ARTICLE

Efficacy of intravenous Lidocaine in controlling emergence agitation in children for surgery under Sevoflurane anesthesia: a meta-analysis

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BACKGROUND: Emergence delirium is a state of mental confusion and agitation after wakening from anesthesia that may result in traumatic injuries to the child. Limited drugs have been studied or used to prevent this occurrence.

OBJECTIVE: To determine the efficacy and safety of intravenous lidocaine in controlling emergence agitation (EA) in children undergoing surgeries done under general anesthesia compared to placebo or other intravenous anesthetics.

METHODOLOGY: This study is a meta-analysis, where published articles were obtained using PubMed, Cochrane Library, Clinical Trials, and Google Scholar up to August 2022. The primary outcome measure includes incidence of emergence delirium while secondary outcomes are postoperative pain and adverse effects comparing lidocaine and other intravenous drugs. The latter includes nausea and vomiting, untoward airway events and local anesthetic toxicity (LAST). Review Manager 5.4 was used for statistical analysis.

RESULTS: There were a total of 6 articles included for quantitative and qualitative analysis. The overall incidence of emergence agitation (RR=1.03, 95% CI [0.50, 2.13], P=0.94) and adverse events were higher in the Lidocaine group, although the differences were not significant. Subgroup analysis by comparator showed significant increased risk of developing EA with Lidocaine compared to other intravenous drugs (RR=2.06, 95% CI [1.32, 2.32], P=0.002). The risk for developing postoperative pain is decreased with Lidocaine compared to placebo and other drugs.

CONCLUSION: Intravenous lidocaine given to children undergoing general anesthesia with sevoflurane increased their risk for emergence delirium, compared to both placebo and other intravenous anesthetics.

KEYWORDS: *lidocaine, emergence agitation/delirium, children, pediatric, anesthesia, sevoflurane anesthesia, general anesthesia*

INTRODUCTION

First described in the early 1960s, emergence agitation (EA), also referred to as emergence delirium (ED) or emergence excitement is defined as a state of mental confusion, agitation and disinhibition particularly upon wakening from anesthesia [1]. This manifests as hyperexcitability, crying, restlessness, self-injury and hallucinations despite attempts to reorient the patient through verbal or other means [2, 3].

Its incidence varies from 20-80%, more commonly seen in children aged 2-7 years old [4, 5] who undergo painful surgical procedures under general inhaled anesthesia [5]. Suggested risk factors include rapid awakening in an unknown environment, agitation during anesthetic induction, preoperative anxiety, airway obstruction, environmental disorders, use of pre-anesthetic medication, anesthetic technique, type of anesthetic used (volatile, intravenous) and postoperative pain [6].

This may last from a few minutes to as long as thirty minutes and may resolve spontaneously. However, though short in duration, it may cause a great deal of stress for both parents and healthcare personnel. Emergence agitation may result in traumatic injuries to the child, pulling out of intravenous lines and drains, self-extubation and emotional trauma for the caregiver [7]. There is limited literature on the pathophysiology of emergence agitation in children. Some say that it is because of increased sympathetic tone and prolongation of the excited state during anesthesia recovery [13]. Others say that it is due to differential recovery rates in brain function due to differences in clearance on emergence [13]. Elevated lactate and glucose concentrations in the parietal cortex due to sevoflurane anesthesia, and the occurrence of clinically silent sevoflurane-induced epileptogenic activity have also been proposed [13]. A functional MRI was used by the team of Bouxveraoux et al, to explain the mechanisms underlying the alteration of consciousness during anesthesia [15,16]. It was found that during emergence from general anesthesia, thalamocortical connectivity in sensory networks, and activated midbrain reticular formation are preserved. However, delayed recovery of subcortical thalamoregulatory systems could contribute to defects in cortical integration of information, which could lead to confusion or an agitated state [9, 15]. Thus, various medications namely, midazolam, ketamine, alpha 2 agonists and propofol, have been studied to reduce the incidence of this complication. Of these, propofol is the preferred drug for the prevention and treatment of emergence agitation [13]. According to the study of Auoad et. al with children, 1 mg/kg propofol at the end of surgery after discontinuation of sevoflurane decreases the incidence of agitation [17]. However, propofol, along with the mentioned drugs, poses some undesirable side effects including delayed postoperative awakening, hypotension, bradycardia and asystole [13].

Lidocaine is a tertiary amine derived from xylidine. This drug is commonly used for local anesthesia, often combined with epinephrine [20]. It can also be given intravenously for advanced airway management as an adjuvant to tracheal intubation by obtunding the hypertensive response to laryngoscopy [20]. Other uses of lidocaine besides reduction in pain are reduction of nausea, ileus duration, opioid requirement and length of stay in hospital [14]. Aside from minimizing the patient's pain on emergence by sodium channel blockade, Lidocaine diminishes the nociceptive signaling to central nervous system through inhibition of G-protein mediated effects and reducing sensitivity and activity of spinal horn neurons particularly targeting glycine and NMDA receptor-mediated [14]. Additionally, in a journal by Dunn et. al, systemic lidocaine blocks excitatory responses in wide dynamic range neurons in the rat spinal cord through a mechanism probably involving strychnine-sensitive glycine receptors [14]. Its other mechanism of action includes blockade of muscarinic, nicotinic and dopaminergic receptors, enhancement of gamma-aminobutyric acidinergic pathways, inhibition of opiate receptors, anti-inflammatory properties and inhibition of release of substance P, a potent NK1 agonist [18, 19]. Toxicity from perioperative lidocaine is exceedingly rare [14]. Among the dreaded adverse effects of the provision of local anesthesia is local anesthetic systemic toxicity (LAST) manifesting as cardiac and central nervous system symptoms. Drowsiness was reported in 2 of 18 patients who received perioperative lidocaine infusion for abdominal surgery.

