 displayed significantly greater induction characteristics and parent satisfaction levels than Group S.	Premedication with intranasal Dexmedetomidine results in a dose-dependent reduction in the minimum alveolar concentration for sevoflurane laryngeal mask airway insertion and ED in the PACU.	28
In order to determine whether Dexmedetomidine would minimize IOP elevation, maintain hemodynamic stability, and reduce extubation reaction and EA in young children undergoing vitreoretinal surgery, this study reviewed the benefits of the drug in ocular surgery.	RCT	60	3 to 7 years	Vitreoretinal surgery	Sevoflurane	Dexmedetomidine 0.5 µg/kg	Saline	The incidence and severity of emergence agitation was measured according to the paediatric anaesthesia emergence agitation scale: 1, calm; 2, not calm but could be easily calmed; 3, not easily calmed, moderately agitated or restless; and 4, combative, excited, or disoriented	Intraocular pressure did not significantly differ among the groups at any of the two time points. Following anaesthetic induction, mean arterial pressure and heart rate dropped from baseline in both groups. In comparison to the control group, the Dexmedetomidine group experienced a reduction in the increase in mean arterial pressure and heart rate that was related with extubation from intraoperative values. Compared to the control group, the Dexmedetomidine group experienced less coughing following extubation. The groups did not differ significantly in terms of extubation. Compared to the control group, the Dexmedetomidine group had emerging agitation less frequently. There was no discernible difference in the prevalence of oxygen desaturation, laryngospasm, bronchospasm, or breath holding between the groups.	Dexmedetomidine 0.5 µg/kg reduced the hemodynamic response to extubation and decreased emergence agitation in young patients undergoing vitreoretinal surgery, but it had no influence on perioperative hemodynamics or intraocular pressure.	29

Table 1 Continued….

To determine whether giving children having adenotonsillectomy after sevoflurane-based anaesthetic an infusion of intraoperative low-dose ketamine and then intravenous Dexmedetomidine could lower the incidence of EA.	RCT	92	3–7 years	Adenotonsillectomy	Sevoflurane	Dexmedetomidine 0.3 μg/kg	saline	OPS and PAED scores	KETODEX group had a lower incidence and severity of EA than the controls. The KETODEX group experienced fewer fentanyl rescues than the controls. When compared to children who received KETODEX, the control group's heart rate during extubation was considerably higher (P<0.05). The KETODEX group experienced a considerably lower incidence of postoperative discomfort (15.5% vs. 63.8%, P<0.05). The KETODEX group experienced significantly longer durations to interaction and extubation (P<0.05).	KETODEX facilitates a smooth extubation and lowers the frequency and severity of EA in children having adenotonsillectomy after sevoflurane-based anaesthesia.	22
The study aims to study the effect of intraoperative Dexmedetomidine on an early and smooth recovery and reduce EA and postoperative pain.	RCT	36		Surgery for spinal dysraphism	Sevoflurane	Dexmedetomidine 1 mg/kg infused for 10 min followed by a maintenance dose of 0.5 mg/kg/h	saline	Modified objective pain score, agitation Cole score, and modified Aldrete score.	Demographics, anaesthetic duration, emergence, and extubation timings did not significantly differ between the two groups. The Dexmedetomidine group had a lower mean heart rate and considerably reduced intraoperative sevoflurane and fentanyl consumption. The incidence of bradycardia and hypotension, as well as the average systolic blood pressure, were similar in the two groups. Children in the Dexmedetomidine group experienced significantly reduced pain scores, agitation scores and time to complete the Aldrete score after surgery. The Dexmedetomidine group consumed significantly less fentanyl after surgery and they also needed analgesics for a longer period of time. While there was no difference in respiratory rate or arterial oxygen saturation, the placebo group had greater mean heart rate and systolic blood pressure. In the Dexmedetomidine group, there were significantly fewer patients experiencing postoperative nausea and vomiting.	Children having spine surgery who receive intraoperative Dexmedetomidine have a good recovery profile with less EA and postoperative pain and no negative perioperative hemodynamic consequences.	13

Table 1 Continued….

