ARTICLE

Efficacy of intranasal Dexmedetomidine in combination with Ketamine as premedication and sedation in pediatric patients: a systematic review and meta-analysis

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OBJECTIVE: To compare the efficacy and safety of the combination of Dexmedetomidine (Dex) and Ketamine (Ket) administered via the intranasal (IN) route on sedation of children aged 0 to 12 years old prior to elective surgery or procedural sedation as compared to Intranasal Dexmedetomidine.

METHOD: Relevant studies were identified after a literature search on electronic databases as PubMed, Cochrane Library, Google Scholar and Science Direct. Meta-analyses of mean differences were performed to examine differences in sedation onset and recovery times between IN Dex-Ket and IN Dex. Meta-analyses of proportions were performed to estimate the incidence of sedation success, satisfactory sedation at parental separation and mask induction, and incidence of adverse events. Review Manager 5.4.1 was used for statistical analysis.

RESULT: Six articles (388 patients) were included. The overall incidence of sedation success was higher among children premedicated with IN Dex-Ket (RR = 1.05; 95%CI = 0.97,1.13; P = 0.27, I^2 = 20%) however was not statistically significant. Children given IN Dex-Ket had faster sedation onset time (WMD = -7.17; 95%CI = -12.44, -1.89; P=0.008) with greater incidence of satisfactory sedation at mask induction (RR = 0.71; 95%CI = 0.53, 0.94; P = 0.02). There was no significant difference as to recovery time and incidence of adverse events among the groups.

CONCLUSION: Premedication with IN Dex-Ket is as safe as IN Dex but of better efficacy as evidenced by faster sedation onset time and smoother inhalational induction without increasing clinically relevant adverse events.

KEYWORDS: *Dexmedetomidine, ketamine, premedication, intranasal, pediatric*

INTRODUCTION

The preoperative period can be a stressful and traumatic time for children undergoing surgery and worrisome for the anesthesiologist and caregiver [1]. Anesthesiologists therefore must adopt strategies to reduce potential psychological trauma to children induced by forced inhalational induction of anesthesia. Premedication in children is helpful for both separating the

of anesthesia. A variety of pharmacological or behavioral interventions have been proposed as preoperative anxiolytics to minimize the distress of children in the operating room, however, no technique or pharmacologic agent has been found to be completely satisfactory in children. Despite its high bioavailability and rapid onset, the disadvantage of intravenous premedication is the requisite for cannulation. Intranasal administration is easy, non-invasive and usually well tolerated. Among children, it avoids the necessity of injections or bitter tasting oral drugs. Pooled studies on effective premedication via the intranasal route may foster increase in its use with a consequent decrease in observed parental separation anxiety, stormy inhalational induction and postoperative delirium and agitation.

Dexmedetomidine (Dex) is a highly selective a2-agonist that provides sedation which parallels natural sleep, anxiolysis, sympatholysis and an anesthetic-sparing effect without clinically significant respiratory depression; however, it is associated with modest reductions in heart rate and blood pressure [2,3]. Currently, dexmedetomidine is not approved for use in children in any country. As an off-label medication, it has been administered as an adjunct to anesthesia, both general and regional, in and out of the operating room for both surgical and medical procedures in children and for sedation in the pediatric ICU (PICU) with beneficial results [4]. A study by Li et al on the bioavailability of dexmedetomidine, revealed a marked difference between the nasal (40.7%), buccal (81%) and oral (16%) route [5,6]. A recent meta-analysis by Tervonen and colleagues on intranasal dexmedetomidine premedication in children concluded that it provided a more satisfactory sedation at parent separation and reduced the need for rescue analgesics compared with intranasal ketamine and oral midazolam [7]. As with intravenous dexmedetomidine, the intranasal route has the additional benefit of reduced postoperative nausea and vomiting and need for rescue analgesics[8]. However, there are some disadvantages of dexmedetomidine when it is used alone. First, the sedative effects of dexmedetomidine are concentration dependent. When the plasma concentration of dexmedetomidine is between 0.2 and 0.3 ng/ mL, the patients may be of arousable sedation, at a concentration above 1.9 ng/mL, the patients will be in deep sedation and difficult to arouse [9]. Similarly, dexmedetomidine has a dose dependent effect on mean arterial pressure (MAP) and heart rate. Where intravenous dexmedetomidine was used as a sole sedative for children undergoing procedural sedation, the incidence of bradycardia given intravenously and intranasally was 16% and 14% respectively [10,11]. Given the concentration dependent effects of dexmedetomidine on hemodynamics and arousal, it may be more effective to combine dexmedetomidine with another drug to compensate for the disadvantages of dexmedetomidine sedation rather than to simply increase the dose. Ketamine (Ket),