There are anecdotal reports that patients who receive perioperative lidocaine appear to be sleepier during emergence from anesthesia. Also, it is thought that the apparent delayed awakening results from patients being less responsive to the endotracheal tube [14]. Perioperative lidocaine has been shown not to affect time to PACU discharge [14]. These findings are supported by the retrospective study by Both et. al. It explores the use of perioperative intravenous lidocaine administration in children undergoing laparoscopic procedures. This analysis did not reveal any adverse effects in pediatric patients receiving intravenous lidocaine for surgeries done under general anesthesia [9]. Given its superior safety profile compared to older local anesthetic agents [20] and easy accessibility, lidocaine shows immense potential for reduction of emergence agitation. Several clinical trials have shown that Lidocaine can significantly reduce the incidence of emergence agitation in children who underwent surgery under general anesthesia [8, 9], while others state it has no effect [10,11]. Other studies have used it as an adjunct for prevention of emergence agitation and showed favorable results [4, 12]. To date, no meta-analysis has been conducted with regards to this topic.

The general objective of this study is to determine the efficacy and safety of intravenous lidocaine in controlling emergence agitation in children undergoing surgeries done under general anesthesia compared to placebo or other intravenous anesthetics. Specifically, to determine whether there is a difference in the incidence of emergence agitation, postoperative pain and adverse events among pediatric surgical patients done under general anesthesia via sevoflurane given intravenous lidocaine versus placebo or other intravenous anesthetics.

The adverse events that were considered include nausea and vomiting, untoward airway events and LAST.

Materials and Methodology

This meta-analysis followed the recommendations of the PRISMA-P 2020 statement and Cochrane Collaborations for systematic reviews and meta-analysis. Included journals were obtained through PubMed, Cochrane Library, Clinical Trials and Google Scholar from August 2022. The search terms were “randomized controlled trial”, “clinical controlled trial”, “Lidocaine”, “emergence agitation/ delirium”, “adjuvant”, “children”, “pediatrics”, “anesthesia”, “general anesthesia” and “sevoflurane anesthesia”.

The studies reviewed were randomized controlled trials that assessed the safety and effectiveness of intravenous lidocaine in decreasing the incidence of emergence agitation among children of any age group under 18 years of age with American Society of Anesthesiologist (ASA) functional classification I-II undergoing surgery under general anesthesia via sevoflurane. These include lidocaine dosed at 1-2mg/kg intravenous bolus either at induction or prior to extubation which may be followed by an infusion at 1.5mg/kg/hr or not. This intervention was compared to a placebo or other intravenous anesthetics. Studies wherein lidocaine given through local or aerosolized, other forms of general anesthesia and articles that included children with central nervous system, hepatic or renal dysfunction, developmental delay or preceding psychological or psychiatric disorders were excluded. The primary outcome measure is the incidence of emergence agitation assessed using any emergence agitation scoring

scale such as the PAED scale or other 4- or 5- point The secondary outcome measures are as follows: 1) postoperative pain scores using scoring tools for pain, and 2) adverse events including nausea and vomiting, untoward airway events and LAST.

The presence of emergence agitation is defined by: a) Cravero 5-point emergence agitation scoring system, with five steps from obtunded and unresponsive to wild thrashing behavior requiring restraint [22]. A score of more than 4 is indicative of emergence agitation; b) Cole 5-point scale with five categories: asleep, awake and calm, irritable or consolable crying, inconsolable crying, and severe restlessness [4]. A score of more than 4 is indicative of emergence agitation; c) PAED score with 5 criteria scored using a 5-point scale. The maximum achievable score is 20 [22]. A score of more than 10 is indicative of emergence agitation; and d) WATCHA 4 -point scale which is a simpler tool to use in clinical practice and may have a higher overall sensitivity and specificity [22]. A score of more than 4 is indicative of emergence agitation.

On the other hand, the presence of postoperative pain is defined by the following pain scoring systems: a) Children's Hospital of Eastern Ontario pain scale (CHEOPS) which is an observational scale for measuring postoperative pain in children aged 1-7 years. This scale includes six categories of pain behavior: (cry, facial, verbal, torso, touch, and legs). A score ranging from 0 to 2 or 1 to 3 is assigned to each activity and the total score ranges between 4 and 13 [23]. A score of more than 6 will denote pain in the child; b) objective pain scale (OPS) incorporates four pain behaviors (crying, movement, agitation, and verbalization) and blood pressure change. Each of these categories is scored from 0 to 2 [23]. A score of more than 6 will denote pain in the child; and c) children and infants postoperative pain scale (CHIPPS) is used for those less than 6 years old or unable to understand the visual pain scale. A score of more than 4 will denote pain in the child.

Data was extracted by two authors and cross-checked by another independent author for accuracy and completeness. Assessment for risk of bias was performed using the Review Manager program. The following biases were assessed: selection bias, performance bias, detection bias, reporting bias, attrition bias, and other author-reported bias. Each criterion was assessed as having low, unclear, or high risk for bias. Risk of bias assessment was performed independently by two review authors. Conflict resolution was done through consensus. A third reviewer who is a content expert was called upon if disagreements are not resolved.

Review Manager (RevMan) 5.4 was used for statistical analysis. Risk ratio was used to compare the incidence of emergence delirium, postoperative pain and adverse effects between Lidocaine versus placebo and other drugs. Under adverse effects, the incidence of nausea and vomiting, untoward airway events and LAST between the said comparators were included. Subgroup analysis was performed for incidence of emergence delirium by comparator and dose. Random effects model was used as there was substantial heterogeneity, graded as I^2 of >60%, seen in the groups.

Results

A total of nine hundred eighty-four (984) studies were identified through electronic databases and hand searches (Figure 1). One hundred forty-five studies were included in the title and abstract screening after removing duplicates. Of these, only twenty-two studies met the criteria for full-text review. From these twenty-two studies, fourteen were excluded: six studies had incomplete data, one study had no available full text article and seven studies had different routes of administration of comparator drug. In all, a total of six studies were included for meta-analysis.

