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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 post-operative complications in relation to other premeditations.

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-adrenoceptoractivating 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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KEYWORDS

Intranasal dexmedetomidine; premedication; pediatric; meta-analysis

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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

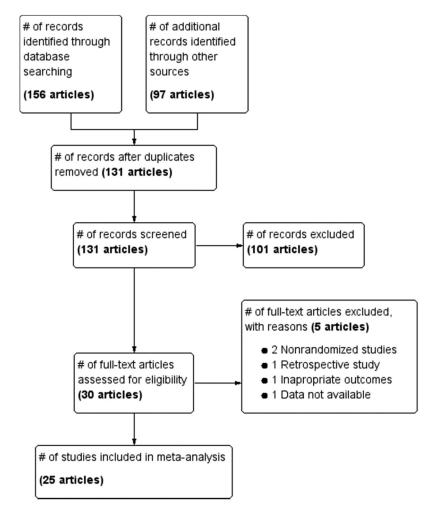


Figure 1. (PRISMA) flow chart representing the search and selection process.

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

Single of A (3) (5) (1) (N DEX (1 mode) (More sugery Mondrese (4, 2) (5) (2) N DEX $2.94.0$ (3) $3.4.13.0$ (3) (More sugery Moderse (4, 2) (5) (2) N DEX $2.94.0$ (3) $3.2.13.0$ (3) (More sugery Moderse (4, 2) (5) (2) N DEX $2.94.13.0$ (3) (More sugery (More sugery) More (4, 2) (5) (2) N DEX $1.90.0$ (3) $3.2.13.0$ (3) (More sugery) More (4, 2) (5) (2) N DEX $1.90.0$ (3) $3.2.13.0$ (3) (More sugery) More (4, 2) (5) (2) N DEX $1.90.0$ (3) $3.2.13.0$ (3) (More sugery) More (4, 2) (5) (2) N DEX $1.90.0$ (3) $3.2.13.0$ (3) (More sugery) More (4, 2) (5) (3) N DEX $1.90.0$ (3) $3.2.13.0$ (3) (More sugery) More (4, 2) (5) (3) N DEX $1.90.0$ (3) $3.2.13.0$ (3) (More sugery) More (4, 2) (5) (3) N DEX $1.90.0$ (3) $3.2.13.0$ (3) (More sugery) More (4, 2) (5) (2) N DEX $2.91.3.0$ (3) (More sugery) (More sugery)	Study ID	Intervention	Dose	Nm.	Age	Timing of injection	Surgery
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05 [23] N DEX $2 \mod 643$ $2 \mod 643$ $2 \mod 643$ $3 \odot 712$ $3 \odot 723$ $3 \odot 712$ $3 \odot 723$ $3 \odot 712$ $3 \odot 723$ $3 $			4 mcg/kg	94	3.0 ± 1.9 yrs.		
41 Nalme 1 add S1/11 305	ajalakshmi et al. 2015 [23]	IN DEX.	2 mcg/kg	90	4.83 ± 2.12 yrs.	In the holding	Cardiac surgeries
4) Oral chool Phydrate 70 mg/kg 50 13.54.56 mon. Before the procedure 6 (28) N DEX. 3 mcg/kg 50 13.44.85 mon. NDEX. 45-60 min. before aneacthetic 6 (28) N DEX. 1 mcg/kg 41 453-16.01% Rote the procedure 6 (28) N DEX. 1 mcg/kg 51 3 mcg/kg 51 3 mcg/kg 7. 28] N DEX. 3 mcg/kg 3 512-9.1% 35-60 min. before aneacthetic 7. 28] N DEX. 2 mon. (22.0-2) 2 mon. (22.0-2) 2 mon. (23.0-2) 7. 28] N DEX. 2 mon. (23.0-2) 2 mon. (23.0-2) 2 mon. (23.0-2) 7. 28] N DEX. 1 mcg/kg 3 55-9 yrs. 3 min. prior to surgery 8 N DEX. 1 mcg/kg 3 475-1.18/yrs. 3 min. prior to surgery 8 N DEX. 1 mcg/kg 3 475-1.18/yrs. 3 min. prior to surgery 8 N DEX. 1 mcg/kg 3 475-1.18/yrs. 3 min. prior to surgery 8 N DEX. 1 mcg/kg 3 min. prior to surgery 3 475-1.18/yrs.		IN Saline	l m	30	5.17 ± 1.89 yrs.	are23,29,32,33,37,39,41,43,44,45)a	
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		IN DEX. 2	2 mcg/kg	50	13.7 ± 8.6 mon.		
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		IN DEX. 3	3 mcg/kg	50	15.4±8.5 mon.		
	et al. 2016 [25]	IN DEX.	1 mcg/kg	40	43.6 ± 9.2 yrs.	45–60 min. before anaesthetic	Elective suspension laryngoscopy
6 [26]IN DEX. + oral placebo3 mcg/kg4423.3 mon. (195-Before the procedure7, 281Oral chloral hydrate + IN saline5 mg/kg355 [2-9], yrs.30 min. prior to surgery7, 281N DEX.2 µg/kg355 [2-9], yrs.30 min. prior to surgeryN clonidine3 µg/kg304.04 ± 168 yrs.30 min. prior to surgeryN DEX.1 µg/kg304.04 ± 168 yrs.30 min. prior to surgery131N DEX.1 µg/kg314.04 ± 168 yrs.30 min. prior to surgery31N DEX.2 µg/kg334.04 ± 168 yrs.30 min. prior to surgery31N DEX.1 µg/kg31 4.04 ± 1.68 yrs.30 min. before anexthesia induction31N DEX.2 µg/kg322.44 ± 1.3 yrs.30 min. before anexthesia induction31N DEX.1 µg/kg332.68 ± 1.1 yrs.30 min. before anexthesia induction31N DEX.1 µg/kg332.68 ± 1.1 yrs.30 min. before anexthesia induction31N DEX.1 µg/kg332.68 ± 1.1 yrs.30 min. before anexthesia induction32N DEX.1 µg/kg332.68 ± 1.1 yrs.3		A placebo	1 ml	41	45.9 ± 10.1 yrs.	induction	
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7, 28]Oral chloral hydrate + N saline50 mg/kg4125,6 mon, (22,0-1)7, 28]N LORN LOR3 gg/kg355 [2-9], yrs.30 min, prior to surgeryN Cancidine3 gg/kg355 [2-9], yrs.30 min, prior to surgeryN DEX1 mg/kg355 [2-9], yrs.30 min, prior to surgeryN DEX1 mg/kg30475 ± 1 88 yrs.30 min, prior to surgeryN DEX1 mg/kg30475 ± 1 88 yrs.30 min, prior to surgeryN DEX1 mg/kg30475 ± 1 88 yrs.30 min, prior to surgeryN SalineSame volume2747 ± 5 yrs.40 min, before anesthesia inductionN DEX1 μg/kg2847 ± 5 yrs.40 min, before anesthesia inductionN DEX1 μg/kg2847 ± 5 yrs.40 min, before anesthesia inductionN DEX1 μg/kg2847 ± 5 yrs.40 min, before anesthesia inductionN DEX1 μg/kg2847 ± 5 yrs.40 min, before anesthesia inductionN DEX1 μg/kg2847 ± 5 yrs.40 min, before anesthesia inductionN DEX1 μg/kg2847 ± 5 yrs.40 min, before anesthesia inductionN DEX1 μg/kg2847 ± 5 yrs.40 min, before anesthesia inductionN DEX1 μg/kg2847 ± 5 yrs.40 min, before anesthesia inductionN DEX1 μg/kg2847 ± 5 yrs.44 ± 13 yrs.N DEX1 N DEX1 mg/kg3328 ± 4 ± 13 yrs.N Saline OO1 m/kg + VS S					27.2)		
7, 28]placebo 290 0 7, 28]N DEX. $2 \mu g / kg$ $5 \Gamma - 9 J / x$. $0.5 m h$ $3 \Gamma - 9 J / x$. $0.5 m h$ $3 \Gamma - 9 J / x$. $0.5 m h$ $3 \Gamma - 9 J / x$. $3 m h$ $0.5 m h$ $3 \Gamma - 9 J / x$. $3 m h$ $0.5 m h$ $3 \Gamma - 9 J / x$. $3 m h$ $0.5 m h$ $3 \Gamma - 9 J / x$. $3 m h$ $0.5 m h$ $3 \Gamma - 9 J / x$. $3 m h$ $0.5 m h$ $3 \Gamma - 9 J / x$. $3 m h$ $0.5 m h$ $3 \Gamma - 9 J / x$. $3 m h$ $0 m h$		Oral chloral hydrate + IN saline	50 mg/kg	41	25.6 mon. (22.0-		
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	lhu et al. 2016 [27, 28]	IN DEX.	2 µg/kg	35	5 [2–9], yrs.	30 min. prior to surgery	Various surgeries
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		IN clonidine	3 µg/kg	35	5 [2–9], yrs.		
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		IN Saline	0.5 ml	35	5 [2–9], yrs.		
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	n 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
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		IN DEX.	2 mcg/kg	30	4.04 ± 1.68 yrs.		
