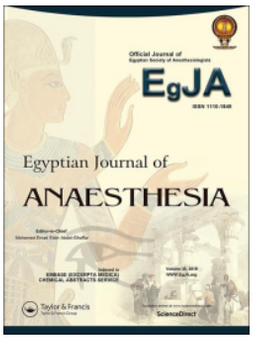

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Challenge of using Intranasal dexmedetomidine as a premedication modality in pediatric patients: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Intranasal dexmedetomidine premedication has been employed in children for controlling stress before induction of general anesthesia. Until now, the effect of intranasal dexmedetomidine in relation to other premeditations remains incompletely studied.

Objectives: This study was conducted to study the effectiveness and safety of intranasal dexmedetomidine premedication in pediatrics.

Sittings: Meta-analysis-based study following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Methods: Systematic searches of the databases MEDLINE, EMBASE, PubMed, and Cochrane were conducted to collect all published randomized, controlled, clinical trials in the last seven years which compare the intranasal dexmedetomidine premedication with other methods of premedication in different procedures.

Results: Twenty-five studies were collected for inclusion in this research including 2601 patients. The bias risk was low. Meta-analysis showed that the use of dexmedetomidine intranasally as a premedication when compared with other premedication regimes results in significant evidence of decreasing emergence agitation (RR = 0.64 [0.54, 0.77] 95% CI; $I_2 = 84\%$; $P = 0.0001$) fewer sedation scores (Mean difference = 51 [0.38, 0.65]; 95% CI; $I^2 = 99\%$; $P = 0.00001$), significantly less incidence of postoperative nausea and vomiting ((RR = 0.30 [0.20, 0.45] 95% CI; $I^2 = 12\%$; $P = 0.00001$), significantly decreased BP ((Mean difference = -2.28 [−3.42, −1.14]; 95% CI; $I^2 = 88\%$; $P = 0.0001$), and significantly decreased heart rate and (mean difference = -6.67 [−8.37, −4.97]; 95% CI; $I^2 = 94\%$; $P = 0.00001$).

Conclusion: Intranasal dexmedetomidine provided a satisfactory level of emergence agitation, more satisfactory sedation, more hemodynamic stability, and reduced the incidence of postoperative complications in relation to other premeditations.

ARTICLE HISTORY
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KEYWORDS
Intranasal dexmedetomidine; premedication; pediatric; meta-analysis

1. Introduction

All over the world, there is a marked increase in the number of children undergoing surgery and diagnostic procedures that need sedation. Children undergoing surgeries often suffer from anxiety, pain, stress, unfamiliar persons and environment, fear of operating room setting, fasting, and the most important factor is separating from parents [1]. Which may lead to occurrence of many complications, such as preoperative hemodynamic instability, metabolic disorder, increased postoperative agitation, postoperative behavioral changes, postoperative sleep disorders, eating disorders, and nocturnal enuresis [2]. So, it is important to challenge anesthesia doctors to manage their pre-operative stress. Hence, premeditation is a good choice to eliminate preoperative stress and help smooth induction of anesthesia without such complications.

Dexmedetomidine is considered an α2-adrenoceptor-activating drug used in preoperative sedation. Also, Dexmedetomidine has antiemetic and analgesic effects compared with other premeditations [3]. Patients with preoperative Dexmedetomidine still arousal [4]. Furthermore, Dexmedetomidine also has fewer effects on respiration [5,6], so it is commonly used in intensive care in pediatrics [7]. On the other hand, Dexmedetomidine has been used in pediatric patients undergoing many procedures such as MRI, and it has been reported to be used safely in ambulatory sedation in pediatric [8–11].

There is now marked evidence to encourage the wide use of Dexmedetomidine as a premedication, sedative, and anesthetic aid in pediatric [12,13] for painless [14] and also painful procedures [15].

Premedication drugs used must have many properties like less-traumatic, tolerable route of administration and fewer side effects. Intranasal administered

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Dexmedetomidine showed to be effective, tolerated safely, noninvasive route, and also has a rapid onset of action because of high vascularization of the nasal mucosa in the pediatric age group [16,17]

This study tried to observe the effect and safety of intranasal Dexmedetomidine as a premedication to decrease preoperative and postoperative stress in children.

2. Materials and methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. No patient consent or ethical approval was needed because all analyzed data were collected from previously published literature.

3. Search strategy

To find all published randomized clinical trials, this meta-analysis searched MEDLINE, EMBASE, PubMed, and the Cochrane Library (from 2015:2022). The search was conducted by using Boolean operators (AND/OR) to link the following keywords: dexmedetomidine, intranasal, and randomized trial. Studies were limited to humans with no language restrictions. Most papers search were done in May 2022, and another search was done in December 2022 to find more papers related to our article. The search process steps are described in Figure 1.

4. Eligibility criteria

With the aid of predetermined selection criteria, two reviewers independently identified all the studies. Disagreements that arose during the selection of the primary study were arbitrated by a third reviewer. The following criteria should be met by studies to be included in this meta-analysis:

(1) Subject: pediatric patients who will receive premedication before going to surgery.
(2) Interventions: studies which Analyze the impact of the dexmedetomidine premedication.
(3) Comparisons: Control group received other premedication regimes
(4) Outcomes: emergence agitation, sedation score, blood pressure, heart rate, and incidence of

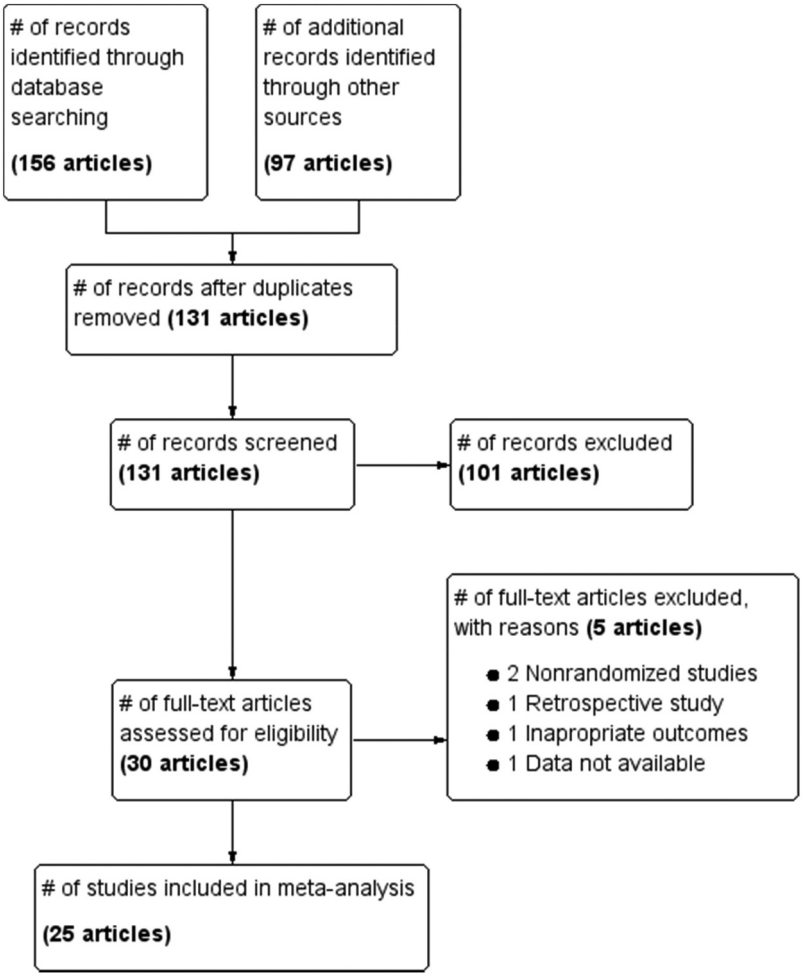


Figure 1. (PRISMA) flow chart representing the search and selection process.

postoperative complications. The included study must have reported at least one of the results.