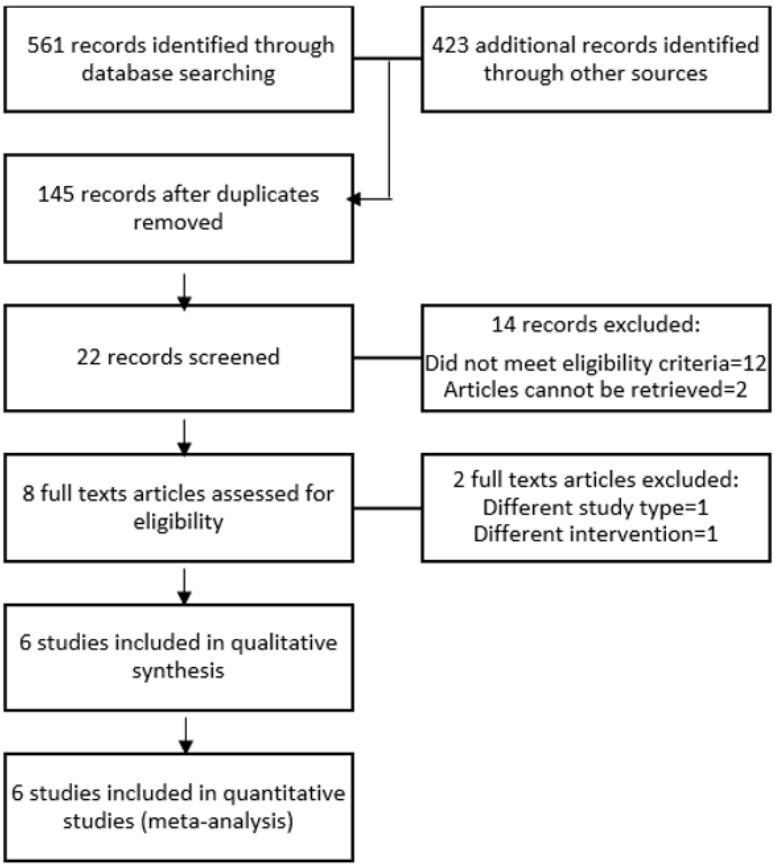

Figure 1. Prisma Flow Diagram

Description of the included studies

Six (6) randomized controlled trials published from 2005 to 2022 that assessed the effectiveness of intravenous lidocaine in decreasing the incidence of emergence agitation postoperatively, compared with placebo and other intravenous drugs such as Propofol, Esmolol and Magnesium sulfate in children with age range of 2 to 14 years, classified ASA I – II under general anesthesia were included. Table 1 shows the studies' population, sample size, intervention and comparator, primary and secondary outcomes.

Table 1. Characteristics of Included Studies (n=5)

Primary Author	Year	N	Type of study	Age , ASA status, type of surgery	Intervention (Dose and Administration)	Comparator	Primary Outcome	Secondary Outcome
Jang, Y	2005	85	RCT	2-7 years old; ASA 1 and 2; Lower abdominal surgery	1.5mg/kg Lidocaine (over 30-45s) 5 minutes before discontinuation of anesthetic	Saline	EA score (5-point score by Cravero; >4)	CHEOPS, modified Aldrete postanesthesia score
Lee, J	2007	120	RCT	3-9 years old; ASA 1 and 2; tonsillectomy and adenoidectomy	1% 1mg/kg or 2% 2mg/kg at 1 minute (over 10s) after beginning of spontaneous respiration (before extubation)	Saline	Arousal Excitement (5 point scale by Cravero; >4)	Sedation score (UMSS>2), incidence of cough
Echevarria, G	2018	92	RCT	2-12 years old; ASA 1 and 2	IV lidocaine (1.5 mg/kg intravenous lidocaine over 5 min followed by 2 mg/kg/h) prior to intubation	Saline	POV	EA (WATCHA scale > 3), Time to extubation, postop pain, plasma concentration
Ji, J	2019	84	RCT	3-9 years old, ASA 1 and 2; Strabismus surgery	Lidocaine 1.5mg/kg after the gas was turned off and the patient started to move voluntarily	Esmolol 0.5mg/kg; Saline	Cole 5 point score (EA) >4	Objective pains score (OPS) and RASS
Manouchehrian, N	2022	102	RCT	3-14 years old; ASA 1 and 2	At the end of the surgery, two minutes before endotracheal extubation, 2% Lidocaine 1mg/kg	Propofol 0.5mg/kg	Laryngospasm	Agitation nausea and vomiting, shivering
Manouchehrian, N	2022	62	RCT	3-14 years old; ASA 1 and 2	After intubation, 2% Lidocaine 1mg/kg	Magnesium sulfate 15mg/kg	Laryngospasm	Agitation nausea and vomiting, agitation, sedation score

Five (5) studies were assessed as having low risk of bias and one (1) study was assessed as having unclear risk/some concerns mainly due to unspecified information on allocation concealment (Fig 2).