ItemValueSame volume27 $48 \pm 4yrs.$ 30 min. following nasal medication1 N DEX.1 µg/kg26 $47 \pm 4yrs.$ 40 min. before anesthesia induction1 N DEX.1 µg/kg203.44 yrs.40 min. before anesthesia induction1 N DEX.2 µg/kg203.44 yrs.10 min. before anesthesia induction1 N DEX.1 µg/kg203.44 yrs.10 min. before anesthesia induction1 N DEX.1 mcg/kg203.44 yrs.10 min. before anesthesia induction1 N DEX.1 mcg/kg312.68 ± 1.54 yrs.10 min. before anesthesia induction1 N DEX.1 mcg/kg312.68 ± 1.54 yrs.10 min. before anesthesia induction1 N Saline0.1 mg/kg312.68 ± 1.54 yrs.Petor outance to the operation room1 N Saline0.1 mg/kg32.68 ± 1.54 yrs.At ± 1.3 yrs.1 N Saline 0.01 ml/kg + Propofol302.74 ± 1.3 yrs.At ± 1.3 yrs.1 N Saline 0.01 ml/kg + Propofol302.67 ± 4.8 yrs.N drugs (45 min. before surgery)1 N DEX. 0.1 mcg/kgN DEX. 0.1 mcg/kg + Propofol302.67 ± 4.8 yrs.N drugs (45 min. before surgery)1 N DEX. 0.1 mcg/kgN Saline 0.01 ml/kg + Propofol302.67 ± 4.8 yrs.N drugs (45 min. before surgery)1 N DEX. 0.1 mcg/kgN DEX. 0.1 mcg/kg + 70 out workg + 70 out		IN Saline	Same volume	30	4.15 ± 1.58 yrs.		
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$ \begin{array}{llllllllllllllllllllllllllllllllllll$		IN DEX.	1 µg/kg	26	47 ± 4 yrs.	40 min. before anesthesia induction	
IV DEX. $1 \mu g/kg$ 27 $47 \pm 5 yr.$ $10 \min befyrs.ore aresthesia inductionIN DEX.2 \mod kg3.15 yr.10 \min befyrs.ore aresthesia inductionIN DEX.1 \mod kg/kg3.15 yr.10 \min befyrs.ore aresthesia inductionIN DEX.1 \mod kg/kg3.15 yr.3.15 yr.IN Midazolam0.4 \mod kg332.68 \pm 1.54 yr.Prior to surgeryIN Midazolam0.1 \mod kg/g332.48 \pm 1.17 yr.Before entrance to the operation roomIN Saline1 \mod g/kg332.48 \pm 1.17 yr.Before entrance to the operation roomIN Saline1 \mod g/kg332.48 \pm 1.17 yr.After the induction of generalIN Saline0.1 \mod k/g + Propofol322.67 \pm 4.8 yrs.After the induction of generalIN Saline0.01 \mod k/g + V Saline 0.04 \mod k/g + Propofol3026.7 \pm 4.8 yrs.IN drugs (During induction of GA)IN DEX. 0.1 mcg/kg + IV Saline 0.04 \mod k/g + Propofol3027.3 \pm 4.5 yrs.IN drugs (During induction of GA)IN DEX. 0.1 mcg/kg + IV Sufentanil 0.1 mcg/kg3027.3 \pm 4.5 yrs.IN drugs (During induction of GA)IN DEX. 0.1 m/kg + IV Sufentanil 0.1 mcg/kg3027.3 \pm 4.5 yrs.IN drugs (During induction of GA)IN DEX.IN DEX.10 - 31 - 30 - 2.5 \pm 4.5 yrs.30 - 2.73 \pm 4.5 yrs.IN DEX.IN DEX.IN DEX.10 - 2.5 \mod k/g = 30 - 2.73 \pm 4.5 yrs.30 - 2.73 \pm 4.5 yrs.30 - 2.73 \pm 4.5 yrs.IN DEX.IN DEX.10 - 2.5 \mod k/g = 30 - 2.73 \pm 4.5 yrs.30 - $		IN DEX.	2 ua/ka	28	47 ± 5 vrs.	40 min. before anesthesia induction	
IN DEX. $2 m G/Kg$ 20 $3.44 yr.s.$ Prior to surgeryIN Midazolam $0.4 m G/Kg$ 18 $3.15 yr.s.$ Prior to surgeryIN DEX. $1 m G/Kg$ 33 $2.68 \pm 1.54 yr.s.$ Prior to surgeryIN Midazolam $0.1 m G/Kg$ 33 $2.68 \pm 1.54 yr.s.$ Before entrance to the operation roomIN Saline $0.1 m G/Kg$ 33 $2.68 \pm 1.54 yr.s.$ Before entrance to the operation roomIN DEX. $1 m d$ 32 $2.78 \pm 1.67 yr.s.$ After the induction of generalIN DEX. $1 m d$ 32 $2.78 \pm 1.67 yr.s.$ After the induction of generalIN Saline $0.01 m//kg + Propofol 2302.6.7 \pm 4.8 yr.s.-IN drugs (45 min. before surgery)IN DEX.0.1 m//kg + Propofol 23026.7 \pm 4.8 yr.s.-IN drugs (During induction of GA)IN DEX.0.1 m//kg + V Saline 0.04 m//kg + Propofol 23026.7 \pm 4.8 yr.s.-IN drugs (During induction of GA)IN DEX.0.1 m//kg + V Saline 0.04 m//kg + Propofol 23026.7 \pm 4.8 yr.s.-IN drugs (During induction of GA)IN DEX.0.1 m//kg + V Saline 0.04 m//kg + Propofol 23026.7 \pm 4.8 yr.s.-IN drugs (During induction of GA)IN DEX.0.1 m//kg + V Saline 0.04 m//kg + Propofol 23027.3 \pm 4.5 yr.s.-IN drugs (Puring induction of GA)IN DEX.V = 0.01 m//kg + V Saline 0.01 m//kg + Propofol 23027.3 \pm 4.5 yr.s.-IN drugs (Puring induction of GA)IN DEX.V = 0.01 m//kg + V Saline 0.01 m//kg + 3 m/s Fract/kg + 3 m/s Fract/kg + 3 $		IV DEX.	1 ua/ka	27	47 ± 5 vrs.	10 min. befvrs.ore anesthesia induction	
IN Midzolam 0.4 mg/kg 18 3.15 yrs. Incorrection 0.4 mg/kg 33 5.5 yrs. Incorrection 0.1 mg/kg 33 5.5 yrs. Incorrection to experision IN Midazolam 0.1 mg/kg 33 2.68 ± 1.57 yrs. Before entrance to the operation room IN DEX. 1 mcg/kg 33 2.68 ± 1.57 yrs. Before entrance to the operation room IN DEX. 1 mcg/kg 33 2.68 ± 1.57 yrs. Before entrance to the operation room IN DEX. 1 mcg/kg 33 2.68 ± 1.57 yrs. Before entrance to the operation room IN DEX. N Saline 0.01 ml/kg + IV Saline 0.04 ml/kg + Propofol 2 30 26.7 ± 4.8 yrs. IN drugs (45 min. before surgery) IN DEX. 0.1 mcg/kg + N Saline 0.04 ml/kg + Propofol 2 30 26.7 ± 4.8 yrs. IN drugs (0uring induction of GA) IN DEX. 0.1 mcg/kg + N Saline 0.04 ml/kg + Propofol 2 30 26.7 ± 4.8 yrs. IN drugs (45 min. before surgery) IN DEX. 0.1 mcg/kg + N Saline 0.04 ml/kg + Propofol 2 30 26.7 ± 4.8 yrs. IN drugs (45 min. before surgery) IN DEX. 0.1 mcg/kg + N Saline 0.01 ml/kg + Propofol 2 30 26.7 ± 4.8 yrs. I	ville et al 2016 [31]				3 44 Vrc	Prior to surgery	Dadiatric laceration renairs
IN Midazolam U4.110/Kg Imcg/kg 33 2.68 ± 11.5 4 yrs. Before entrance to the operation room IN DEX. 1 mcg/kg 33 2.68 ± 1.67 yrs. Before entrance to the operation room IN DEX. 1 mcg/kg 33 2.68 ± 1.67 yrs. Before entrance to the operation room IN DEX. 1 mcg/kg 32 2.78 ± 1.67 yrs. After the induction of general IN DEX. 1 mcg/kg 43 4.2 ± 0.93 yrs. anesthesia IN Saline 0.1 ml/kg + IV Saline 0.04 ml/kg + Propofol 2 30 26.7 ± 4.8 yrs. IN drugs (During induction of GA) IN DEX. 0.1 mcg/kg mg/kg 0.5 ml in each 33 2.8 ± 4.1 yrs. IN drugs (During induction of GA) IN DEX. 0.1 mcg/kg + N Suline 0.04 ml/kg + Propofol 2 30 28 ± 4.1 yrs. IN drugs (During induction of GA) IN DEX. 0.1 mcg/kg + N Suline 0.01 ml/kg + W Suffentanil 0.1 mcg/kg + 3 30 27.3 ± 4.5 yrs. IN drugs (During induction of GA) IN DEX. Horal ketamine 2.5 mcg/kg + 3 32 2.7 ± 4.5 yrs. 30 min. before the induction of kg IN DEX. Horal ketamine 0.01 ml/kg + 1.3 5.6 ± 1.36 yrs. 30 min. before				7 7	.ciy ++.c		ר בטומנו ור ומרבו מנוטו דב לאמווס
$ \begin{array}{llllllllllllllllllllllllllllllllllll$			0.4 mg/kg	<u>o</u>	siy ci.c	•	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	delaziz et al. 2016 [32]	IN DEX.	1 mcg/kg	33	2.68 ± 1.54 yrs.	Before entrance to the operation room	Strabismus surgery