This study set out to investigate the idea that using Dexmedetomidine as a preventative measure lowers the incidence of emerging agitation in children following sevoflurane-based anaesthesia due to its calming effects.	RCT	90	1 to 10 years	Inguinal hernia repair	Sevoflurane	Group 2-DEX 0.15 µg/kg Group 3-DEX 0.30 µg/kg	Group1-saline	CHIPPS score	The three groups' intraoperative characteristics were comparable. Group 1 was 7.5 ± 5.0 min, Group 2 was 8.2 ± 5.0 min, and Group 3 was 9.8 ± 4.0 min. In Group 1, the incidence of agitation was 37%, in Group 2 17% and in Group 3, it was 10%. When comparing Group 1 to Group 3, paired comparisons revealed a significant difference. For all three groups, the postanesthesia care unit discharge timeline was comparable.	The study find that children's postsevoflurane agitation is decreased and no negative side effects are observed when 0.3 µg/kg of Dexmedetomidine is given after anaesthesia is induced.	10
to monitor the tonsillectomy recovery and extubation process in paediatric patients under anaesthesia using either high-concentration sevoflurane by itself or low-concentration sevoflurane in conjunction with a single intravenous dose of Dexmedetomidine as a premedication.	RCT	75	3-7 years	Tonsillectomy	Sevoflurane	Group D1-1 µg/kg of DEX Group D2- 2 µg/kg of DEX	Group D0-saline	PAED scale	During deep anaesthesia, all three groups' tracheal tubes were effectively removed. To keep their airways open after being extubated, Group D0 (9 patients), Group D1 (3 patients), and Group D2 (2 patients) needed oral airways. Compared to Group D0, the pace of oral airway utilization in groups D1 and D2 was considerably lower. Additionally, compared to Group D0, the rates of patients experiencing ED and fentanyl demands in Groups D1 and group D2 were much lower. Group D2 experienced a longer duration between extubation and spontaneous eye opening compared to Groups D0 and D1. Groups D0 and D2 experienced longer post-anaesthesia care unit release periods than Group D1. No additional respiratory issues	When combined with low-concentration sevoflurane at the conclusion of surgery, a single intravenous dose of Dexmedetomidine as pre-medication allowed for a safe and easy deep extubation and reduced EA in children receiving tonsillectomy under sevoflurane anesthesia. 1 µg/kg of preoperative Dexmedetomidine did not lengthen the recovery period following surgery.	23

3.4. Emergency agitation and postoperative pain assessment

Emergence delirium was evaluated using the paediatric anaesthesia emergence delirium (PAED) scale and diagnosed if the patient had a score >10.[28] In children undergoing liver surgery, PAED scores were lower in children who received DEX along with remifentanil and Sevoflurane compared to the placebo group.[27] Similarly, children who received DEX preoperative to adenotonsillectomy had average PAED scores of 3 to 5 without any significance.[21,22] Also, in children who underwent palatoplasty, the Dex group's EA and PS ratings were considerably lower than those of the saline group from the time of extubation until 120 minutes after they arrived in the PACU.[20] In children undergoing strabismus surgery, only 11% in DEX group had PAED score ≥ 10 compared to placebo group.[24] Children who underwent spinal dysraphism agitation as well as postoperative scores were significantly lower in DEX group.[13] Postoperative EA scores in patients who underwent paediatric ambulatory surgery were lower in DEX group (28%) compared to placebo group.[26] All the studies showed statistically significantly lower ED scores in DEX groups compared to placebo group (not given DEX). Preooperative infusion of DEX was found to significantly reduce EA.[19,23,29-30] Most studies used the faces, legs, activity, cry, and consolability ability (FLACC) score to measure postoperative pain. Fentanyl (0.5µg kg-1) was used as rescue analgesia if the score was greater than 3.