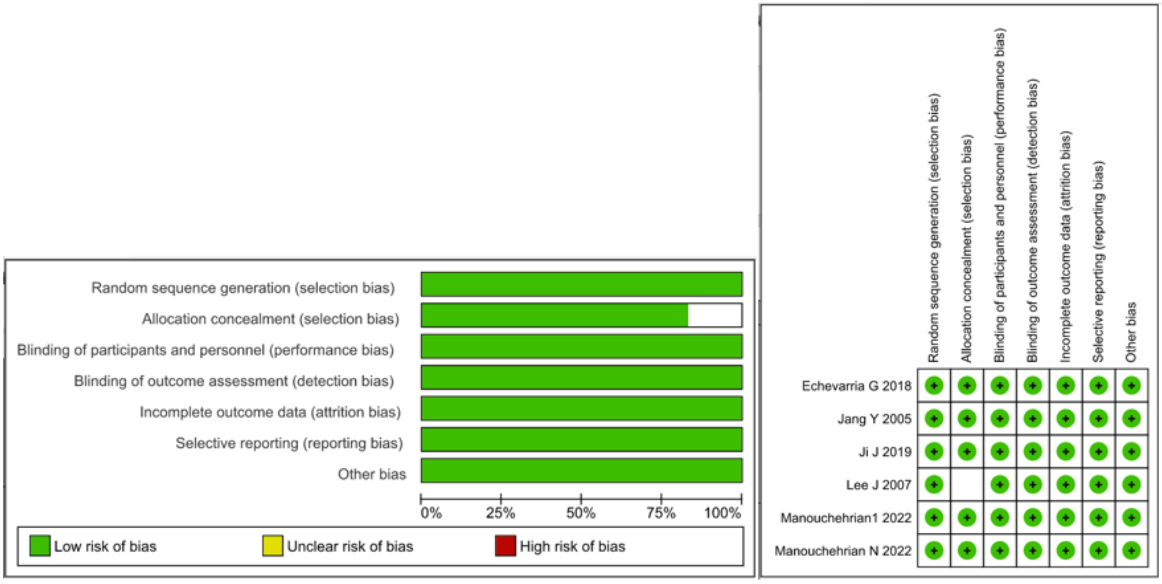

Figure 2. Cochrane risk of bias assessment.

Effect of Interventions

1. Incidence of Emergence Agitation

Data for the incidence of emergence agitation were available for all six (6) studies. There was a total of five hundred forty-three (543): two hundred seventy-three (273) patients in the lidocaine group and two-hundred seventy (270) patients in the comparator group. Forest plot showed increased risk of developing EA in patients given Lidocaine compared to comparators (RR=1.03, 95% CI [0.50, 2.13], P=0.94) however, not statistically significant. Considerable heterogeneity was observed when these studies were pooled (□2= 34.1, I2=86%, P<0.00001) (Fig 3).

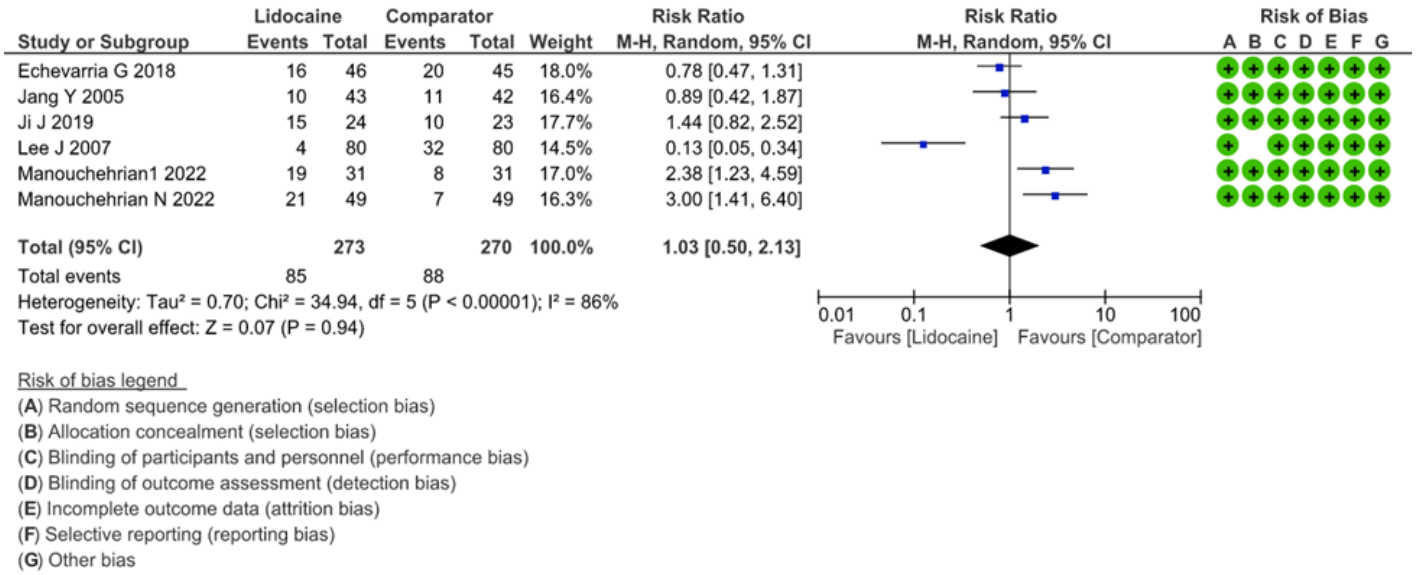

Figure 3. Incidence of Emergence Agitation (EA): Lidocaine vs. Comparator

a. Subgroup Analysis by Comparator

Differing types of comparators can influence the treatment effect [10, 11]. Subgroup analysis between placebo vs other intravenous anesthetics, namely Propofol, Esmolol, and Magnesium Sulfate. The test for subgroup differences yielded a $p<0.05$, hence significant. No significant difference was seen in the incidence of ED with the use of Lidocaine vs placebo. On the other hand, three studies showed favor to comparators. There was twice the increased risk of developing ED in the Lidocaine group vs comparators (RR=2.06, 95% CI [1.32, 2.32], P=0.002). Moderate heterogeneity was observed but not significant (χ^2=2.58, I2=30%, P=0.24) (Fig 4).