IN Saline1 ml32 2.78 ± 1.67 yrs. 1 mcg/kg 1 mlIN DEX.1 mcg/kg 1 mcg/kg 33 4.4 ± 1.3 yrs. 4.2 ± 0.93 yrs.After the induction of general anesthesiaIN Saline0.01 ml/kg + IV Saline0.04 ml/kg + Propofol 30 26.7 ± 4.8 yrs. 26.7 ± 4.8 yrs.IN drugs (45 min. before surgery) -IN drugs (During induction of GA)IN DEX.0.1 ml/kg + IV Saline $0.04 ml/kg + Propofol3026.7 \pm 4.8 yrs.26.7 \pm 4.8 yrs.IN drugs (45 min. before surgery)-IN drugs (During induction of GA)IN DEX.0.1 mcg/kg + N Saline0.04 ml/kg + Propofol3028 \pm 4.1 yrs.26.7 \pm 4.8 yrs.IN drugs (45 min. before surgery)-IN drugs (During induction of GA)IN DEX.0.1 mcg/kg + N Saline0.04 ml/kg + Propofol3028 \pm 4.1 yrs.IN DEX.0.1 ml/kg + IV Sufentanil0.1 mg/kg4237.3 \pm 4.5 yrs.IN DEX.Propofol2.5 mcg/kg423.6 \pm 1.50 yrs.IN DEX.N DEX.2.5 mcg/kg413.76 \pm 1.36 yrs.IN DEX.Oral ketamine6 mg/kg414.41 \pm 1.28 yrs.IN DEX.10 \text{ DEX.}2 \text{ mog/kg}7118 [10–25] mon.Oral ketamine6 mg/kg7014.5 (8.8–232)Oral chloral hydrate80 \text{ mg/kg}7014.5 (8.8–232)$		IN Midazolam	0.1 mg/kg	33	2.48 ± 1.17 yrs.		
$ \begin{array}{llllllllllllllllllllllllllllllllllll$		IN Saline	1 ml	32	2.78 ± 1.67 yrs.		
IN Saline 0.5 ml in each 43 $4.2 \pm 0.93 \text{ yrs.}$ anesthesia nostril nostril nostril 103 mostril 103 mostril 103 mostril IN Saline 0.01 ml/kg + IV Saline 0.04 ml/kg + Propofol 2 30 $26.7 \pm 4.8 \text{ yrs.}$ $-\text{IN}$ drugs (45 min. before surgery)IN DEX. 0.1 mcg/kg + N Saline 0.04 ml/kg + Propofol 2 30 $28 \pm 4.1 \text{ yrs.}$ $-\text{IN}$ drugs (During induction of GA)IN DEX. 0.1 mcg/kg + V Sufentanil 0.1 mcg/kg + 3 30 $27.3 \pm 4.5 \text{ yrs.}$ $-\text{IN}$ drugs (During induction of GA)IN DEX. 0.1 ml/kg + V Sufentanil 0.1 mcg/kg + 3 30 $27.3 \pm 4.5 \text{ yrs.}$ $30 \text{ min. before the induction of GA}IN DEX. 0.1 ml/kg + V Sufentanil 0.1 mcg/kg + 33027.3 \pm 4.5 \text{ yrs.}30 \text{ min. before the induction of GA}IN DEX. 0.1 ml/kg + V Sufentanie2.5 \text{ mcg/kg + 3 mg}413.76 \pm 1.36 \text{ yrs.}30 \text{ min. before the induction of kg}IN DEX. 1N DEX. 0.1 M DEX. 0.21 ml/kg + 3 mg/kg414.41 \pm 1.28 \text{ yrs.}30 \text{ min. before the procedureIN DEX. 0.3 cm/kg7118 [10-25] \text{ mon.}14.5 (8.8-23.2)30 \text{ morthere}Oral chloral hydrate80 \text{ mg/kg}7014.5 (8.8-23.2)30 \text{ morthere}$	d El-Hamid and Yassin. 2017	IN DEX.	1 mcg/kg	43	4.4 ± 1.3 yrs.	After the induction of general	Tonsillectomy and/or adenoidectomy under general anesthesia witl
nostril IN Saline 0.01 m/kg + IV Saline 0.04 m/kg + Propofol 230 26.7 ± 4.8 yrs. 26.7 ± 4.8 yrs.IN drugs (45 min. before surgery) -IN drugs (During induction of GA)IN DEX. 0.1 mcg/kg + IV Saline 0.04 m/kg + Propofol 230 28 ± 4.1 yrs.IN drugs (During induction of GA)IN DEX. 0.1 mcg/kg + IV Suffentanil 0.1 mcg/kg +30 27.3 ± 4.5 yrs.IN drugs (During induction of GA)IN Saline 0.01 m/kg + IV Suffentanil 0.1 mcg/kg +30 27.3 ± 4.5 yrs.30 min. before the induction ofIN DEX.Propofol 2 mg/kg42 3.96 ± 1.50 yrs.30 min. before the induction ofIN DEX.Oral ketamine $2 mcg/kg + 3 mg/$ 41 3.76 ± 1.36 yrs.anesthesiaOral ketamine6 mg/kg41 4.41 ± 1.28 yrs.anesthesiaIN DEX.2 mcg/kg7118 [10-25] mon.Before the procedureOral chloral hydrate80 mg/kg7014.5 (8.8-23.2)	[33]	IN Saline	0.5 ml in each	43	4.2 ± 0.93 yrs.	anesthesia	sevoflurane
IN Saline 0.01 m/kg + IV Saline 0.04 m/kg + Propofol 230 $2.6.7 \pm 4.8$ yrsIN drugs (45 min. before surgery)mg/kgmg/kg			nostril				
mg/kgmg/kg-IV drugs (During induction of GA)IN DEX. 0.1 mcg/kg + IV Saline 0.04 ml/kg + Propofol 230 28 ± 4.1 yrs.mg/kgmg/kg27.3 \pm 4.5 yrs.IN Saline 0.01 ml/kg + IV Sufentanil 0.1 mcg/kg +30 27.3 ± 4.5 yrs.Propofol 2 mg/kg423.96 \pm 1.50 yrs.30 min. before the induction of kgIN DEX.2.5 mcg/kg + 3 mg/41 3.76 ± 1.36 yrs.30 min. before the induction of kgOral ketamine2 mcg/kg + 3 mg/41 3.76 ± 1.36 yrs.anesthesiaOral ketamine6 mg/kg41 4.41 ± 1.28 yrs.anesthesiaIN DEX.2 mcg/kg7118 [10-25] mon.Before the procedureOral chloral hydrate80 mg/kg7014.5 (8.8-23.2)	i et al. 2017 [34]	IN Saline 0.01 ml/kg + IV Saline 0.04	1 ml/kg + Propofol 2	30	26.7 ± 4.8 yrs.	-IN drugs (45 min. before surgery)	Termination of first trimester pregnancy
$\label{eq:relation} \begin{array}{ c c c c c c c c c c c c c c c c c c c$		mg/kg				-IV drugs (During induction of GA)	
mg/kgmg/kgIN Saline 0.01 ml/kg + IV Sufentanil 0.1 mcg/kg +30 27.3 ± 4.5 yrs.Propofol 2 mg/kg 25 mcg/kg + 3.96 ± 1.50 yrs. 30 min. before the induction ofIN DEX. 2.5 mcg/kg + 41 3.76 ± 1.36 yrs. 30 min. before the induction ofIN DEX.+ Oral ketamine 2 mcg/kg + 41 3.76 ± 1.36 yrs. 3 min. before the induction ofOral ketamine 6 mg/kg 41 4.41 ± 1.28 yrs. 3 mosthesiaIN DEX. 2 mcg/kg 71 18 [10–25] mon.Before the procedureOral chloral hydrate 80 mg/kg 70 14.5 ($8.8-23.2$)		IN DEX. 0.1 mcg/kg + IV Saline 0.04	: ml/kg + Propofol 2	30	28 ± 4.1 yrs.	1	
$\begin{array}{llllllllllllllllllllllllllllllllllll$		mg/kg					
IN DEX. The proceeding 42 3.96 ± 1.50 yrs. 30 min. before the induction of NDEX. + Oral ketamine $2 \text{ mg}/\text{kg} + 3 \text{ mg}/41 = 3.76 \pm 1.36$ yrs. anesthesia oral ketamine $8 \text{ mg}/\text{kg} = 41 = 4.41 \pm 1.28$ yrs. IN DEX. 2 mcg/kg 71 $18 [10-25]$ mon. Before the procedure Oral chloral hydrate $80 \text{ mg}/\text{kg} = 70 = 14.5 (8.8-23.2)$		IN Saline 0.01 ml/kg + IV Sufenta Pronofol 2 mg/kg	nil 0.1 mcg/kg + י	30	27.3 ± 4.5 yrs.		
IN DEX. + Oral ketamine $2 \text{ mcg/kg} + 3 \text{ mg/}$ 41 $3.76 \pm 1.36 \text{ yrs.}$ anesthesia Oral ketamine kg IN DEX. 2 mcg/kg 41 $4.41 \pm 1.28 \text{ yrs.}$ Oral chloral hydrate 80 mg/kg 70 $14.5 (8.8-23.2)$	ao et al. 2017 [35]	IN DEX.		42	3.96 ± 1.50 vrs.	30 min. before the induction of	Eve surgerv under general anesthesia
\check{kg} \check{kg} J $A.41 \pm 1.28$ yrs. Oral ketamine 6 mg/kg $41 + 4.41 \pm 1.28$ yrs. IN DEX. 2 mcg/kg $71 + 18 [10-25]$ mon. Before the procedure Oral chloral hydrate 80 mg/kg $70 + 14.5 (8.8-23.2)$		IN DEX. + Oral ketamine	2 mcg/kg +3 mg/	41	3.76 ± 1.36 yrs.	anesthesia	
Oral ketamine 6 mg/kg 41 4.41±1.28 yrs. IN DEX. 2 mcg/kg 71 18 [10–25] mon. Before the procedure Oral chloral hydrate 80 mg/kg 70 14.5 (8.8–23.2)			kg				
IN DEX. 2 mcg/kg 71 18 [10–25] mon. Before the procedure Oral chloral hydrate 80 mg/kg 70 14.5 (8.8–23.2)		Oral ketamine	6 mg/kg	41	4.41 ± 1.28 yrs.		
80 mg/kg 70	ao 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)		