(5) Type of literature: Clinically randomized controlled trials (RCTs) all published journals.

5. Selection criteria

After database search, the three reviewers checked the abstracts of the collected studies independently. After that, the reviewers checked the full text of the articles included in meta-analysis which matched the inclusion criteria. Any conflicts about the studies to include were resolved by the most senior author.

6. Exclusion criteria

Studies were excluded if they did not follow eligibility, criteria, data reported in the form of conference abstracts, case reports, protocols, or reviews, or absent data, or The authors of the studies were inaccessible or did not respond when further data from their trials were sought.

7. Data extraction

Data were extracted from the included papers by the three authors independently. Extraction of data from the included randomized trial was performed and documented in a worksheet: the initial author, publication year, study design, sample size, setting, surgery type, intervention timing, type, dose, and route of all used premedication in addition to all relevant results. The incidence of emerging agitation served as the primary endpoint of this investigation. Secondary outcomes included sedation and side effects (hypotension and bradycardia).

8. Quality assessment and risk of bias

The reviewers evaluated the quality of each RCT using the Cochrane Handbook for Systematic Reviews of Interventions as a guide. The risk of bias table is explained in part-2, Chapter-8.5 of the handbook [19]. Other potential causes of bias. For each item: Yes, No, or Unclear was recorded. Any discrepancies were found and discussed in order to be addressed.

9. Statistical analysis

We carried out this meta-analysis to combine the outcomes of trials comparing the intranasal dexmedetomidine premedication with other premedication regimes used for sedation in a variety of surgical procedures using Review Manager (RevMan), Version 5.3, (Cochrane Collaboration, Oxford, UK) software. For heterogeneity measurement, chi-square test was used to calculate P and I square values. No significant heterogeneity was identified if ($P > 0.10$) and ($I2 < 50\%$), so a fixed-effect model for analysis of data was applied. When the heterogeneity was significant, a random-effects model is applied. For studies that only provide the interquartile range (IQR) for outcomes based on continuous measures, such (as emergence agitation and sedation score). By dividing the IQR by 1.35, we were able to determine the standard deviation (S.D.) from the data [20]. For dichotomous outcomes including postoperative nausea and vomiting, hypotension, and bradycardia, we estimated risk ratios (R.R.s) and their accompanying 95% confidence intervals (C.I.s). The definition of statistical significance used a two-sided alpha of 0.05, and clinical significance interpretations focused on C.

10. Identification of studies and characteristics of the studies

The database search resulted in the identification of 156 studies in total, and 97 studies were identified through other sources. After removing duplicate studies, 131 studies were acquired for additional evaluation. Then, after reviewing the titles and abstracts, 101 studies were eliminated. After reviewing the remaining 30 complete publications, 30 RCTs that satisfied all the inclusion criteria were ultimately found and included in this meta-analysis. There were 2601 patients involved in all 25 trials (Figure 1).

The involved studies were done from 2015 to 2022 in different countries; the fundamental features of the included studies were listed in Table 1.

11. Quality of the involved studies

To determine the probability of bias in RCTs, Cochrane Handbook tool was used. All RCTs defined their randomization approach using computer software and offered clear inclusion and exclusion criteria. The percentage of all included trials across every risk of bias item is displayed in Figure 2a.

The quality assessment of the study's methodology is summarized in Figure 2b.

In general, the risk of bias in the 25 studies was deemed to be minimal. (Figure 2a,b)

11.1. Outcomes for meta-analysis

After excluding unsuitable studies, the remarkable finding in *studies involved in this meta-analysis was:*

11.1.1. Emergence agitation incidence

The incidence of emergence agitation was derived from 11 studies [22,29,32,33,37,39–41,43–45] in a total of **532** patients pooled that intranasal dexmedetomidine premedication showed a significant decrease in emergence agitation when compared to

Table 1. Characteristics of included studies.

Study ID	Intervention	Dose	Nm.	Age	Timing of injection	Surgery
Singla et al. 2015 [21]	IN DEX.	1 mcg/kg	30	5.86 ± 0.4 yrs.	30 min. before induction	Minor surgery
	IN midazolam	0.2 mg/kg	30	5.9 ± 0.46 yrs.		
Mukherjee et al. 2015 [22]	IN DEX.	1 mcg/kg	40	5.3 ± 1.8 yrs.	45 min. before induction	Day case surgery
	IN Clonidine	4 mcg/kg	40	5.6 ± 1.9 yrs.		
Rajalakshmi et al. 2015 [23]	IN DEX.	2 mcg/kg	30	4.83 ± 2.12 yrs.	In the holding are23,29,32,33,37,39,41,43,44,45)a	Cardiac surgeries
	IN Saline	1 ml	30	5.17 ± 1.89 yrs.		
Millar et al. 2016 [24]	Oral chloral hydrate	70 mg/kg	50	13.6 ± 7.6 mon	Before the procedure	Transthoracic echocardiography
	IN DEX. 2	2 mcg/kg	50	13.7 ± 8.6 mon.		
	IN DEX. 3	3 mcg/kg	50	15.4 ± 8.5 mon.		
Lu et al. 2016 [25]	IN DEX.	1 mcg/kg	40	43.6 ± 9.2 yrs.	45–60 min. before anaesthetic induction	Elective suspension laryngoscopy
	A placebo	1 ml	41	45.9 ± 10.1 yrs.		
Reynolds et al. 2016 [26]	IN DEX. + oral placebo	3 mcg/kg	44	23.3 mon. (19.5–27.2)	Before the procedure	Auditory brainstem response (ABR) testing
	Oral chloral hydrate + IN saline placebo	50 mg/kg	41	25.6 mon. (22.0–29.0)		
Sidhu et al. 2016 [27, 28]	IN DEX.	2 µg/kg	35	5 [2–9], yrs.	30 min. prior to surgery	Various surgeries
	IN clonidine	3 µg/kg	35	5 [2–9], yrs.		
	IN Saline	0.5 ml	35	5 [2–9], yrs.		
Lin et al. 2016 [29]	IN DEX.	1 mcg/kg	30	4.75 ± 1.86 yrs.	45 min. before induction of anesthesia	Cataract surgery with sevoflurane
	IN DEX.	2 mcg/kg	30	4.04 ± 1.68 yrs.		
	IN Saline	Same volume	30	4.15 ± 1.58 yrs.		
Wu et al. 2016 [30]	IV Saline	Same volume	27	48 ± 4 yrs.	30 min. following nasal medication	Elective hysterectomy
	IN DEX.	1 µg/kg	26	47 ± 4 yrs.	40 min. before anesthesia induction	
	IN DEX,	2 µg/kg	28	47 ± 5 yrs.	40 min. before anesthesia induction	
	IV DEX.	1 µg/kg	27	47 ± 5 yrs.	10 min. befyrs.ore anesthesia induction	
Neville et al. 2016 [31]	IN DEX.	2 mcg/kg	20	3.44 yrs.	Prior to surgery	Pediatric laceration repairs
	IN Midazolam	0.4 mg/kg	18	3.15 yrs.		
Abdelaziz et al. 2016 [32]	IN DEX.	1 mcg/kg	33	2.68 ± 1.54 yrs.	Before entrance to the operation room	Strabismus surgery
	IN Midazolam	0.1 mg/kg	33	2.48 ± 1.17 yrs.		
	IN Saline	1 ml	32	2.78 ± 1.67 yrs.		
Abd El-Hamid and Yassin. 2017 [33]	IN DEX.	1 mcg/kg	43	4.4 ± 1.3 yrs.	After the induction of general anesthesia	Tonsillectomy and/or adenoidectomy under general anesthesia with sevoflurane
	IN Saline	0.5 ml in each nostril	43	4.2 ± 0.93 yrs.		
Shi et al. 2017 [34]	IN Saline 0.01 ml/kg + IV Saline 0.04 ml/kg + Propofol 2 mg/kg		30	26.7 ± 4.8 yrs.	-IN drugs (45 min. before surgery) -IV drugs (During induction of GA)	Termination of first trimester pregnancy
	IN DEX. 0.1 mcg/kg + IV Saline 0.04 ml/kg + Propofol 2 mg/kg		30	28 ± 4.1 yrs.		
	IN Saline 0.01 ml/kg + IV Sufentanil 0.1 mcg/kg + Propofol 2 mg/kg		30	27.3 ± 4.5 yrs.		
Qiao et al. 2017 [35]	IN DEX.	2.5 mcg/kg	42	3.96 ± 1.50 yrs.	30 min. before the induction of anesthesia	Eye surgery under general anesthesia
	IN DEX. + Oral ketamine	2 mcg/kg +3 mg/kg	41	3.76 ± 1.36 yrs.		
	Oral ketamine	6 mg/kg	41	4.41 ± 1.28 yrs.		
Cao et al. 2017 [36]	IN DEX.	2 mcg/kg	71	18 [10–25] mon.	Before the procedure	Ophthalmic examinations
	Oral chloral hydrate	80 mg/kg	70	14.5 (8.8–23.2) mon.		