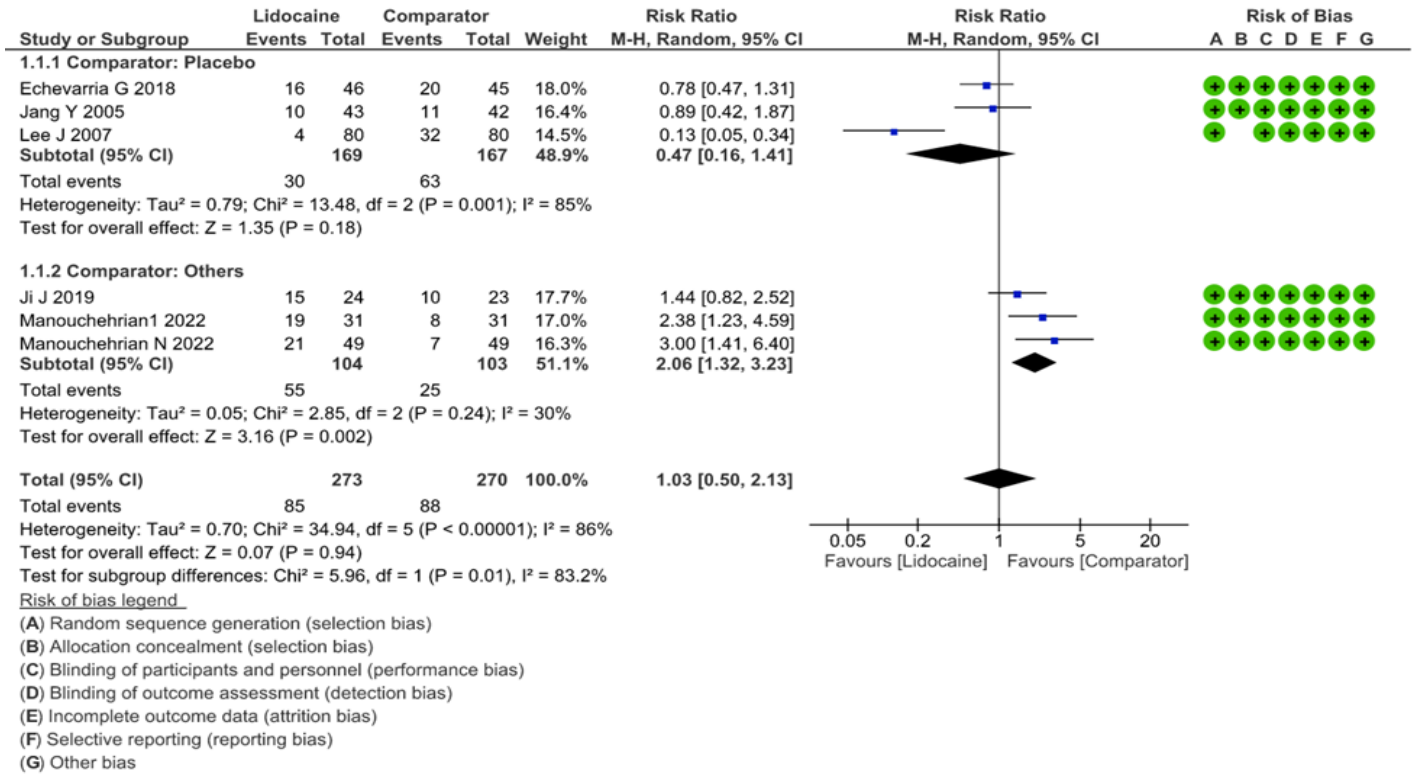

Figure 4. Incidence of Emergence Agitation (EA) by Compara-

b. Subgroup Analysis by Dose

Multiple studies have used different doses of Lidocaine to determine if it will decrease EA, however, conflicting results were found [10]. Hence, we did a subgroup analysis of differing dose of Lidocaine. The groups were divided into two: dose of $\leq$1.5mg/kg which included three studies and dose of >1.5mg/kg which included two studies. These cut off doses of intravenous lidocaine were based on the study of Both, et. al on pediatric patients done in 2018 (9).

Forest plot shows the mean effect of pooled trials was in favor of Lidocaine for both doses (Overall RR=0.90, 95% CI [0.46, 1.79], P=0.30) (Figure 6). Due to significant substantial heterogeneity, there was contradicting mean effect in each dose. It was observed that less than or equal to 1.5mg/kg dose of Lidocaine had increased risk of developing EA (RR=1.22, 95% CI [0.58, 2.55], P=0.60) while greater than 1.5mg/kg dose of Lidocaine showed a decreased risk of developing EA (RR=0.25, 95% CI [0.01, 4.41], P=0.35). These