(Continued)

ID Intervention Dose Nn. Age Timing of injection rt al. 2017 [37] Chloral hydrate syrup+ IN Saline 50 mg/kg 107 24 mon. 30 min. before the procedure stray spray 3 mg/kg 87 3.25 mon. 30 min. before the procedure t al. 2017 [38] Dalcebo syrup + IN DEX. 25 mg/kg 30 3.8 ± 2.1 yrs. 30 min. before the procedure t al. 2018 [39] NDEX. 2.5 mg/kg 30 3.8 ± 2.1 yrs. 30 min. before the procedure t al. 2018 [30] NDEX. 2.5 mg/kg 30 4.3 ± 1.1 yrs. 30 min. before surgery t al. 2018 [40] NDEX. 2 mg/kg 30 4.3 ± 1.1 yrs. 30 min. before surgery t al. 2018 [41] NDEX. 1 mcg/kg 30 4.3 ± 1.1 yrs. 30 min. before surgery t al. 2018 [41] NDEX. 1 mcg/kg 30 4.3 ± 1.1 yrs. 30 min. before surgery t al. 2019 [42] NDEX. 1 mcg/kg 30 4.3 ± 1.1 yrs. 30 -40 min. before surgery t DOPEX. NDEX. 1 mcg/kg	lable I. (continuea).						
Chloral hydrate syrup+ IN Saline 50 mg/kg 107 24 mon . 30 min , before the procedure $spray$ $spray$ $spray$ $spray$ $spray$ placebo syrup+ IN DEX. Spray 3 mcg/kg 32 mcg/kg 32 min , after EMLA cream applicationIN DEX. 25 mcg/kg 30 min , $31 \pm 13 \text{ yrs}$. 30 min , after EMLA cream applicationOral Midazolam 0.5 mg/kg 30 min , $31 \pm 1.3 \text{ yrs}$. 30 min , after EMLA cream applicationIn DEX. 2.5 mcg/kg 30 min , $31 \pm 1.3 \text{ yrs}$. 30 min , before operationN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.17 \text{ yrs}$. 30 min , before surgeryN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.17 \text{ yrs}$. 30 min , before surgeryN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.17 \text{ yrs}$. 30 min , before surgeryN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.17 \text{ yrs}$. 30 min , before surgeryN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.17 \text{ yrs}$. 30 min , before the procedureN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.07 \text{ yrs}$. 30 min , before the procedureN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.07 \text{ yrs}$. 30 min , before the procedureN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.07 \text{ yrs}$. 30 min , before the procedureN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.07 \text{ yrs}$. 30 min , before the procedureN DEX. 1 mcg/kg $30 \text{ 4.42} \pm 1.07 \text{ yrs}$. $30 \text{ 4.40} min$	Study ID	Intervention	Dose	Nm.	Age	Timing of injection	Surgery
83placebo syrup + IN DEX. Spray 3 mG/kg 87 32.5 mon. 83IN DEX. 2.5 mG/kg 30 $3.8 \pm 2.1 \text{ yrs.}$ $30 \text{ min. after EMLA cream application}$ (39)Oral Midazolam 0.5 mg/kg 30 $3.8 \pm 2.1 \text{ yrs.}$ $30 \text{ min. after EMLA cream application}$ (39)Oral pentobarbital 2.5 mG/kg 30 $3.8 \pm 2.1 \text{ yrs.}$ $30 \text{ min. after EMLA cream application}$ (39)Oral pentobarbital 5 mg/kg 30 $4.52 \pm 10.07 \text{ yrs.}$ $30 \text{ min. before operation}$ (10)N DEX. 2.7 mG/kg 30 $4.52 \pm 10.07 \text{ yrs.}$ $30 \text{ min. before operation}$ (10)N Saline 0.02 m/kg 30 $4.37 \pm 1.17 \text{ yrs.}$ $25 \text{ to 40 \text{ min. before surgery}$ (11)N DEX. 1 more Surgery $4.37 \pm 1.37 \text{ yrs.}$ $25 \text{ mon. before anesthesia induction}$ (10)N DEX. 1 more Surgery $3.66.6 \text{ mon.}$ $3.76.04.6.0 \text{ yrs.}$ (11)N DEX. + buccal midazolam $3 \text{ mcg/kg} + 0.2 \text{ mg}$ $3.32.04.4.8$ $30-40 \text{ min. before the procedure}$ (11)N DEX. + buccal midazolam $3 \text{ mcg/kg} + 0.2 \text{ mg}$ $3.32.04.8.0 \text{ yrs.}$ $30-40 \text{ min. before the procedure}$ (12)N DEX. + buccal midazolam $3 \text{ mcg/kg} + 0.2 \text{ mg}$ $3.32.03.03.0-44.8$ $30-40 \text{ min. before the procedure}$ (13)N DEX. + buccal midazolam $3 \text{ mcg/kg} + 0.2 \text{ mg}$ $3.32.03.03.0-44.8$ $30-40 \text{ min. before the procedure}$ (13)N DEX. + buccal midazolam	Yuen et al. 2017 [37]	Chloral hydrate syrup+ IN Saline spray	50 mg/kg	107	24 mon.	30 min. before the procedure	Computerized tomography
Oral Induction $2.5 m c_{J} m_{J} m_{$		placebo syrup + IN DEX. Spray	3 mcg/kg	87	32.5 mon.	aritarilarea araan A IMT araa aira oo	
[39] IN DEX. 2.5 mcg/kg 140 $12.5 [8-17] \text{ mon.}$ Before the procedure (0) N DEX. 2 mcg/kg 30 $45.2 \pm 10.07 \text{ yrs.}$ $30 \text{ min. before operation}$ (10) N DEX. 1 mcg/kg 30 $45.2 \pm 10.07 \text{ yrs.}$ $30 \text{ min. before operation}$ (10) N DEX. 1 mcg/kg 30 4.35 tr_1 $30 \text{ min. before surgery}$ (10) N DEX. 1 mcg/kg 30 $4.37 \pm 1.17 \text{ yrs.}$ $30 \text{ min. before surgery}$ (11) N DEX. 1 mcg/kg 30 $4.37 \pm 1.13 \text{ yrs.}$ $30 \text{ min. before surgery}$ (11) DEX. + buccal midazolam 3 mcg/kg 30 $4.37 \pm 1.3 \text{ yrs.}$ $30 - 40 \text{ min. before surgery}$ (11) DEX. + buccal midazolam 3 mcg/kg 36 $33.7 (28.0 - 44.8)$ $30 - 40 \text{ min. before surgery}$ (12) DEX. + buccal midazolam 3 mcg/kg $35.0 (28.0 - 44.8)$ $30 - 40 \text{ min. before surgery}$ (12) DEX. + buccal midazolam 3 mcg/kg $33.7 (28.0 - 44.6)$ $30 - 40 \text{ min. before surgery}$ (12) DEX. + buccal midazolam	unai et al. 2017 [38]	IN UEA. Oral Midazolam	2.5 mcg/kg 0.5 ma/ka	29 20 29	3.8 ± 2.1 yrs. 3.1 ± 1.3 vrs.	зо ты. атег Емьа сгеат аррисатол	CL Imaging
(1) Oral pentobarbital 5 mg/kg 13 13 [9-17] mon. (N DEX. N DEX. 2 mcg/kg 30 $4.52 \pm 10.07 \text{ yrs.}$ 30 min. before operation (N DEX.1 1 mcg/kg 30 $4.37 \pm 1.37 \text{ yrs.}$ 30 min. before operation (N DEX.1 1 mcg/kg 30 $4.47 \pm 1.17 \text{ yrs.}$ 25 to 40 min. before surgery (N DEX.2 2 mcg/kg 30 $4.37 \pm 1.3 \text{ yrs.}$ 25 to 40 min. before surgery (N DEX.4 1 mcg/kg 30 $4.37 \pm 1.3 \text{ yrs.}$ 26 min. before surgery (N DEX.4 0 NDEX.2 2 mcg/kg 136 $3.20 (28.0 - 44.8)$ 30 - 40 min. before the procedure (N DEX.4 buccal midazolam 3 mcg/kg 136 $3.20 (28.0 - 44.8)$ 30 - 40 min. before the procedure (N DEX.4 buccal midazolam 3 mcg/kg 13 3.125 yrs. $3.0 - 40.0 \text{ yrs.}$ $3.0 - 40.0 \text{ yrs.}$ (N DEX.4 buccal midazolam 3 mcg/kg 138 $3.28 \pm 0.8 \text{ yrs.}$ $1.6 + 0.0 \text{ mse}$ (N DEX.4 buccal midazolam 3 mcg/kg 20 $1.72 \pm 6.5 \text{ mon.}$ 2.0 mse	Millar et al. 2018 [39]	IN DEX.	2.5 mcg/kg	140	12.5 [8–17] mon.	Before the procedure	Outpatient TTEcho