a racemic nonbarbiturate cyclohexamine derivative that exerts its effects via noncompetitive antagonism to N-methyl-D-aspartate (NMDA) receptors, is one of the most widely used drugs in pediatric anesthesia. In subanesthetic doses, Ketamine has sedative and analgesic properties with the benefit of retaining airway reflexes and can be given via several routes, including intranasally [12,13]. In children, sedation takes effect after approximately 5-10 minutes with peak plasma concentration in 20 minutes. Its undesirable effects include nausea and vomiting, increased salivation, excitatory behavior and its hemodynamic effects namely high blood pressure, tachycardia, and high cardiac output [14-16]. Recent literature supports that dexmedetomidine provides a synergy with ketamine, which would be advantageous in enabling a decrease in dosing of both sedatives. A retrospective analysis by Yang et al., on pediatric patients undergoing procedural sedation with a combination of intranasal dexmedetomidine and ketamine, showed a sedation success rate of 93% with onset time of 15 minutes, lower rates of adverse effects, in particular, bradycardia or hypotension than those in previous studies of dexmedetomidine as sole sedative [17]. In 2019, Oriby compared the effects of combined intranasal dexmedetomidine and oral ketamine versus intranasal midazolam as sedative premedication for children undergoing dental procedures, the study results revealed the combination had significantly more satisfactory and rapid onset of sedation, with more postoperative analgesia and less postoperative shivering in comparison to midazolam [18]. The potential of dexmedetomidine to attenuate the sympathetic response, provide sedation and decrease emergence agitation are properties that may be favorable in its combination with ketamine. The combination of dexmedetomidine with ketamine has a pharmacologic rationale, as the two medications exhibit complementary pharmacologic effects. Though there have been reviews on the combined usage of Dexmedetomidine and Ketamine as premedication for procedural sedation, none have been published to date on its efficacy and safety with combined use solely via the intranasal route.

The general objective of this study is to compare the efficacy and safety of the combination of Dexmedetomidine and Ketamine administered via the intranasal route on sedation of children aged 0 to 12 years old prior to elective surgery or procedural sedation as compared to Intranasal Dexmedetomidine. The specific objectives are to determine differences in sedation onset time, incidence of satisfactory sedation at parent separation, incidence of satisfactory sedation at mask induction, recovery time and incidence of adverse events such as bradycardia, hypotension, hypoxemia, postoperative nausea and vomiting (PONV), nasal irritation and emergence agitation using combination of Dexmedetomidine and Ketamine administered

via intranasal route as compared to intranasal Dexmedetomidine.

METHODOLOGY

A systematic approach was used to identify publications that evaluated the efficacy and safety of a combination of intranasal dexmedetomidine and ketamine premedication in children. This systematic review and meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 and the Cochrane Review Methods [19]. Articles were lifted from the electronic databases of PubMed, Cochrane Library, Clinical Trials, Science Direct, Google Scholar and local databases such as Herdin Plus from its establishment until August 2023 and restricted only to studies written in English language. The search was conducted using the following MeSH terms: ("dexmedetomidine", AND "ketamine" OR "Ketodex") AND ("premedication" OR "sedation") AND ("intranasal" or "intranasally") AND ("pediatric" OR "child" OR "children) AND ("anesthesia") AND ("randomized trial" OR "randomized controlled trial" OR "RCT"). Additional articles were obtained via cross-referencing from selected articles.