(*Continued*)

Table 1. (Continued).

Study ID	Intervention	Dose	Nm.	Age	Timing of injection	Surgery
Yuen et al. 2017 [37]	Chloral hydrate syrup+ IN Saline spray	50 mg/kg	107	24 mon.	30 min. before the procedure	Computerized tomography
	placebo syrup + IN DEX. Spray	3 mcg/kg	87	32.5 mon.		
Ghai et al. 2017 [38]	IN DEX.	2.5 mcg/kg	30	3.8 ± 2.1 yrs.	30 min. after EMLA cream application	CT imaging
	Oral Midazolam	0.5 mg/kg	29	3.1 ± 1.3 yrs.		
Millar et al. 2018 [39]	IN DEX.	2.5 mcg/kg	140	12.5 [8–17] mon.	Before the procedure	Outpatient TTEcho
	Oral pentobarbital	5 mg/kg	139	13 [9–17] mon.		
GAO et al. 2018 [40]	IN DEX.	2 mcg/kg	30	46.2 ± 10.07 yrs.	30 min. before operation	Dental rehabilitation under GA
	IN Saline	0.02 ml/kg	30	43.6 ± 12.92 yrs.		
Li et al. 2018 [41]	IN DEX. 1	1 mcg/kg	30	4.47 ± 1.17 yrs.	25 to 40 min. before surgery	Adenoidectomy with or without tonsillectomy
	IN DEX. 2	2 mcg/kg	30	4.53 ± 1.55 yrs.		
	IN Saline	In the same volume	30	4.37 ± 1.3 yrs.		
Li et al. 2019 [42]	IN DEX. + buccal placebo	3 mcg/kg	136	35.0 (28.0–44.8) yrs.	30–40 min. before the procedure	Nonpainful Procedural Sedation in Children with Autism
	IN DEX. + buccal midazolam	3 mcg/kg +0.2 mg	139	34 (28.0–46.0) yrs.		
Bi et al. 2019 [43]	IN DEX.	1 mcg/kg	20	17.2 ± 6.3 mon.	25 min. before anesthesia induction	Removal of inhaled foreign bodies in children by flexible fiberoptic bronchoscopy
	IN Saline	0.01 ml/kg	20	18.0 ± 6.6 mon.		
Aly.A(2020) [44]	IN DEX.	2 mcg/kg	88	2.8 ± 0.8 yrs	1 h before the procedure	Cardiac catheterization
	IN KETAMINE	.5 mg/kg				
	IN DEX +IN KETAMINE	3 mg/kg + 1 mcg/kg				
Wang et al(2020) [45]	IN DEX.	2 mcg/kg	60	4.56 ± 0.59 yrs	30 m before the procedure	Dental rehabilitation under GA
	Oral Midazolam	0.5 mg/kg				
Arun et al(2022) [46]	IN DEX.	1mcg/kg	60	5.14 ± 160 yrs	30 m before the procedure	Various surgeries
	IN KETAMINE	.5 mg/kg				

other premedication treatments. (RR = 0.64 [0.54, 0.77] 95% CI; $I_2 = 84\%$; $P = 0.0001$) (Figure 3).

11.1.2. Sedation score

According to sedation scores and data extracted from eight studies [21,23–25,27,35,44,46] in total **321** patients Intranasal dexmedetomidine premedication showed fewer sedation scores when compared with premedication with other drugs (Mean difference = 51 [0.38, 0.65]; 95% CI; $I^2 = 99\%$; $P = 0.00001$). (Figure 4)

11.1.3. Nausea and vomiting

Postoperative nausea and vomiting incidence was collected from 11 studies [22,25,31–37,44,46] in a total of **498** patients showed that cases given intranasal dexmedetomidine premedication showed a significant decrease in postoperative nausea and vomiting incidence in comparison to other premedication techniques (RR = 0.30 [0.20, 0.45] 95% CI; $I^2 = 12\%$; $P = 0.00001$) (Figure 5).

11.1.4. Arterial blood pressure

We extracted the ABP data from 4 studies [21,22,27,44] in total **169** patients showed Intranasal dexmedetomidine premedication significantly decreased BP (Mean difference = −2.28 [−3.42, −1.14]; 95% CI; $I^2 = 88\%$; $P = 0.0001$) (Figure 6).

11.1.5. Heart rate

Heart rate was reported from 8 studies [21,22,24,27,35,43,44,46] in total 311 patients showed premedication with Intranasal dexmedetomidine also significantly lowered heart rate (Mean difference = −6.67 [−8.37, −4.97]; 95% CI; $I^2 = 94\%$; $P = 0.00001$) (Figure 7).

12. Discussion

Perioperative agitation is a significant and anxious problem, especially in children that need to be mentioned because it can result in a variety of complications and morbidities. Unfamiliar environment, fear of strangers persons and separation from the parents make the child nervous, fearful, agitated and aggressive and needs to increase in analgesics consumption unfortunately all have drawbacks [47].

There are many ways of administration of premedication such as oral, intravenous (IV), intramuscular (IM), rectal, and transmucosal. Each route has its flaws, for example, the oral route has less bioavailability, IM and IV routes are adjective and painful, and the rectal route is not comfortable. Sublingual and IN transmucosal routes have been demonstrated to be more well tolerated [48] in addition to being more effective and rapid medication administration methods due to their capacity to avoid first-pass metabolism and high mucosal vascularization [49] in contrast to the Intranasal administration of drugs has some disadvantages like nasal irritation, sneezing, and coughing, which can be Treated by utilizing a little amount of the drug's undiluted solution.

Highly selective α2 adrenergic agonist DEX has some exceptional and unparalleled sedative properties [50], DEX has been investigated for pediatric sedation and anxiolysis when administered intravenously or by alternative routes, like intranasal (IN). Unlike other sedatives, DEX acts primarily in the locus coeruleus of the central nervous system, where it causes a somnolent sleep state that, according to an electroencephalogram, closely mimics non-REM sleep. Dexmedetomidine, therefore, causes conscious drowsiness, meaning that patients can be woken by a gentle tap or vocal order [51]. DEX is a desirable option for paediatric procedural sedation since it maintains spontaneous breathing, has few respiratory side effects, and