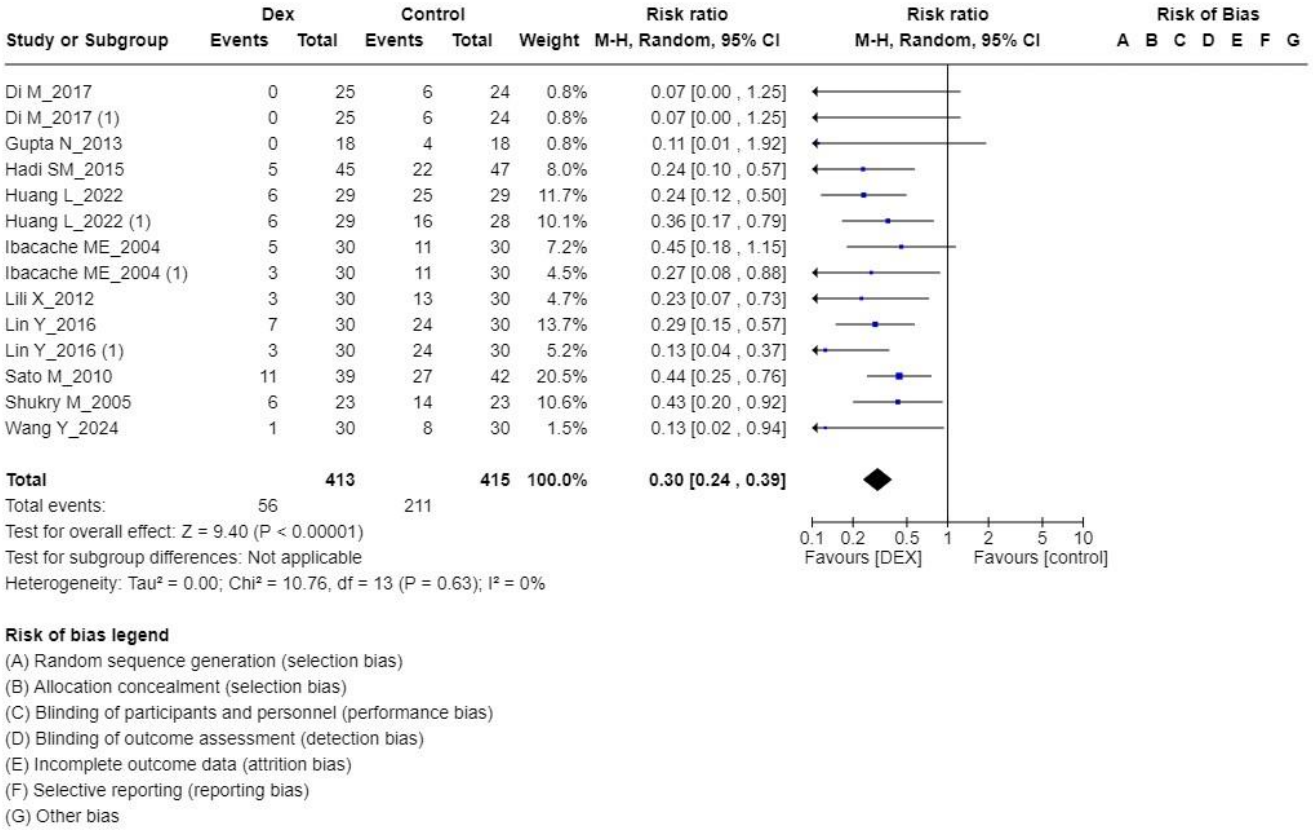

Figure 2: Forest plot of 1 mcg DEX vs saline group using a fixed-effects model; chi-square and confidence interval (CI)