(1) IN DEX. 2 mcg/kg 30 46.2 ± 10.07 yrs. 30 min. before operation IN DEX.1 IN Saline 0.02 m/kg 30 4.67 ± 1.17 yrs. 2 mcg/kg 30 4.77 ± 1.17 yrs. 2 mcg/kg 30 4.67 ± 1.17 yrs. 2 mcg/kg 30 4.67 ± ± 1.17 yrs. 2 mcg/kg 30 4.67 ± ± 1.17 yrs. 2 mcg/kg 30 4.67 ± ± ± ± 5.57 yrs. 30 4.67 ± ± ± ± ± ± ± ± ± ± ± ± ± ± ± ± ± ± ±		Oral pentobarbital	5 mg/kg	139	13 [9–17] mon.		
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	GAO et al. 2018 [40]	IN DEX.	2 mcg/kg	30	46.2 ± 10.07 yrs.	30 min. before operation	Dental rehabilitation under GA
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		IN Saline	0.02 ml/kg	30	43.6 ± 12.92 yrs.		
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	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 SalineIn the same 30 4.37 ± 1.3 yrs.IN DEX. + buccal placebo $3 mcg/kg$ 136 $3.50.028.0-44.8$) $30-40$ min. before the procedureIN DEX. + buccal midazolam $3 mcg/kg$ 136 $35.0(28.0-44.8)$ $30-40$ min. before the procedureIN DEX. + buccal midazolam $3 mcg/kg$ 136 $34.(28.0-46.0)$ yrs. $1100000000000000000000000000000000000$		IN DEX. 2	2 mcg/kg	30	4.53 ± 1.55 yrs.		
volumevolumeIN DEX. + buccal placebo3 mcg/kg13635.0 (28.0-44.8)30-40 min. before the procedureIN DEX. + buccal midazolam3 mcg/kg+0.2 mg13934 (28.0-46.0) yrs.IN DEX. + buccal midazolam3 mcg/kg-0.2 mg13934 (28.0-46.0) yrs.IN DEX. + buccal midazolam3 mcg/kg2017.2 ± 6.3 mon.25 min. before anesthesia inductionIN DEX. + buccal midazolam3 mcg/kg2017.2 ± 6.3 mon.25 min. before anesthesia inductionIN DEX. + IN DEX.2 mcg/kg882.8 ± 0.8 yrs1 h before the procedureIN DEX. + IN KETAMINE3 mg/kg + 1 mcg/kg604.56 ± 0.59 yrs30 m before the procedureOral Midazolam0.5 mg/kg604.56 ± 0.59 yrs30 m before the procedureIN DEX. + DUEX. + DUEX		IN Saline	In the same	30	4.37 ± 1.3 yrs.		
IN DEX. + buccal placebo 3 mcg/kg 136 35.0 (28.0-44.8) 30-40 min. before the procedure ND EX. + buccal midazolam $3 mcg/kg + 0.2 mg$ 138 $yrs.$ $yrs.$ IN DEX. + buccal midazolam $3 mcg/kg + 0.2 mg$ 139 $34 (28.0-46.0) yrs.$ $30-40 \text{ min. before the procedure}$ IN DEX. + buccal midazolam $3 mcg/kg + 0.2 mg$ 139 $34 (28.0-46.0) yrs.$ 100 more IN DEX. + buccal midazolam $3 mcg/kg + 0.2 mg$ $20 - 17.2 \pm 6.3 \text{ mon.}$ $25 \text{ min. before anesthesia induction}$ IN DEX. $2.01 m/kg$ $20 - 17.2 \pm 6.3 \text{ mon.}$ 10 more IN DEX. $2.01 m/kg$ $20 - 17.2 \pm 6.3 \text{ mon.}$ 10 more IN DEX. $3 mg/kg + 1 mcg/kg$ $88 - 2.8 \pm 0.8 yrs$ $11 \text{ before the procedure}$ IN DEX. $3 mg/kg + 1 mcg/kg$ $60 - 4.56 \pm 0.59 yrs$ $30 \text{ m before the procedure}$ IN DEX. $0.5 mg/kg$ $60 - 5.14 \pm 160 yrs$ $30 \text{ m before the procedure}$			volume				
NDEX. + buccal midazolam $3mcg/kg + 0.2 mg$ 139 $34(28.0 - 46.0)$ yrs.IN DEX.I N DEX.1 mcg/kg + 0.2 mg 139 $34(28.0 - 46.0)$ yrs.IN DEX.0.01 m/kg 20 17.2 ± 6.3 mon. 25 min. before anesthesia inductionIN DEX.0.01 m/kg 20 18.0 ± 6.6 mon. 180 ± 6.6 mon.IN DEX.2.001 m/kg 20 18.0 ± 6.6 mon. 180 ± 6.6 mon.IN DEX.2.001 m/kg 20 18.0 ± 6.6 mon. 11 before the procedureIN DEX.3.mg/kg + 1 mcg/kg kg kg kg IN DEX.2.mcg/kg 60 4.56 ± 0.59 yrs 30 m before the procedureOral Midazolam $0.5 mg/kg$ 60 5.14 ± 160 yrs 30 m before the procedureIN METAMINE $5 mo/kg$ 60 5.14 ± 160 yrs 30 m before the procedure	Li et al. 2019 [42]	IN DEX. + buccal placebo	3 mcg/kg		35.0 (28.0-44.8)	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.IN DEX.1 mcg/kg 20 17.2 ± 6.3 mon. 25 min. before anesthesia inductionIN DEX.0.01 m//kg 20 17.2 ± 6.3 mon. 25 min. before anesthesia inductionIN DEX. $2.0 \sin/kg$ 20 17.2 ± 6.3 mon. 25 min. before anesthesia inductionIN DEX. $2.0 \sin/kg$ 20 18.0 ± 6.6 mon. 16 mon.IN DEX. $2 mcg/kg$ 88 2.8 ± 0.8 yrs 1 h before the procedureIN DEX. $3 mg/kg + 1 mcg/kg$ kg kg IN DEX. $2 mcg/kg$ 60 4.56 ± 0.59 yrs 30 m before the procedureOral Midazolam $0.5 mg/kg$ 60 5.14 ± 160 yrs 30 m before the procedureIN KETAMINE $5 mc/kg$ 60 5.14 ± 160 yrs 30 m before the procedure					yrs.		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		IN DEX. + buccal midazolam	3 mcg/kg +0.2 mg		34 (28.0-46.0) yrs.		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	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
IN DEX. 2 mcg/kg 88 2.8 \pm 0.8 yrs 1 h before the procedure IN KETAMINE .5 mg/kg 88 2.8 \pm 0.8 yrs 1 h before the procedure IN DEX +IN KETAMINE 3 mg/kg + 1 mcg/ kg kg 60 4.56 \pm 0.59 yrs 30 m before the procedure Oral Midazolam 0.5 mg/kg 60 5.14 \pm 160 yrs 30 m before the procedure IN DEX. 1 mcg/kg 60 5.14 \pm 160 yrs 30 m before the procedure IN METAMINE 5 mcg/kg 60 5.14 \pm 160 yrs 30 m before the procedure IN METAMINE 5 mcg/kg 60 5.14 \pm 160 yrs 30 m before the procedure		IN Saline	0.01 ml/kg	20	18.0±6.6 mon.		bronchoscopy
IN KETAMINE 5 mg/kg IN DEX +IN KETAMINE 3 mg/kg + 1 mcg/ kg N DEX +IN KETAMINE 3 mg/kg + 1 mcg/ kg N DEX. 2 mg/kg 60 4.56 \pm 0.59 yrs 30 m before the procedure Oral Midazolam 0.5 mg/kg 60 5.14 \pm 160 yrs 30 m before the procedure IN METAMINE 5 mod/sg	Aly.A(2020)	IN DEX.	2 mcg/kg	88	2.8 ± 0.8 yrs	1 h before the procedure	Cardiac catheterization
IN DEX +IN KETAMINE $3 \text{ mg/kg} + 1 \text{ mcg/}$ kg N DEX. 2 mcg/kg 60 $4.56 \pm 0.59 \text{ yrs}$ 30 m before the procedure Oral Midazolam 0.5 mg/kg 60 $5.14 \pm 160 \text{ yrs}$ 30 m before the procedure IN DEX. 1 mcg/kg 60 $5.14 \pm 160 \text{ yrs}$ 30 m before the procedure IN KFTAMINE 5 mcd/cg	[44]	IN KETAMINE	.5 mg/kg				
() IN DEX. kg (0 4.56 \pm 0.59 yrs 30 m before the procedure Oral Midazolam 0.5 mg/kg 60 5.14 \pm 160 yrs 30 m before the procedure IN DEX. $1 m g/kg$ 60 5.14 \pm 160 yrs 30 m before the procedure IN KFTAMINE 5 mod/sg		In dex +in ketamine	3 mg/kg + 1 mcg/				
()IN DEX.2 mcg/kg60 4.56 ± 0.59 yrs30 m before the procedureOral Midazolam $0.5 mg/kg$ 60 5.14 ± 160 yrs30 m before the procedureIN DEX.1mcg/kg 60 5.14 ± 160 yrs30 m before the procedure			kg				
Oral Midazolam 0.5mg/kg IN DEX. 1mcg/kg 60 $5.14 \pm 160 \text{yrs}$ 30 m before the procedure IN KETAMINE 5mc/kg	Wang et al(2020)	IN DEX.	2 mcg/kg	60	$4.56 \pm 0.59 \text{ yrs}$	30 m before the procedure	Dental rehabilitation under GA
IN DEX. 1 mcg/kg 60 $5.14 \pm 160 \text{ yrs}$ 30 m before the procedure IN KETAMINE 5 mc/kg	[45]	Oral Midazolam	0.5 mg/kg				
IN KETAMINE	Arun et al(2022)	IN DEX.	1mcg/kg	60	$5.14 \pm 160 \text{ yrs}$	30 m before the procedure	Various surgeries
	[46]	IN KETAMINE	.5 mg/kg				