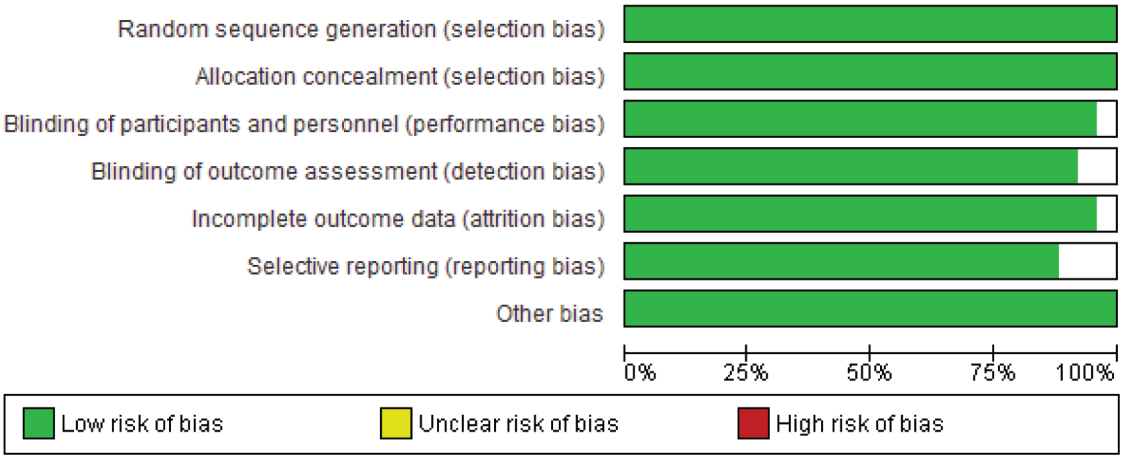


Figure 2a. Bias graph risk of involved studies.

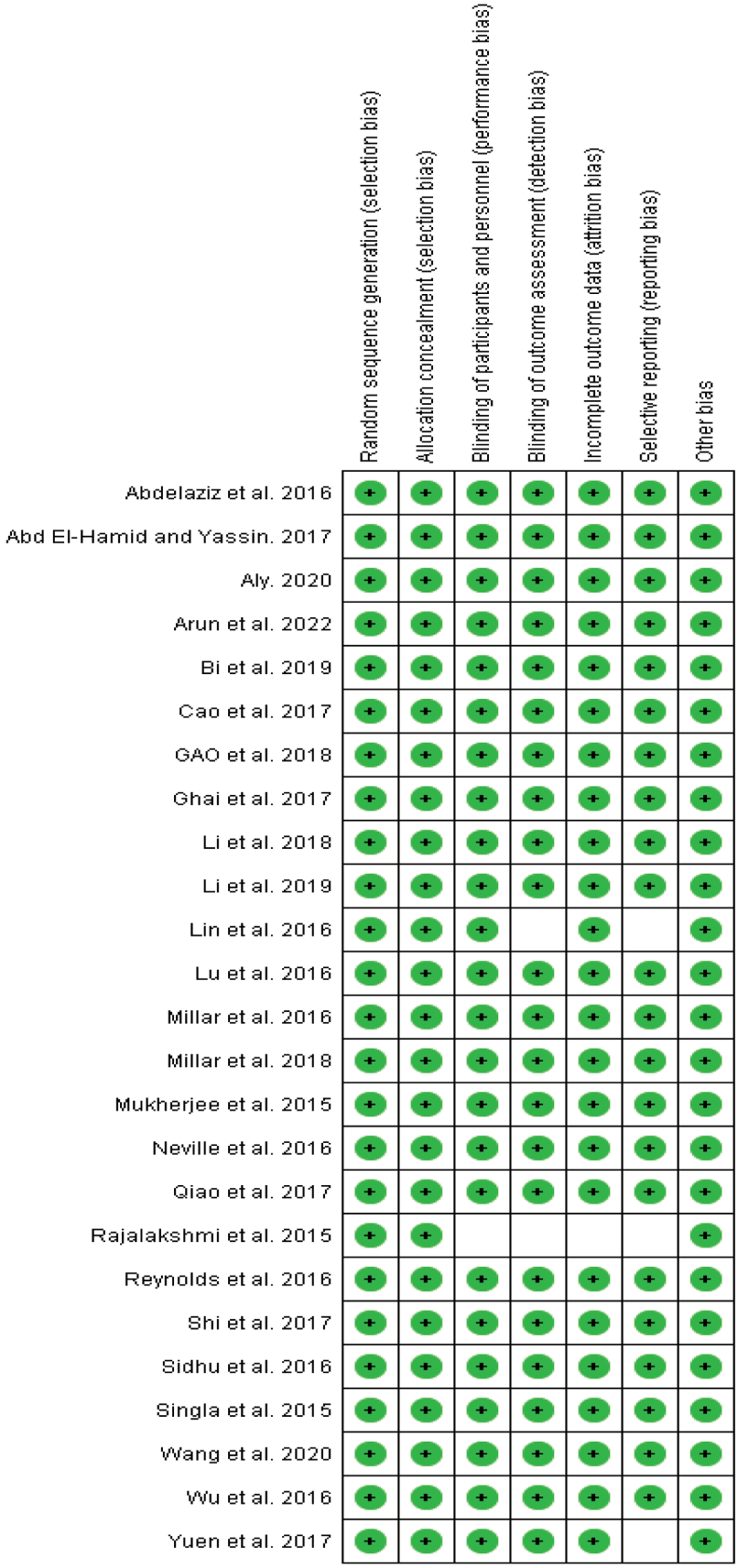
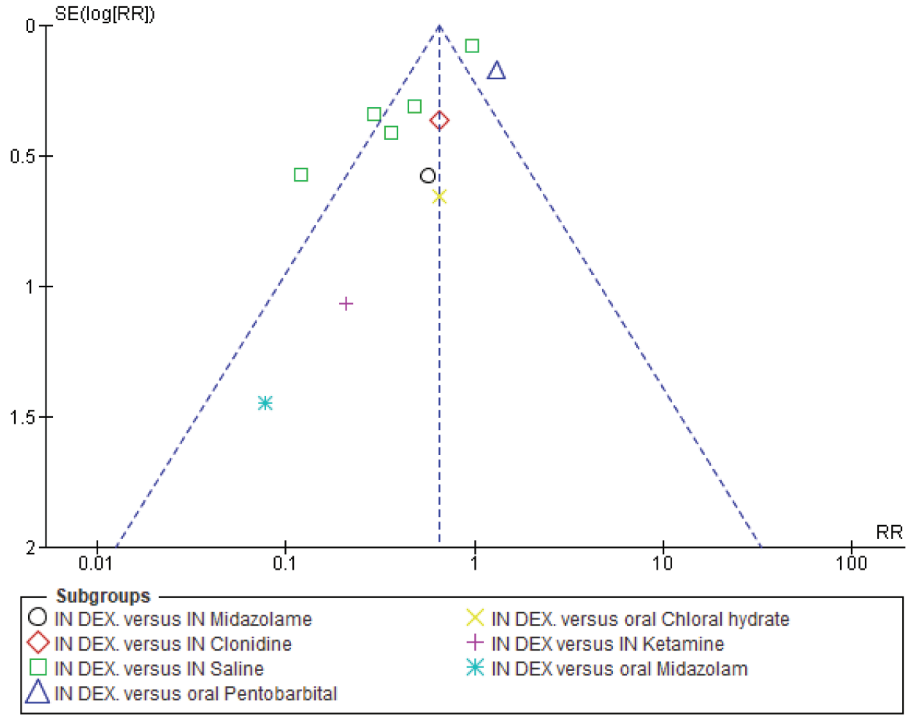


Figure 2b. Bias summary risk depends on Cochrane risk of bias assessment tool; risk of bias domains includes mainly (bias of selection, performance, detection, attrition, and reporting).