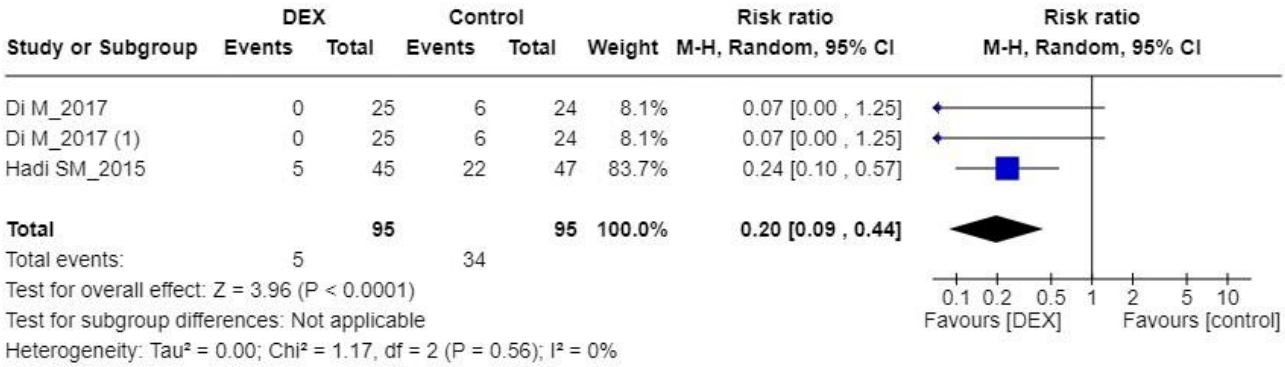

Figure 3: Forest plot of sub-group tonsillectomy using a fixed-effects model; chi-square and confidence interval (CI)

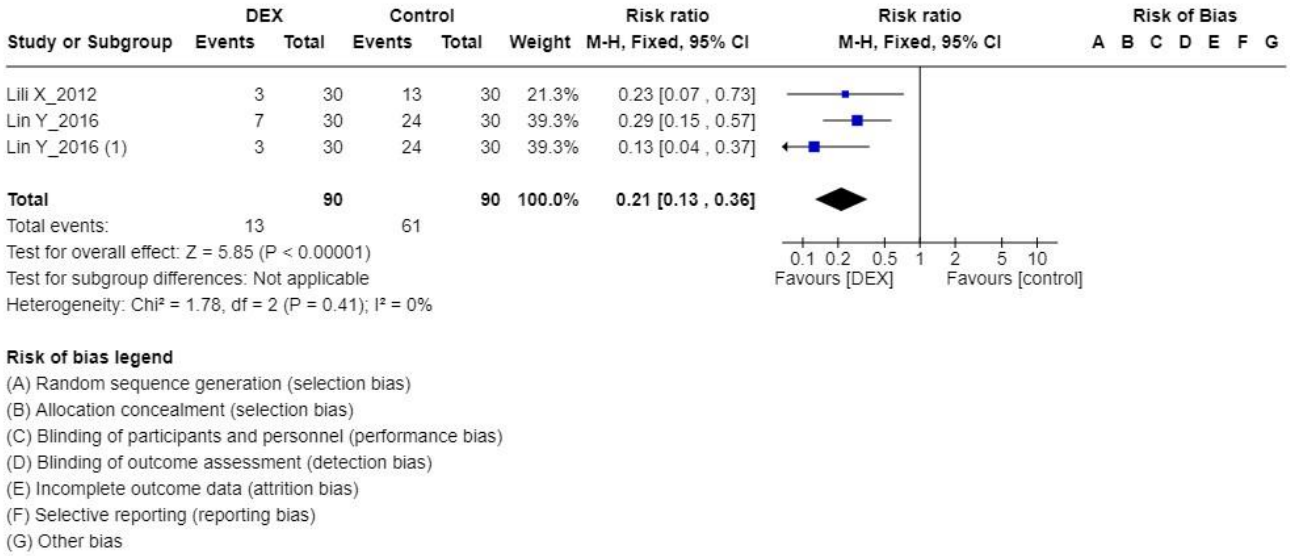

Figure 4: Forest plot of sub-group opthalamic surgery using a fixed-effects model; chi-square and confidence interval (CI)