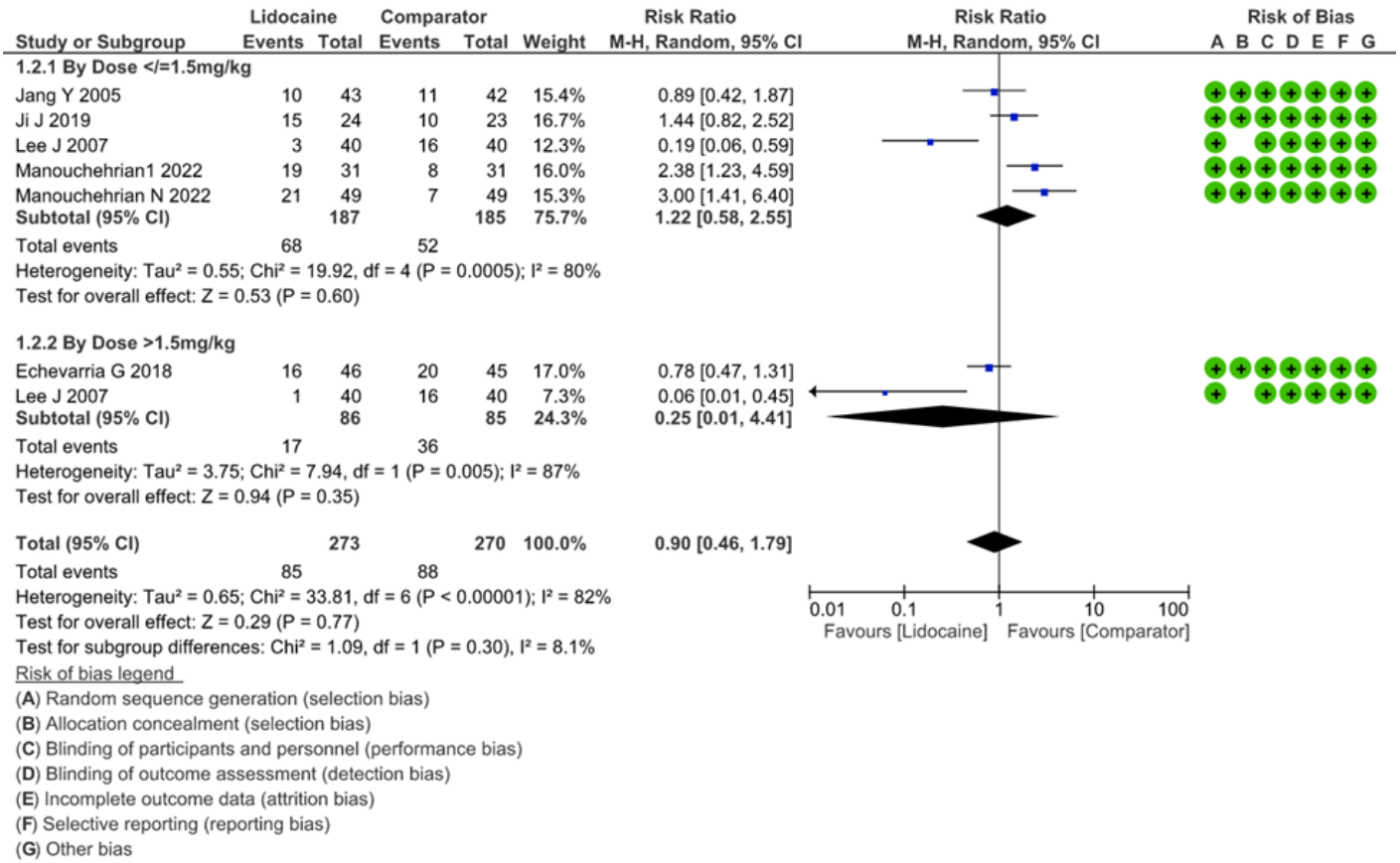

Figure 5. Incidence of Emergence Agitation (EA) by Dose

2. Incidence of Postoperative Pain

Three (3) studies compared the incidence of postoperative pain in children with the use of Lidocaine vs comparators. These studies showed that there were fewer episodes of postoperative pain with the use of Lidocaine compared to placebo and other drugs (Jang 2005: RR=0.78, 95% CI [0.42-1.47], Ji 2019 RR=1.05, 95% CI [0.62-1.76]. However, the results were not statistically significant (Fig 6).

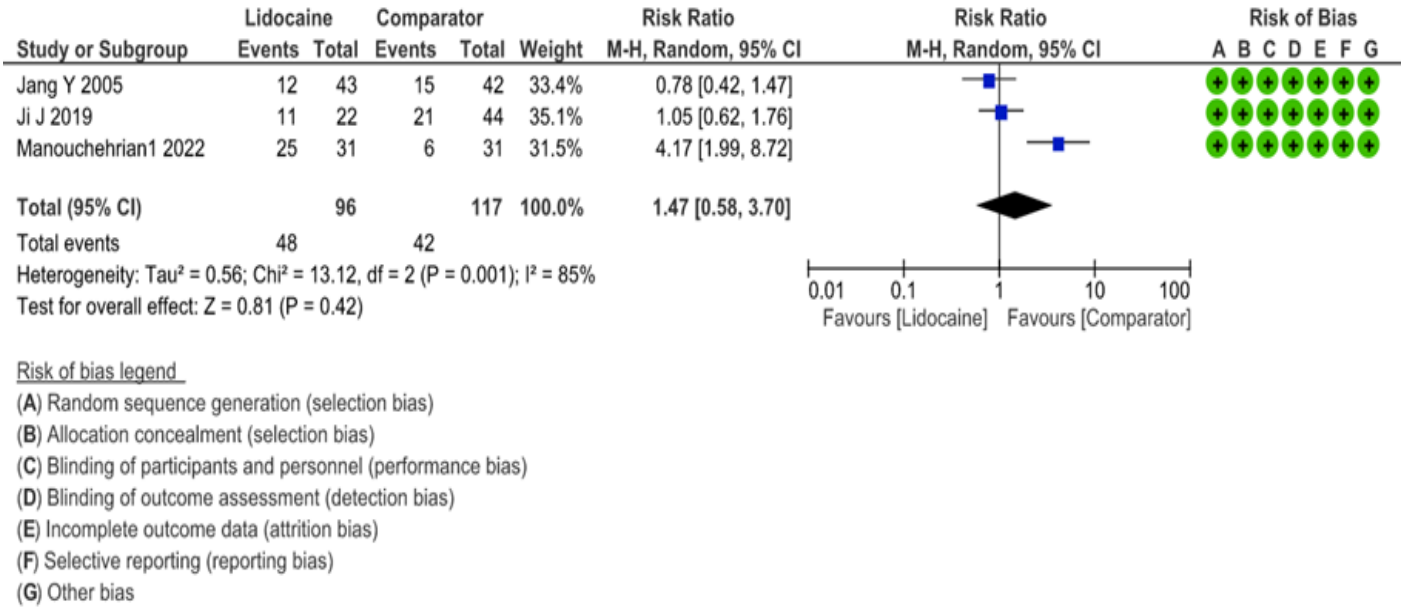

Figure 6. Incidence of Postoperative Pain: Lidocaine vs Comparators

3. Incidence of Adverse Effects

Five (5) studies had data on adverse events with the use of Lidocaine compared to other drugs. Forest plot shows that the use of Lidocaine increased the risk of incidence of adverse effects compared to placebo and other comparators (RR=1.21, 95% CI [0.39, 3.75], P=0.74). This was, however, not statistically significant. Substantial heterogeneity was also seen in this group which was significant (□2=47.95, I2=94%, P<0.00001) (Fig 7).