other premedication treatments. (RR = 0.64 [0.54, 0.77] 95% Cl; $I_2 = 84\%$; 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; I² = 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; I² = 88%; *P* = 0.0001) (Figure 6).

11.1.5. Heart rate

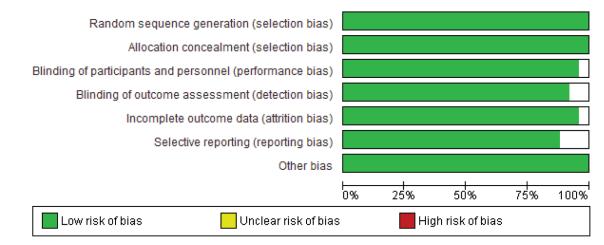
Heart rate was reported from 8 studies [21,22,24,27,35,43,44,46] in total 311 patients showed premedication with Intranasal dexmedetomidine also significantly lowered heart rate (Mean difference = -6.67 [-8.37, -4.97]; 95% CI; $I^2 = 94\%$; P = 0.00001) (Figure 7).

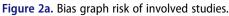
12. Discussion

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





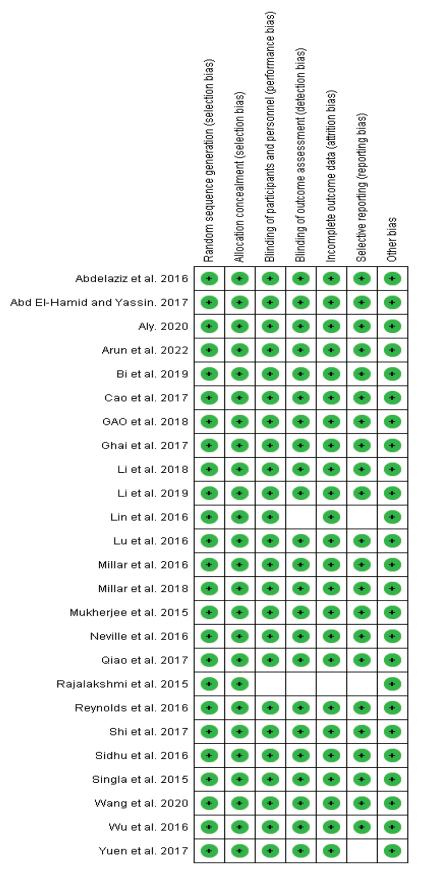
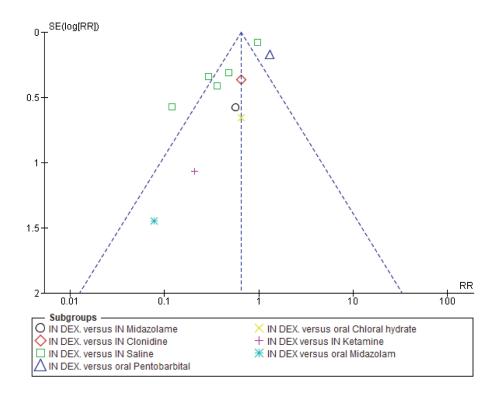
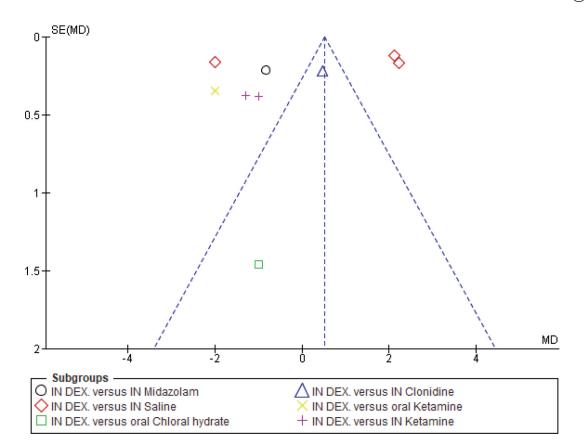


Figure 2b. Bias summary risk depends on Cochrane risk of bias assessment tool; risk of bias domains includes mainly (bias of selection, performance, detection, attrition, and reporting).