Table 2: Supplementary risk of bias analysis of the included studies

Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias	Ref.
Yes	Yes	Yes	Unclear	Yes	No	No	(18)
Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	(19)
Yes	Yes	Yes	Unclear	Yes	Yes	Yes	(30)
Yes	Yes	Yes	Yes	Yes	Unclear	Yes	(20)
Yes	Yes	Yes	Yes	Yes	Yes	Yes	(21)
Yes	Yes	Yes	Yes	Yes	Yes	Unclear	(24)
Yes	Yes	No	No	Yes	Yes	Yes	(25)
Yes	Yes	Yes	Yes	Yes	Unclear	Yes	(26)
Yes	Yes	No	No	Yes	Yes	Unclear	(27)
Yes	Yes	Yes	Yes	Yes	Yes	Unclear	(28)
Yes	Yes	Yes	Unclear	Yes	Yes	Yes	(29)
Yes	Yes	Yes	Yes	Yes	Yes	Yes	(22)
Yes	Yes	Yes	Yes	Yes	Yes	Yes	(13)
Yes	Yes	Yes	Yes	Yes	Yes	Yes	(10)
yes	unclear	yes	yes	yes	yes	yes	(23)

Ref.: References

3.5. Meta-analysis results of the incidence of emergence agitation

For the meta-analysis of ED prevalence in children anesthetized with sevoflurane and Dexmedetomidine, a total of 10 included studies described the ED incidence on the PAED scale[10,13,18,22,23,25,27-29,30] and analysed using fixed effect model. Ten studies involving 413 patients in the experimental group and 415 cases in the control group employed 1 mcg of Dexmedetomidine. This subgroup was examined using a FEM (**Figure 2**), and the results of the heterogeneity test revealed no differences between the 10 publications [Chi2=10.76, degree of freedom (df) =13, I2=0%, P=0.63]. The 1 mcg Dexmedetomidine group experienced a statistically significant decrease in the incidence of postoperative emergence agitation compared to the control group (OR =0.30, 95% CI: 0.24, 0.39, P<0.00001). Two publications containing 95 patients in the experimental group and 95 cases in the control group were included in the tonsillectomy surgical subgroup. This subgroup was analysed using a FEM (**Figure 3**), and the results of the heterogeneity test revealed no differences between the two publications [Chi2=1.17, degree of freedom (df) =2, I2=0%, P=0.56]. The tonsillectomy group experienced a statistically significant decrease in the incidence of postoperative emergence agitation compared to the control group (OR =0.20, 95% CI: 0.09, 0.44, P<0.0001). Two publications with 90 cases in the experimental group and 90 cases in the control group were included in the subgroup on ophthalmic surgery. This subgroup was analysed using a FEM (**Figure 4**), and the results of the heterogeneity test revealed no differences between the two publications

[Chi2=1.78, degree of freedom (df) =2, I2=0%, P=0.41]. The ophthalmic group experienced a statistically significant decrease in the incidence of postoperative emergence agitation compared to the control group (OR =0.21, 95% CI: 0.13, 0.36, P<0.00001).