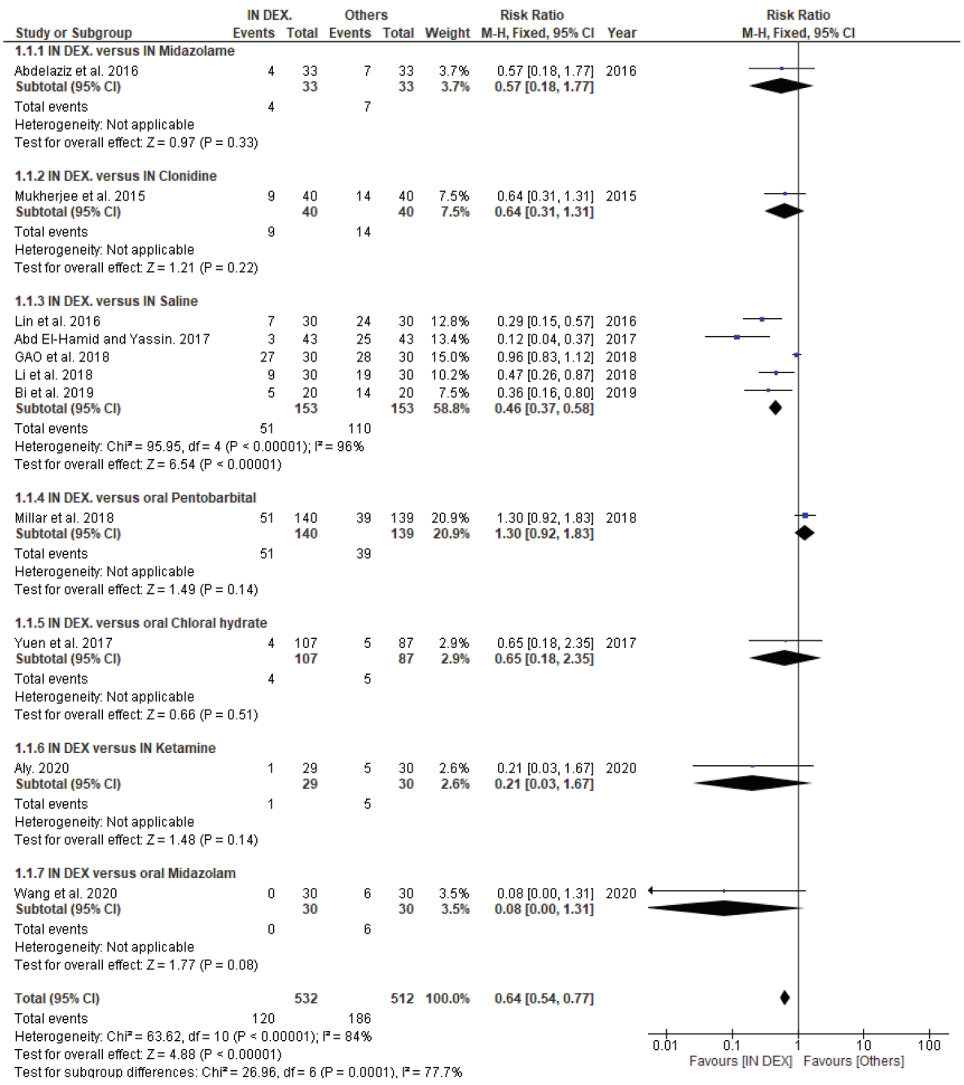
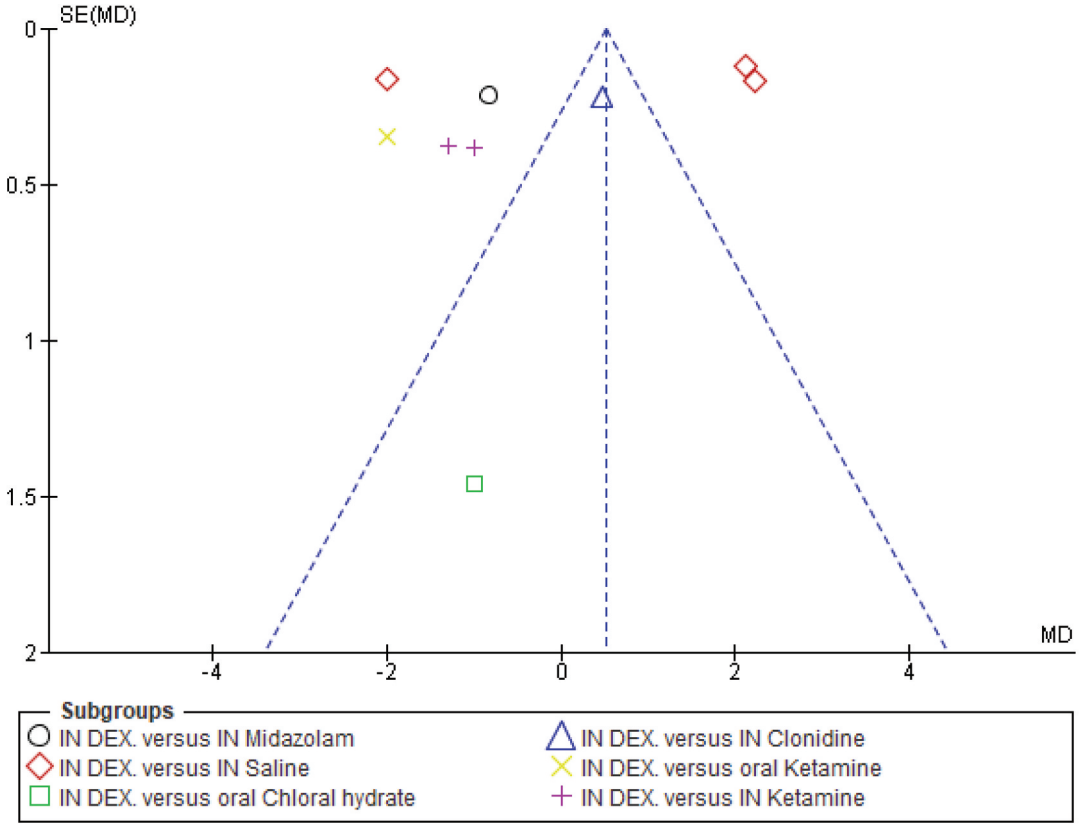


Figure 3. Emergence agitation.