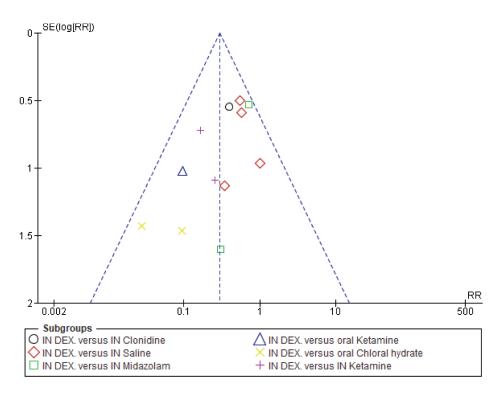
	IN DEX	κ.	Other	S		Risk Ratio		Risk Ratio
Study or Subgroup I.1.1 IN DEX. versus IN Midazolam		Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Abdelaziz et al. 2016	4	33	7	33	3.7%	0.57 [0.18, 1.77]	2016	
Subtotal (95% CI)		33		33	3.7%	0.57 [0.18, 1.77]		-
otal events	4		7					
Heterogeneity: Not applicable								
Fest for overall effect: Z = 0.97 (P =	0.33)							
1.1.2 IN DEX. versus IN Clonidine								
Mukherjee et al. 2015	9	40	14	40	7.5%	0.64 [0.31, 1.31]	2015	
Subtotal (95% CI)		40		40	7.5%	0.64 [0.31, 1.31]		-
Fotal events Heterogeneity: Not applicable	9		14					
Fest for overall effect: Z = 1.21 (P =	0.22)							
I.1.3 IN DEX. versus IN Saline								
_in et al. 2016	7	30	24	30	12.8%	0.29 [0.15, 0.57]	2016	_ _
Abd El-Hamid and Yassin. 2017	3	43	24	43	13.4%	0.12 [0.04, 0.37]		
GAO et al. 2018	27	30	28	30	15.0%	0.96 [0.83, 1.12]		+
ietal. 2018	9	30	19	30	10.2%	0.47 [0.26, 0.87]		
3i et al. 2019	5	20	14	20	7.5%	0.36 [0.16, 0.80]	2019	<u> </u>
Subtotal (95% CI)		153		153	58.8%	0.46 [0.37, 0.58]		•
Fotal events	51		110					
Heterogeneity: Chi ² = 95.95, df = 4 Test for overall effect: Z = 6.54 (P <		001); I ^z	= 96%					
.1.4 IN DEX. versus oral Pentoba								
fillar et al. 2018	51	140	39	139	20.9%	1.30 [0.92, 1.83]	2010	-
Subtotal (95% CI)	51	140	35	139	20.9%	1.30 [0.92, 1.83]	2010	•
otal events	51		39					-
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P =	0.14)							
I.1.5 IN DEX. versus oral Chloral h	ydrate							
/uen et al. 2017	4	107	5	87	2.9%	0.65 [0.18, 2.35]	2017	
Subtotal (95% CI)		107	_	87	2.9%	0.65 [0.18, 2.35]		
Fotal events	4		5					
Heterogeneity: Not applicable	0.61\							
est for overall effect: Z = 0.66 (P =	0.51)							
.1.6 IN DEX versus IN Ketamine								
Ny. 2020 Subtotal (95% CI)	1	29 29	5	30 30	2.6% 2.6%	0.21 [0.03, 1.67] 0.21 [0.03, 1.67]	2020	
otal events	1	29	5	30	2.070	0.21 [0.03, 1.07]		
Heterogeneity: Not applicable	1		5					
est for overall effect: Z = 1.48 (P =	0.14)							
1.1.7 IN DEX versus oral Midazola			-	~~		0.00.00.00.00.00	2022	
Vang et al. 2020 Subtotal (95% CI)	0	30 30	6	30 30	3.5% 3.5%	0.08 [0.00, 1.31] 0.08 [0.00, 1.31]	2020	
fotal events	0	20	6	20	3.3%	0.00 [0.00, 1.31]		
leterogeneity: Not applicable	U		ь					
Fest for overall effect: Z = 1.77 (P =	0.08)							
fotal (95% CI)		532		512	100.0%	0.64 [0.54, 0.77]		•
	120	352	186	512	.00.070	0.04 [0.04, 0.17]		•
otal events			100					1
Γotal events Heteroαeneitv: Chi≅ = 63.62. df = 10		00011	l [≈] = 84%					
otal events Heterogeneity: Chiª = 63.62, df = 10 Test for overall effect: Z = 4.88 (P ≺) (P < 0.00	0001);	I² = 84%					0.01 0.1 1 10 100 Favours [IN DEX] Favours [Others]

Figure 3. Emergence agitation.



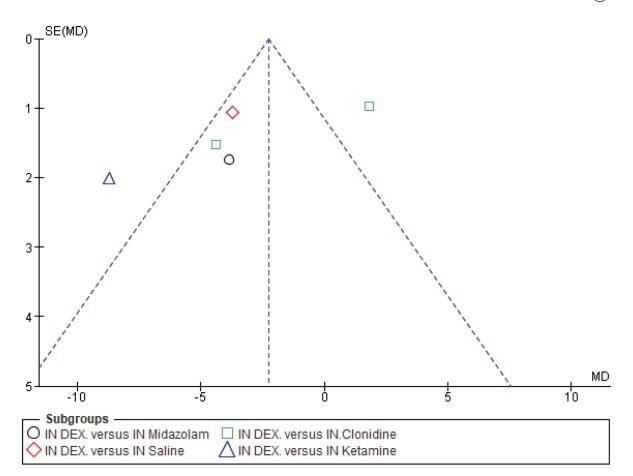
		N DEX.			Others	_		Mean Difference		Mean Difference
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
.1.1 IN DEX. versus IN N				0.00	0.00		10.5%	0.0074.05.0.441	0045	
Singla et al. 2015 Subtotal (95% CI)		0.855	30 <mark>30</mark>	3.23	0.82	30 30	10.5% 10.5%	-0.83 [-1.25, -0.41] -0.83 [-1.25, -0.41]	2015	•
leterogeneity: Not applic		_								
'est for overall effect: Z =	3.84 (P =	: 0.0001)							
.1.2 IN DEX. versus IN S	aline									
ajalakshmi et al. 2015	3.23	0.568	30	1.13	0.345	30	33.4%	2.10 [1.86, 2.34]	2015	-
idhu et al. 2016	3.36	0.938	35	1.14	0.355	35	17.1%	2.22 [1.89, 2.55]	2016	
u et al. 2016 Subtotal (95% CI)	4	0.74	40 105	6	0.74	41 106	18.2% 68.6%	-2.00 [-2.32, -1.68] 1.04 [0.88, 1.21]	2016	- ↓
leterogeneity: Chi² = 468	6.47, df=	2 (P < 0	.00001); I ² = 10	00%					
est for overall effect: Z =	12.35 (P	< 0.000	01)							
.1.3 IN DEX. versus oral	Chloral	hydrate								
1illar et al. 2016	13	5	50	14	9	50	0.2%	-1.00 [-3.85, 1.85]	2016	
Subtotal (95% CI)			50			50	0.2%	-1.00 [-3.85, 1.85]		
leterogeneity: Not applic										
est for overall effect: Z =	0.69 (P =	: 0.49)								
.1.4 IN DEX. versus IN C	lonidine									
idhu et al. 2016	3.36	0.938	35	2.89	0.932	35	9.8%	0.47 (0.03, 0.91)	2016	
Subtotal (95% CI)			35			35	9.8%	0.47 [0.03, 0.91]		◆
leterogeneity: Not applic	able									
est for overall effect: Z =	2.10 (P =	: 0.04)								
.1.5 IN DEX. versus oral	Ketamin	e								
aiao et al. 2017	1	0.18	42	3	2.22	41	4.1%	-2.00 [-2.68, -1.32]	2017	
Subtotal (95% CI)			42			41	4.1%	-2.00 [-2.68, -1.32]		◆
leterogeneity: Not applic										
est for overall effect: Z =	5.75 (P =	0.0000	1)							
.1.6 IN DEX. versus IN K	etamine									
ly. 2020	2	1.48	29	3	1.48	30	3.3%	-1.00 [-1.76, -0.24]	2020	
run et al. 2022	2.5	0.5	30	3.8	2	30		-1.30 [-2.04, -0.56]	2022	
ubtotal (95% CI)			59			60	6.8%	-1.15 [-1.68, -0.63]		◆
leterogeneity: Chi² = 0.3				%						
'est for overall effect: Z =	4.28 (P =	0.0001)							
otal (95% CI)			321			322	100.0%	0.51 [0.38, 0.65]		
leterogeneity: Chi ² = 636	45 df-	0 /0 ~ 0		· IZ - 00	306	JLL	100.0%	0.01 [0.00, 0.00]	-	*
est for overall effect: Z =				, r = 98	9 /0					-4 -2 0 2 4
est for subgroup differen				5 (P <	0 00001	D P= 9	17 1 %			Favours [IN DEX.] Favours [Others]
Source and an an an and a second		- 103.	or, ar=	011 -	5.00001	·				

Figure 4. Sedation score.