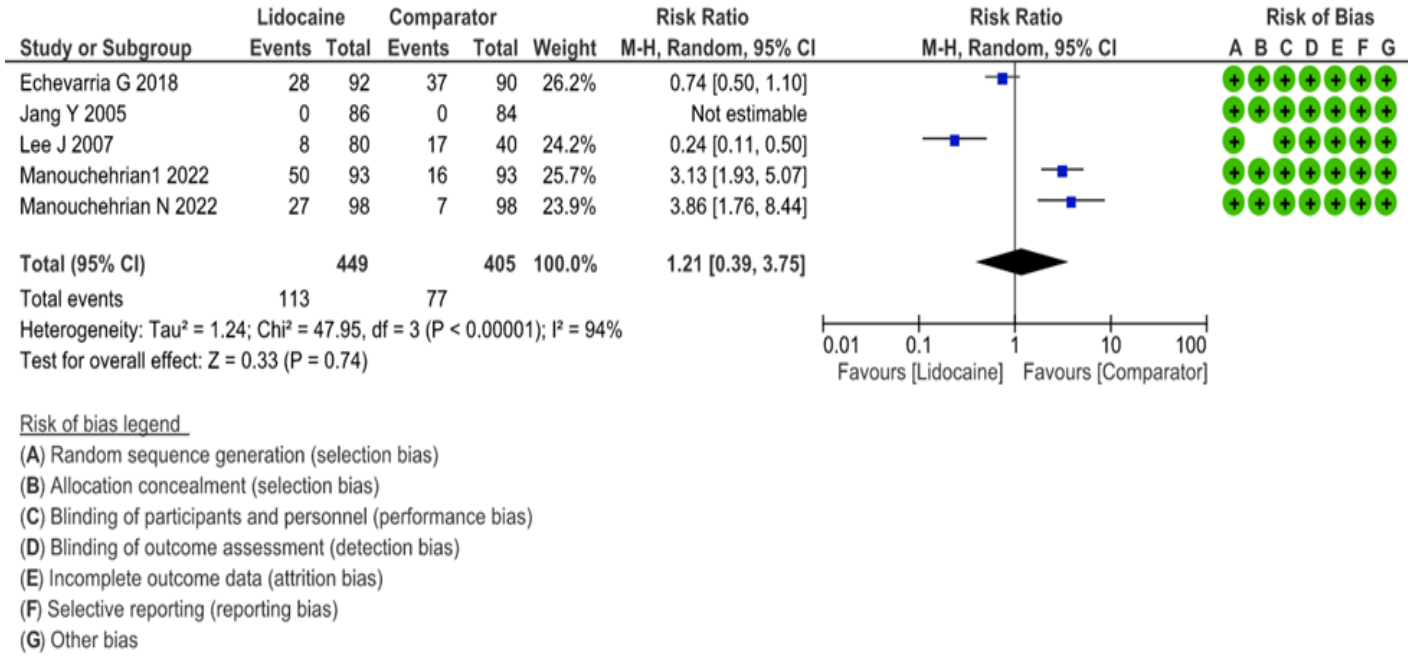

Figure 7. Incidence of Adverse Effects: Lidocaine vs Comparators

Figure 8 showed the breakdown of the mean effect per adverse effect type. The overall effect showed that there was an increased risk of developing adverse effects with the use of Lidocaine (RR=1.49, 95% CI [0.62, 3.57], P=0.85).

Four (4) studies noted the incidence of nausea and vomiting in children if Lidocaine was used compared to placebo and other drugs. Subgroup 1.4.1 showed there was an increase in the likelihood of developing nausea and vomiting from the use of Lidocaine compared to other comparators (RR=1.73, 95% CI [0.52, 5.79], P=0.37). There was also a note of significant substantial heterogeneity in this group (□2=22.41, I2=91%, P<0.00001).

Three (3) studies mentioned untoward airway events, particularly laryngospasm. This subgroup (1.4.2) still favors comparators as there is an increased likelihood of developing untoward airway events with the use of Lidocaine (RR=1.37, 95% CI [0.17, 10.83], P=0.76). Significant substantial heterogeneity was also observed (□2=20.41, I2=90%, P<0.00001).

The two subgroups previously discussed did not show any statistical significance for each type of adverse effect. There were also three (3) studies that described LAST in their paper. No studies reported any incidence of LAST in the course of their study.