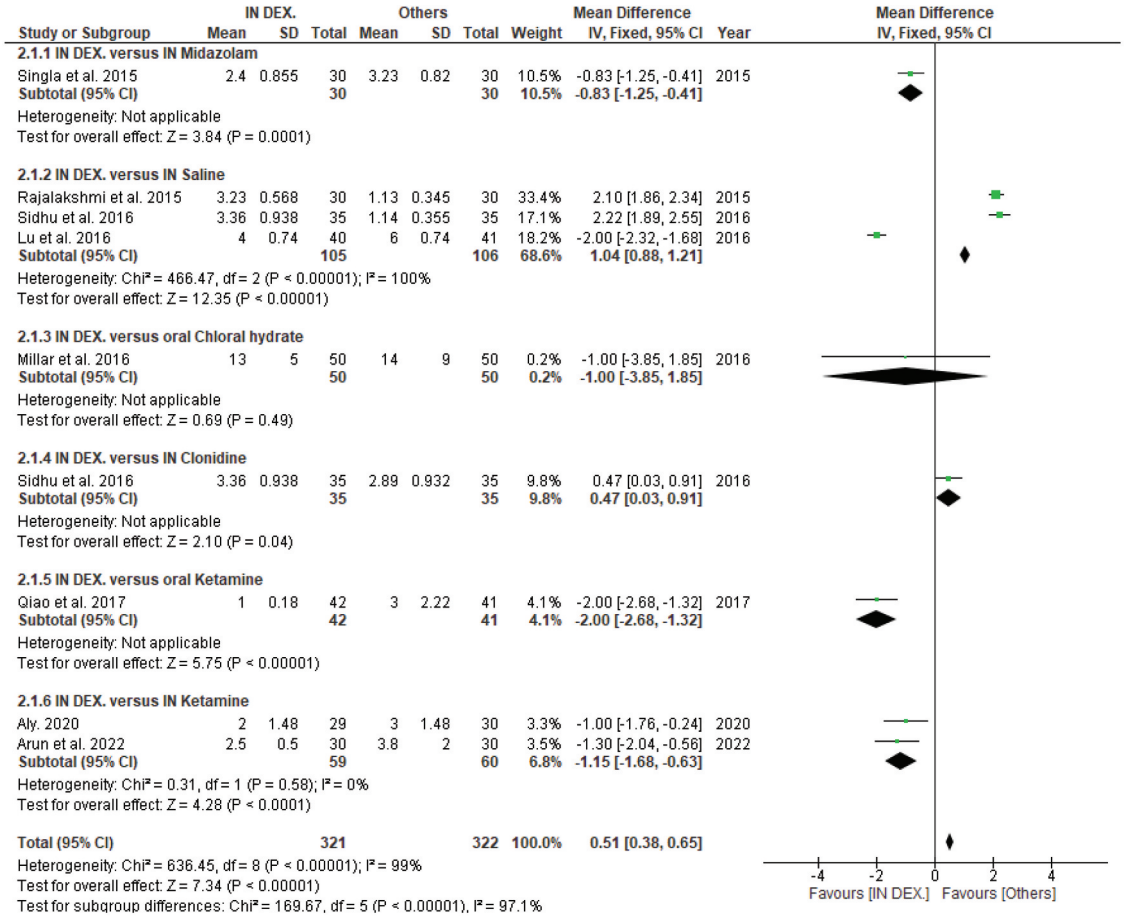
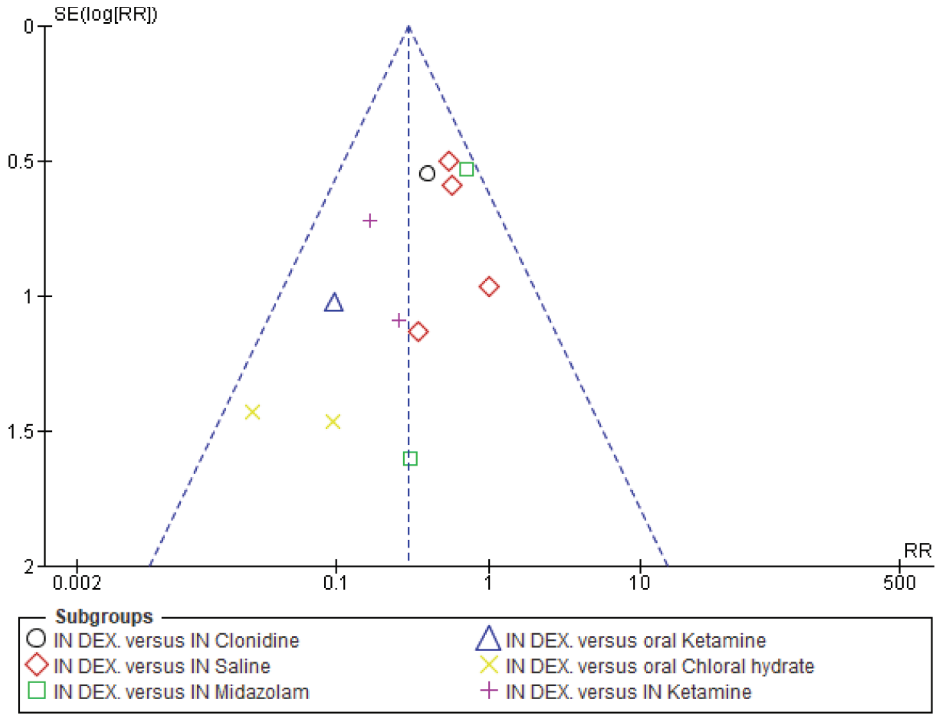


Figure 4. Sedation score.



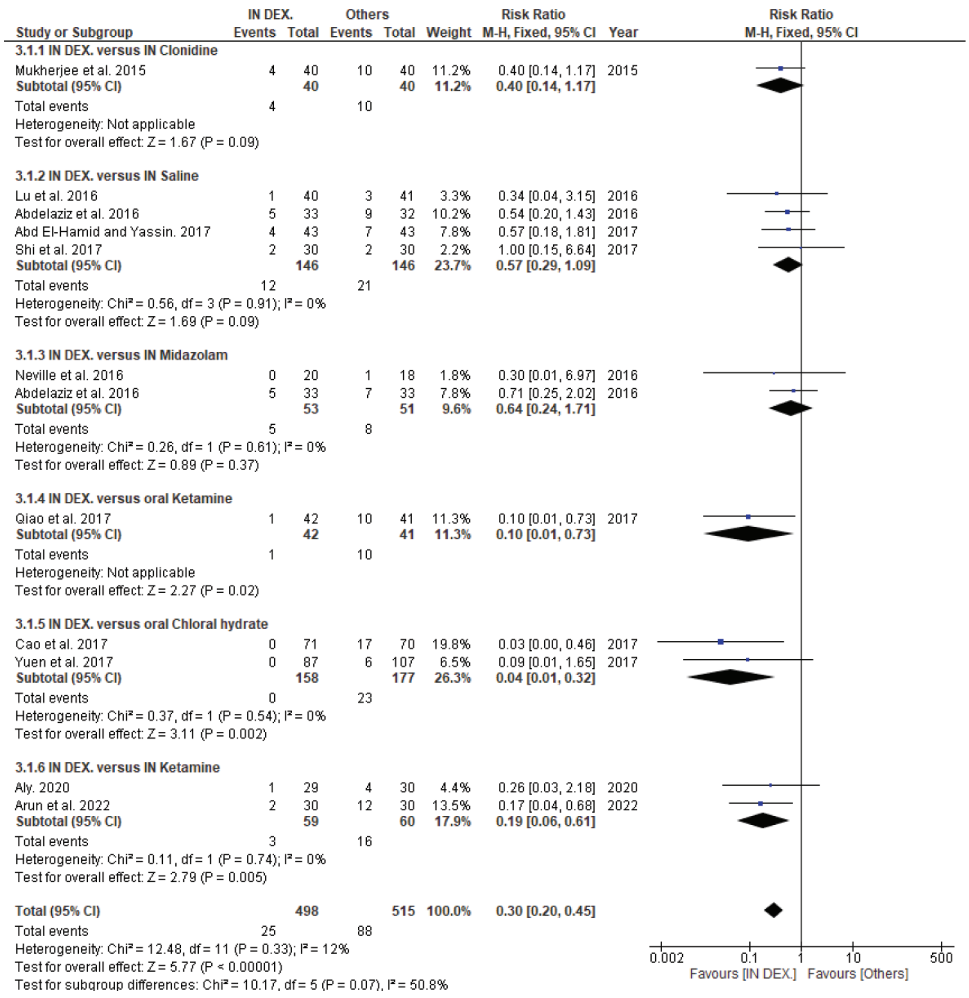
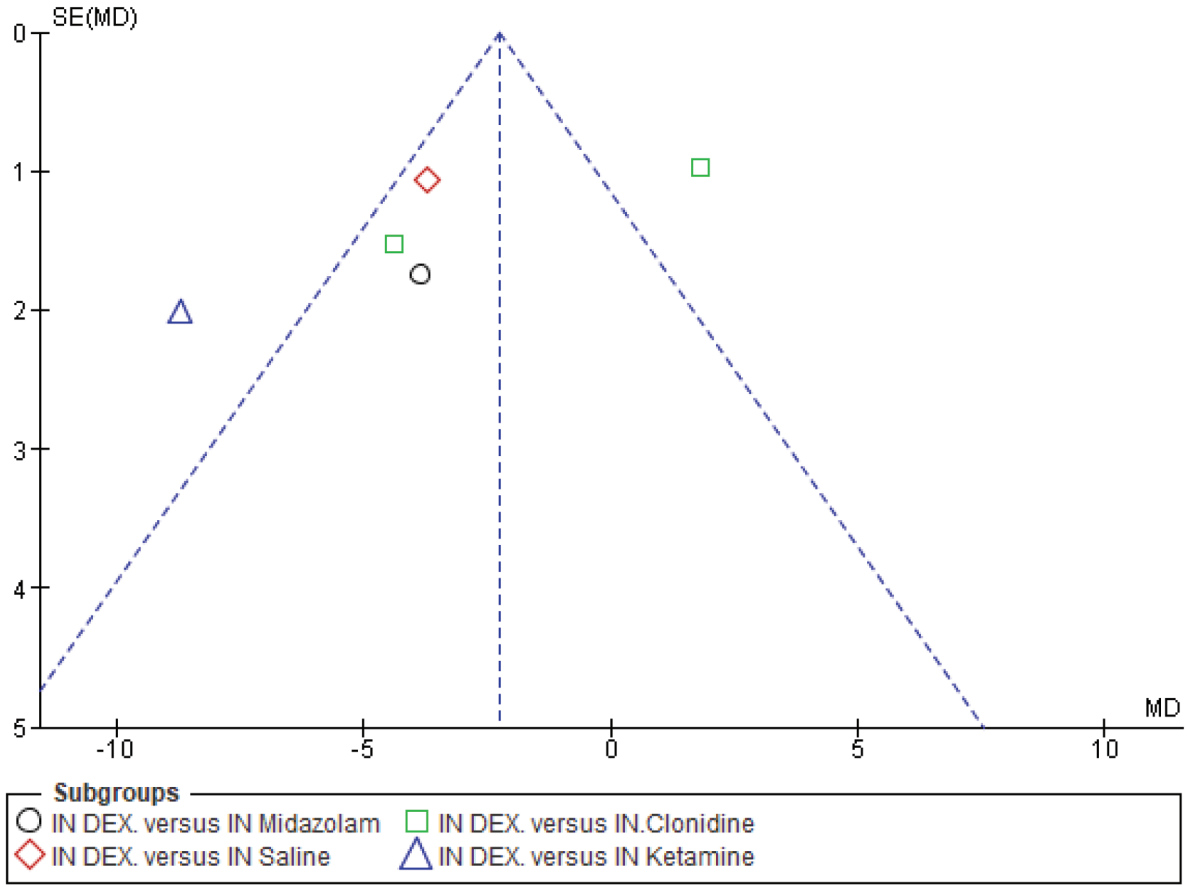