Study of Eularoup	IN DE		Other		Weight	Risk Ratio	Veer	Risk Ratio
Study or Subgroup 3.1.1 IN DEX. versus IN Clonidine	Events	rotal	Events	rotal	weight	M-H, Fixed, 95% Cl	rear	M-H, Fixed, 95% Cl
Mukherjee et al. 2015	4	40	10	40	11.2%	0 40 00 14 1 171	2016	
Subtotal (95% CI)	4	40	10	40	11.2%	0.40 [0.14, 1.17] 0.40 [0.14, 1.17]	2015	.
Total events	4		10			0110 [0111]		-
Heterogeneity: Not applicable								
Fest for overall effect: Z = 1.67 (P =	0.09)							
3.1.2 IN DEX. versus IN Saline								
u et al. 2016	1	40	3	41	3.3%	0.34 [0.04, 3.15]	2016	
Abdelaziz et al. 2016	5	33	9	32	10.2%	0.54 [0.20, 1.43]	2016	
Abd El-Hamid and Yassin. 2017	4	43	7	43	7.8%	0.57 [0.18, 1.81]	2017	
3hi et al. 2017	2	30	2	30	2.2%	1.00 [0.15, 6.64]	2017	
Subtotal (95% CI)		146		146	23.7%	0.57 [0.29, 1.09]		-
Fotal events	12		21					
Heterogeneity: Chi¤ = 0.56, df = 3 (F Fest for overall effect: Z = 1.69 (P =		I ² = 0%						
3.1.3 IN DEX. versus IN Midazolam								
Veville et al. 2016	0	20	1	18	1.8%	0.30 [0.01, 6.97]	2016	
Abdelaziz et al. 2016	5	33	7	33	7.8%	0.71 [0.25, 2.02]	2016	
Subtotal (95% CI)		53		51	9.6%	0.64 [0.24, 1.71]		-
Fotal events Heterogeneity: Chi≇ = 0.26, df = 1 (F Fest for overall effect: Z = 0.89 (P =		I = 0%	8					
3.1.4 IN DEX. versus oral Ketamin	е							
Qiao et al. 2017	1	42	10	41	11.3%	0.10 [0.01, 0.73]	2017	.
Subtotal (95% CI)		42		41	11.3%	0.10 [0.01, 0.73]		
Fotal events	1		10					
Heterogeneity: Not applicable								
Fest for overall effect: Z = 2.27 (P =	0.02)							
8.1.5 IN DEX. versus oral Chloral h	ydrate							
Cao et al. 2017	0	71	17	70	19.8%	0.03 [0.00, 0.46]	2017	
/uen et al. 2017	0	87	6	107	6.5%	0.09 [0.01, 1.65]	2017	
Subtotal (95% CI)		158		177	26.3%	0.04 [0.01, 0.32]		
Fotal events	0		23					
Heterogeneity: Chi² = 0.37, df = 1 (F Fest for overall effect: Z = 3.11 (P =		I* = 0%						
3.1.6 IN DEX. versus IN Ketamine								
Ny. 2020	1	29	4	30	4.4%	0.26 [0.03, 2.18]	2020	
Arun et al. 2022	2	30	12	30	13.5%	0.17 [0.04, 0.68]		I
Subtotal (95% CI)		59		60	17.9%	0.19 [0.06, 0.61]		•
Total events	3		16					
Heterogeneity: Chi² = 0.11, df = 1 (F Fest for overall effect: Z = 2.79 (P =		I² = 0%						
Fotal (95% CI)		498		515	100.0%	0.30 [0.20, 0.45]		◆
Fotal events	25		88					
Heterogeneity: Chi ² = 12.48, df = 11	(P = 0.3	3); I ² = 1						0.002 0.1 1 10 5
	0.00001)							0.002 0.1 1 10 :

Figure 5. Nausea and vomiting.



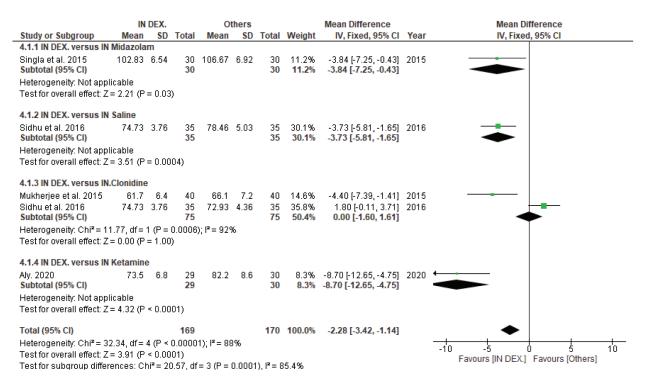
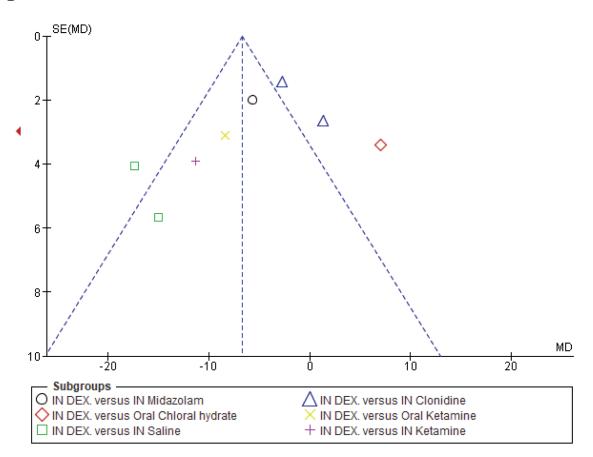


Figure 6. Arterial blood pressure.

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



	IN	DEX.		0	thers			Mean Difference		Mean Difference
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
5.1.1 IN DEX. versus IN	Midazola	m								
Singla et al. 2015 Subtotal (95% CI)	94.23	9.33	30 <mark>30</mark>	99.93	5.71	30 30	18.9% 18.9%	-5.70 [-9.61, -1.79] - 5.70 [-9.61, -1.79]	2015	•
Heterogeneity: Not appli Test for overall effect: Z =		= 0.00	4)							
5.1.2 IN DEX. versus Or	al Chlora	l hydra	ite							
Millar et al. 2016 Subtotal (95% Cl)	35	18	50 50	28	16	50 50	6.5% 6.5%	7.00 [0.32, 13.68] 7.00 [0.32, 13.68]	2016	-
Heterogeneity: Not appli Test for overall effect: Z =		= 0.04))							
5.1.3 IN DEX. versus IN	Saline									
Sidhu et al. 2016	106	7.1	35	123.4	22.9	35	4.6%	-17.40 [-25.34, -9.46]	2016	
Bi et al. 2019 Subtotal (95% CI)	136	21	20 55	151	14	20 55	2.4% 7.0%	-15.00 [-26.06, -3.94] - 16.58 [-23.04, -10.13]	2019 -	•
Heterogeneity: Chi ² = 0.1 Test for overall effect: Z =				= 0%						
5.1.4 IN DEX. versus IN	Clonidine	9								
Mukherjee et al. 2015	60.5	5.7	40	63.2	7.2	40	35.7%	-2.70 [-5.55, 0.15]		
Sidhu et al. 2016 Subtotal (95% CI)	106	7.1	35 75	104.7	14	35 75	10.7% 46.4%	1.30 [-3.90, 6.50] - 1.78 [-4.27, 0.72]	2016	•
Heterogeneity: $Chi^2 = 1.3$ Test for overall effect: Z =				= 43%						
5.1.5 IN DEX. versus Or	al Ketam	ine								
Qiao et al. 2017 Subtotal (95% CI)	94.19	14.89	42 42	102.63	13.29	41 41	7.9% 7.9%	-8.44 [-14.51, -2.37] -8.44 [-14.51, -2.37]	2017	
Heterogeneity: Not appli Test for overall effect: Z =		= 0.00	6)							
5.1.6 IN DEX. versus IN	Ketamin	e								
Aly. 2020	86.9	18.3	29	98.2	10.6	30	4.9%	-11.30 [-18.96, -3.64]	2020	
Arun et al. 2022 Subtotal (95% CI)	78.8	7.34	30 59	112.57	14.64	30 60		-33.77 [-39.63, -27.91] -25.48 [-30.14, -20.82]	2022	
Heterogeneity: Chi ² = 20 Test for overall effect: Z =				1); I² = 98	5%					
Total (95% CI)			311			311	100.0%	-6.67 [-8.37, -4.97]		•
Heterogeneity: $Chi^2 = 12$ Test for overall effect: Z =				01); I 2 = 9	94%				-	-20 -10 0 10 20
Test for subgroup differe				lf=5 (P <	0.0000)1), I²=	95.2%			Favours [IN DEX.] Favours [Others]

Figure 7. Heart rate.

than intravenous administration. Yuen et al. revealed that using $1 \mu g/kg$ Dexmedetomidine nose drops prior to surgery had a good sedative effect in 62% of the children having surgery [16]. Li et al. utilized $1.0 \mu g/kg$ 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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