3.6. Risk of bias analysis

Risk of bias for all included randomized controlled studies had a low risk of bias (**Table 2**). However, in few studies selective reporting[19,20,26] and other biases were not clear.[24,27,28]

4. Discussion

Emergence agitation, a prevalent postoperative complication with a 12% incidence rate that predominantly impacts children aged 3 to 5, usually manifests within the first 15 minutes of waking up following anaesthesia and is characterized by a mental state in which behaviour and consciousness are separated. Numerous risk variables, including age, the type of surgery, the duration of anaesthesia, and the paediatric anaesthesia behaviour score, are linked to its clinical manifestations.[31]

Sevoflurane is commonly used in paediatric anaesthesia because of its minimal blood gas partition coefficient, rapid onset of anaesthesia, and rapid recovery following surgical procedure. Nevertheless, emerging agitation following sevoflurane anaesthesia is common. According to a recent study, children struggled with self-control. The study found propofol and sevoflurane inhalation caused identical extubation and recovery times for the two groups of children, but sevoflurane caused a significantly greater rate of awakening agitation phase than propofol.[32] A condition of separation arises when the subcortical centre has been released but the cerebral cortex continues to remain inhibited. This makes children more perceptive of their surroundings. This state can readily lead to emerging agitation when combined with pain sensations.[33]

Dexmedetomidine is the bioactive dextro-isomer of medetomidine.[34] By activating a pertussis toxin-sensitive G regulatory protein) and subsequently reducing adenylyl cyclase activity, it exerts its end-organ actions through post-synaptic α2-adrenergic receptors. Dexmedetomidine is the bioactive dextro-isomer of medetomidine. By activating a pertussis toxin-sensitive G regulatory protein) and subsequently reducing adenylyl cyclase activity, it exerts its end-organ actions through post-synaptic α2-adrenergic receptors. Dexmedetomidine's sedation and anxiolysis are mostly attributed to central nervous system stimulation of parasympathetic outflow and suppression of sympathetic outflow from the locus cereleus in the brainstem. The physiological effects of Dexmedetomidine include sedation and sympathetic nervous system blunting. Demonstrated efficacy in reducing the pathologic elevations in heart rate and blood pressure in our patients, as well as in managing their agitation and aggressive conduct.[35]

The present systematic review and meta-analysis found that 1 mcg Dexmedetomidine significantly reduced ED incidence when compared to placebos or other medicines. It also decreased the need for rescue analgesia. Similarly, recently conducted a systematic review and meta-analysis comprising 8 studies and a total of 629 paediatric patients found Dexmedetomidine lowers the incidence of ED (RR=0.39; 95% CI 0.25–0.62). The usage of rescue analgesia also decreased (RR=0.38; 95% CI 0.25–0.57).[12] Also, in a similar study comprising16 randomized controlled studies, the findings demonstrate that the 0.5 μg/kg Dexmedetomidine group experienced a statistically significant decrease in emerging agitation incidence compared to the control group (OR =0.22, 95% CI: 0.13, 0.40, P<0.00001). Dexmedetomidine's consistent efficacy in treating ED is supported by many systematic reviews and randomized trials. Its capacity to lessen the need for rescue analgesia implies both enhanced patient comfort and less strain on medical professionals throughout the recuperation phase. Dexmedetomidine offers significant advantages, positioning it as a suitable alternative to conventional sedatives in paediatric anaesthesia. Further research is necessary to improve the dosing regimen across different clinical scenarios, aiming to enhance benefits and reduce possible adverse reactions.

This systematic review's strengths include a thorough search for current evidence across multiple databases. Moreover, only randomized controlled trials were included. All were prospective RCTs with comparable groups or placebo group and blinded. However, this meta-analysis has limitations. The time and dosages of Dexmedetomidine varied, and each trial was founded on a distinct study protocol. Variations in the children's ages, the severity of the underlying illness, and the type of operation were additional possible sources of variability.

5. Conclusion

This meta-analysis evaluated the efficacy of Dexmedetomidine in preventing sevoflurane-induced emergence agitation in children. The findings demonstrate that Dexmedetomidine significantly reduces the incidence of emergence agitation in paediatric patients undergoing a range of surgeries with sevoflurane anaesthesia. These results provide scientific support for the use of Dexmedetomidine as a therapeutic intervention to prevent emergence agitation in children.

6. Source of Funding

None.

7. Conflict of Interest

None.

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