Figure 5. Nausea and vomiting.



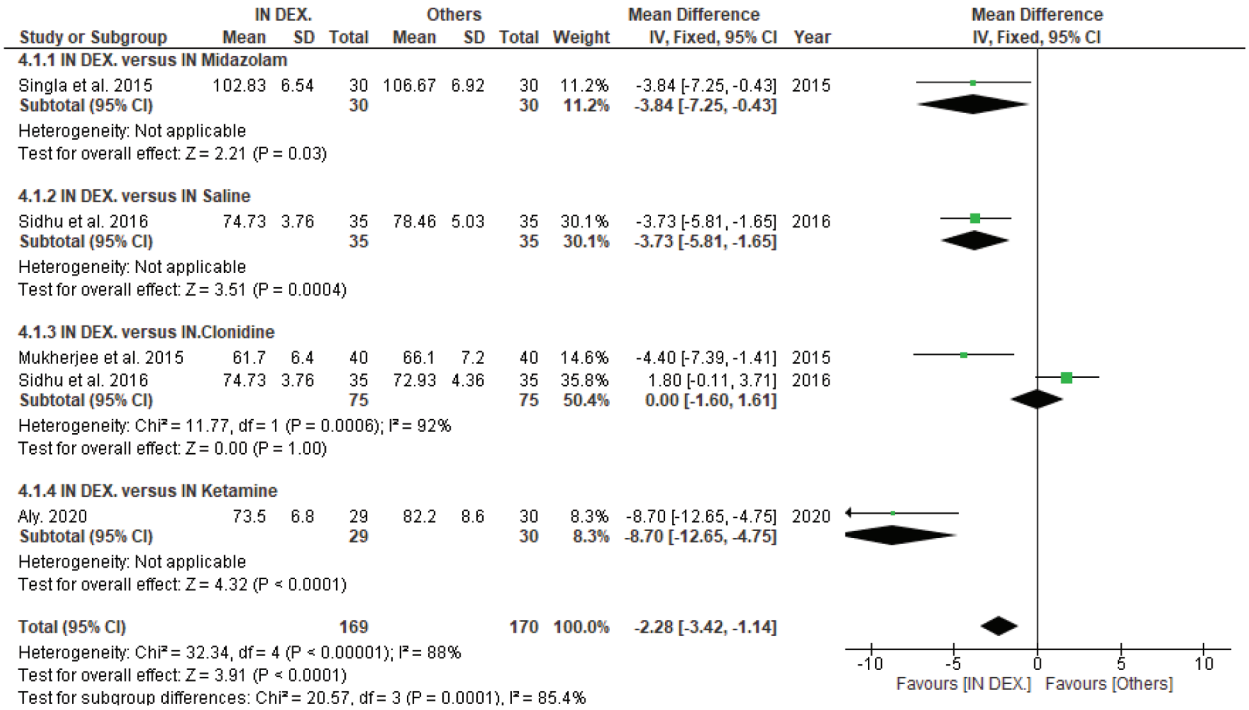
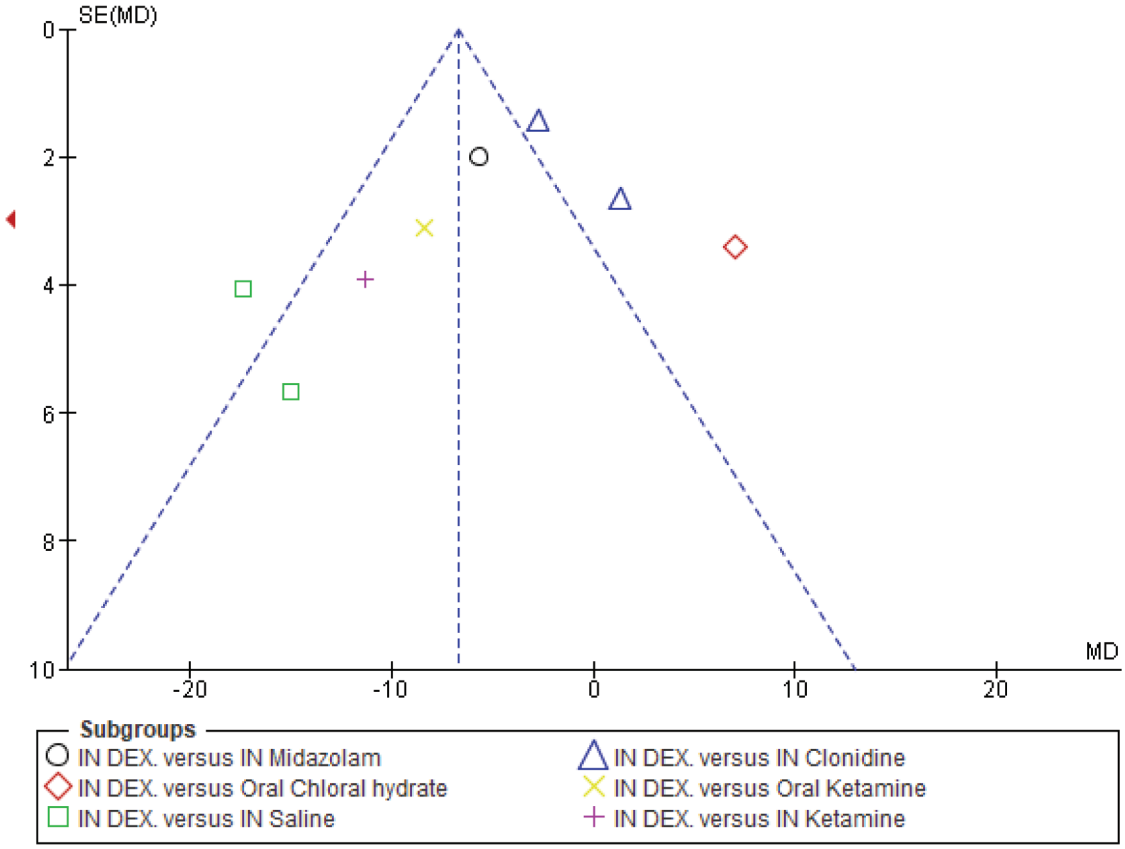


Figure 6. Arterial blood pressure.

maintains upper airway tone. Dexmedetomidine also reduces the likelihood of EA in children undergoing MRIs while they are under general anaesthesia, without causing any respiratory distress or hemodynamic changes that might delay their release from the hospital [52].