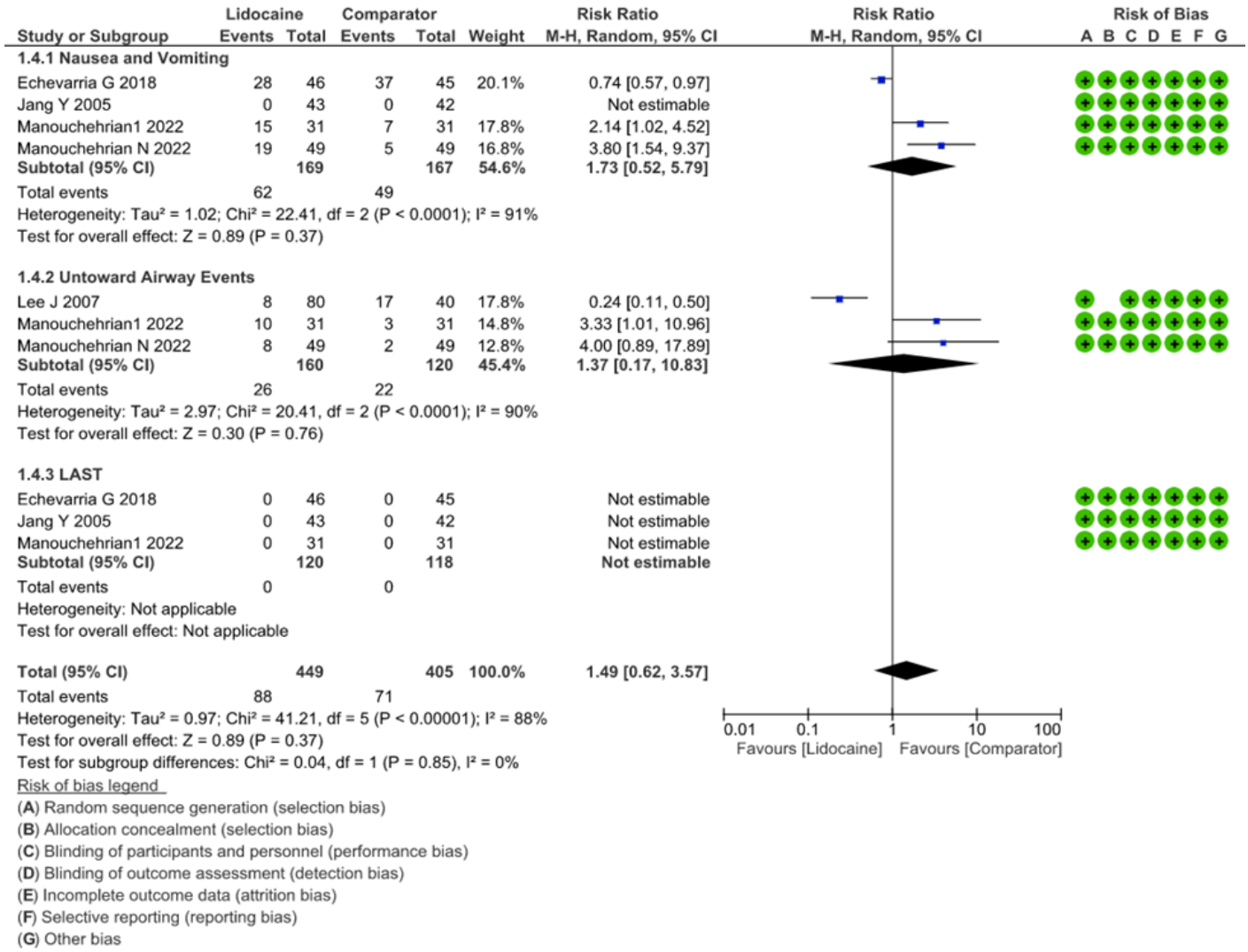

Figure 8. Subgroup Analysis of Adverse Effects: Lidocaine vs Compar-

4. Sensitivity Analysis

This analysis was performed to account for possible sources of heterogeneity. The results of the sensitivity analysis are shown in Table 3. This showed that the pooled effect did not change when the studies with results opposite the direction of the pooled effect were excluded.

Table 2. Sensitivity analysis: Incidence of Emergence Agitation

Study	RR	95% CI	I-squared
Including all (6) RCTs	1.03	0.50, 2.13	86%
Removing Manouchehrian_1 2022	0.83	0.38, 1.84	86%
Removing Manouchehrian 2022	0.86	0.38, 1.96	86%
Removing Lee 2007	1.44	0.87, 2.4	69%

Discussion

This meta-analysis aimed to determine the efficacy and safety of intravenous lidocaine in controlling emergence agitation in children undergoing surgeries done under general anesthesia compared to placebo or other intravenous anesthetics. This was based on studies mentioning the effectivity of using Lidocaine in decreasing the said event in children. However, this study has found the opposite. This study revealed that there was an increased risk of developing emergence agitation with the use of Lidocaine compared to placebo and other drugs. This finding was, however, not statistically significant and the data was heterogeneous. Subgroup analysis was done to look for possible causes of heterogeneity according to type of comparators and different doses of Lidocaine.

In the subgroup analysis by comparator, the studies have compared the effect of Lidocaine with placebo and other drugs namely, Propofol, Esmolol and Magnesium sulfate in preventing emergence agitation. The result showed decreased incidence of EA if Lidocaine was compared to a placebo but an increased incidence of EA if compared to the drugs previously mentioned. Only the latter showed statistical significance.

Many studies have investigated the benefit of using Propofol in preventing emergence agitation including a meta-analysis done by Gupta et. al [27]. On the other hand, Magnesium is a predominantly intracellular cation which has a central nervous system depressant property [28] which addresses the prolonged excited state during anesthesia recovery - hypothesized to be the pathophysiology of emergence agitation [13]. Another drug included in the comparators is Esmolol. This is a beta antagonist which is said to block cortical arousal alleviating agitation [12]. Hence, the following drugs' mechanism of action can explain the seen superior benefit of the comparators over lidocaine.

A subgroup analysis by dose was also done as this may have caused the heterogeneity between the studies. However, the results were contradicting. A dose of less than or equal to 1.5mg/kg showed an increase in developing EA as opposed to a decrease in risk when greater than 1.5mg/kg dose was used. These did not eliminate heterogeneity and the findings were not statistically significant. It can be inferred that increasing Lidocaine's dose will show a more pronounced effect [13] provided that it is within the drug's toxicity dose. Future studies have yet to determine the minimum effective concentration to lessen emergence agitation. Other possible causes of heterogeneity are timing and manner of drug administration. These were, unfortunately, not standardized in each study, therefore, cannot be grouped together.

There was an overall increased risk of experiencing an adverse effect with the use of Lidocaine compared to comparators, although statistically not significant. In particular, there was an increased likelihood of experiencing nausea, vomiting and untoward airway events (laryngospasm and stridor) with the use of Lidocaine. This finding can again be explained by the inherent properties of the comparator drug. It is established that Propofol has intrinsic properties in preventing postoperative nausea and vomiting [28] while Magnesium has the ability to relax muscles and increase flaccidity which decreases airway reactivity hence laryngospasm [27]. No events of LAST were noted for all studies reviewed.

There are several analyses with significant statistical heterogeneity which cannot be resolved by subgroup analyses. Adverse events reported in individual studies were not uniform, and there were limited studies on specific comparators that further analyses cannot be performed on them. Another possible source of the heterogeneity is the different surgical procedures used in the individual studies. This study also did not explore the difference in timing and manner of dose administration since the data available were not standardized. It was also noted that the enrolled trials had small sample sizes which may affect the results.

There also seems to be a publication bias as seen with the funnel plot of the incidence of emergence agitation, even when analyzed by comparator and dose.

Conclusions

Intravenous lidocaine given to children undergoing general anesthesia with sevoflurane increased their risk for emergence agitation, compared to both placebo and other intravenous anesthetics. It, however, may contribute to decreasing postoperative pain in the said group. The risk of adverse effects is also possibly increased with the use of lidocaine hence, caution should be exercised with this subset of patients.

This study recommends adding more studies favorably those with larger sample sizes, good quality databases and high-quality RCT's with evidence on the effectivity of lidocaine on emergence agitation in children undergoing inhalational general anesthesia. It is also recommended to include future studies investigating the effect of lidocaine focusing on standardized timing and mode of dose administration.

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