Many studies have examined the route and dosage of DEX, which can be delivered intravenously, orally, intranasally, and intramuscularly. The best way to administer DEX is yet unknown; however, research has demonstrated that intranasal administration is safe, effective, and less intrusive



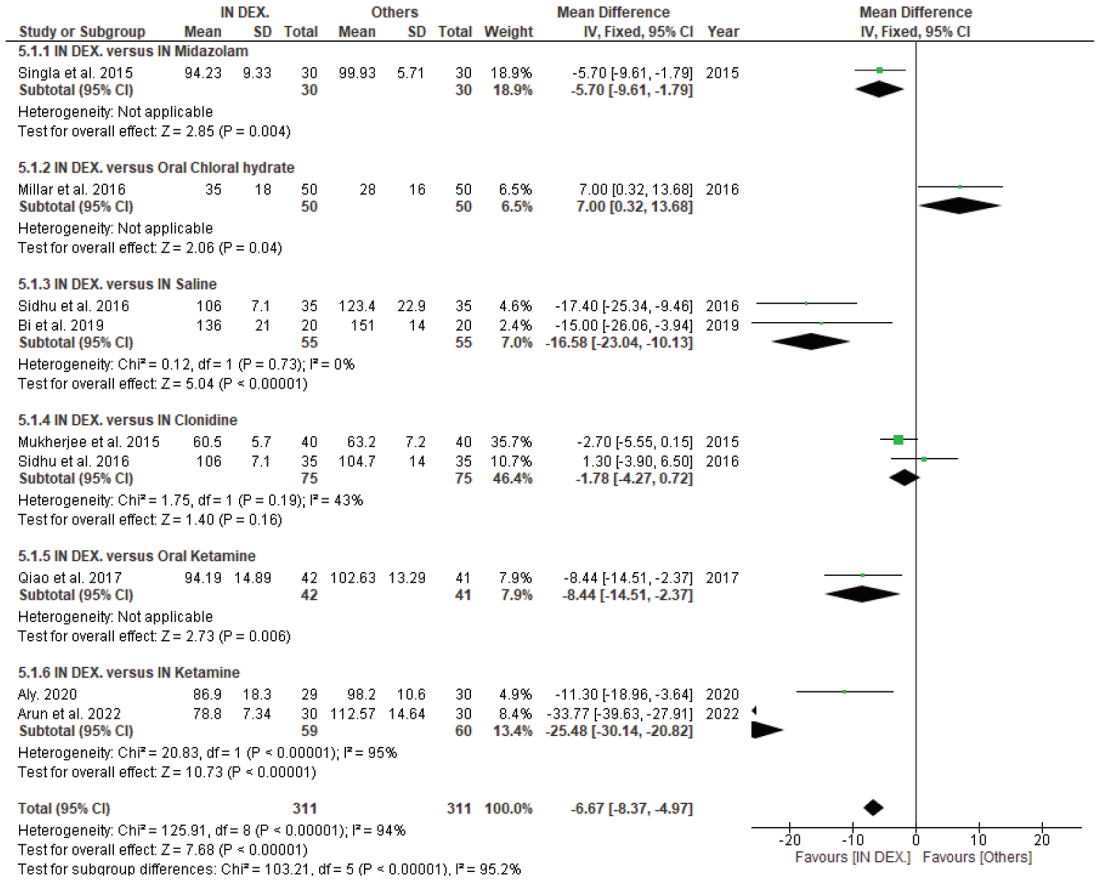


Figure 7. Heart rate.

than intravenous administration. Yuen et al. revealed that using 1 µg/kg Dexmedetomidine nose drops prior to surgery had a good sedative effect in 62% of the children having surgery [16]. **Li et al**. utilized 1.0 µg/kg Dexmedetomidine nasal drops 45 to 60 min prior to the onset of pediatric anaesthesia, which was just as effective as 0.2 mg/kg midazolam nasal drops [53]. Intranasal Dexmedetomidine can be utilized as a sedative agent in pediatric instances and can provide safe and effective premedication, according to the current meta-analysis, which is consistent with meta-analysis carried out by **Ex et al.**

1123 patients and 14 articles that were engaged the results of the meta-analysis revealed that the intranasal dexmedetomidine group's incidence of emergence agitation, adequate sedation upon parent separation, incidence of nausea and vomiting, and the incidence of laryngospasm was different from the control group [54]. Another meta-analysis bone by **Yang et al.** makes our results stronger which included a total of 33 studies, involving 2,549 patients in this meta-analysis. Dexmedetomidine can minimize emerging agitation, regulate postoperative pain, reduce the need for rescue analgesics, and decrease the incidence of postoperative nausea and vomiting compared to saline [55]. In the line with our study, a randomized comparative study done by **Suvvari P et al.** that compare IN dexmedetomidine versus IN ketamine as premedication for the level of sedation in children undergoing radiation therapy observed that dexmedetomidine is better than ketamine in decreasing agitation and providing more sedation [56] With the agreement, **Sun et al**. contrasted the intranasal use of midazolam and dexmedetomidine. They noticed that the dexmedetomidine group had better sedation after accepting the mask when compared to the midazolam group [57]. In addition, a meta-analysis made by **Li Let al.** revealed that intranasal dexmedetomidine is an effective sedative approach rather than oral chloral hydrate for infants and toddlers undergoing diagnostic tests. Although there was a tendency toward decreased blood pressure and heart rate, intranasal dexmedetomidine may be a secure substitute for oral chloral hydrate as a sedative for young children [58].

Other than that, certain studies that have been published have not indicated a difference between the effectiveness of IN dexmedetomidine and other sedatives as premedication, such as **Gyanesh and colleagues** have not discovered any significant differences in how children react to the effectiveness of IN dexmedetomidine) versus IN ketamine premedication for IV insertion [59]. Also, a study made by **Elsayed et al.** compared ketamine versus dexmedetomidine effect on sedation and anxiolysis given by intranasal route to pediatric cases going to adenotonsillectomy and the results were both drugs give an effective sedation level with a better outcome of dexmedetomidine in sedation onset time and sedation score, and also little decrease in mean arterial pressure and heart rate. Additionally, there was a good degree of cannulation and parental separation scores in these sorts of procedures, and the pediatric parents were satisfied with the surgery and grateful to us for easing their children's and parents' worry and anxiety [60]. Remarkably, our results showed that dexmedetomidine results in decreasing blood pressure and heart rate and Dexmedetomidine's ability to lower sympathetic outflow and catecholamine levels in the blood can be used to explain this effect [61].

The strength of this study is that the data collection in our meta-analysis was systematic and carefully analyzed. The results confirmed the notion that dexmedetomidine had little impact on blood pressure and heart rate [62].

12.1. Limitation

On the other hand, it is important to think about certain potential restrictions. First, the heterogeneity among the studies we considered, which mostly resulted from different sedative medication dosages and, diagnostic procedures and the time of administration of Dexmedetomidine reaches its maximum effect of sedation at 30–45 min after intranasal administration, were still significant. We, therefore, conducted a meta-analysis using random effects models. Second, the age of the patients in the relevant research varied, which might have led to discrepancies in the studies since pharmacokinetics and pharmacodynamics differ between the ages of 3 months and 14 years, which may make the results distinguishable.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

On request, the corresponding author will provide the data used to support the study's conclusions.

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