Two reviewers independently identified all the studies using predefined selection criteria. A third reviewer arbitrated disagreements that occurred in the primary study selection. Studies were included in this meta-analysis if they satisfied the following criteria: (1) full text randomized controlled trials, (2) children aged 0 to 12 years old, (3) American Society of Anesthesiologists (ASA) physical status classification I-III, (4) scheduled for elective surgery or procedural sedation, (5) received as premedication a combination of dexmedetomidine and ketamine via the intranasal route. Exclusion criteria include (1) children over 12 years old, (2) ASA IV-V, (3) observational studies, case series, commentaries.

Studies derived from the different electronic databases were screened and checked for duplicates. After which, two researchers independently reviewed each of the titles and abstracts. In case of disagreements between two researchers, this was resolved by discussion. If the disagreement was not resolved, a third researcher was called in to serve as arbitrator. Full-text of all journals that met the eligibility criteria were retrieved for full-text review. Data collection was performed independently by two researchers using a data collection form in Microsoft Excel 2021.

The primary outcome measure of this study was the incidence of sedation success of a combination of intranasal dexmedetomidine and ketamine as compared to intranasal dexmedetomidine given alone. Secondary outcomes include sedation onset time, incidence of satisfactory sedation at parental separation, incidence of satisfactory sedation

sedation at parental separation, incidence of satisfactory sedation at mask induction, recovery time and the incidence of adverse events namely, bradycardia, hypotension, hypoxemia, nasal irritation, PONV and emergence agitation.

The risk of bias among included studies was performed independently by two researchers using the Cochrane risk of bias (RoB 2.0) tool, which considers the methods of random sequence generation, allocation concealment, blinding of participants and the outcome estimator, incomplete reporting of outcome data, selective reporting of outcomes and other sources of bias risk. Studies with more than one area of unclear or high risk of bias were excluded from the analysis.

All statistical analyses were conducted using the Cochrane Collaboration Review Manager Software (RevMan version 5.4.1). The study reports continuous data as mean differences and their associated 95% confidence intervals (CIs) with analyses using weighted mean differences (WMDs) determined via the inverse variance method. Binary outcomes are reported as risk ratio (RR) with 95% CI. Heterogeneity testing was performed using the □2 test and the I^2 statistic. In this study, an I^2 statistic >50% and a □2 test with P value <0.10 was considered significant to indicate statistical heterogeneity. Random effects model was used due to clinical heterogeneity among study variables of included researches, as population (cardiac vs non-cardiac patients) and procedure (e.g. surgical, diagnostic procedures) despite minimal statistical heterogeneity. Subgroup and sensitivity analysis was performed to account for other possible sources of heterogeneity, such as the results of included studies.

The protocol was submitted to PCMC Institutional Review – Ethics Committee for expedited approval prior to proceeding, which was granted exemption from ethics review last August 23, 2023. Data confidentiality was observed throughout the process of this analysis.

RESULTS

Initial search identified 443 articles, with 27 publications from research databases, 33 from online registries, 381 records from website search engines and 2 from citation searching. Among those derived from research databases and registries, 15 full manuscripts were screened after removing 18 duplicated articles and an additional 19 records after screening their titles and abstracts. Among these, 5 publications were identified as potentially relevant studies. Nine studies were excluded due to the following reasons: 4 had a different control group and 5 studies utilized different methods of drug administration. As to publications derived via a website search engine (i.e., Google Scholar), only 3 publications were deemed acceptable after screening for eligibility and duplicates.

Two of these, one of which was a proposal for an ongoing clinical trial, were not retrieved despite attempts to contact its study authors. Thus, only 1 study was included using this search strategy. In total, six studies were included in the meta-analysis (Figure 1). Risk of bias analysis for each included study are shown in Figure 2. Four studies were assessed as having low risk of bias and two studies were assessed as having unclear risk due to unspecified information on allocation concealment. Publication bias was not assessed as the funnel plots derived may be inaccurate due to the low number (i.e., <10) of included studies.

A total of 388 patients, with ages ranging from 1 month to 7 years old, scheduled for elective surgery or procedural sedation with American Society of Anesthesiologists (ASA) classification scores I-III were included in the study. All of the patients received as premedication via the intranasal route either a combination of dexmedetomidine and ketamine or dexmedetomidine alone. The characteristics of the included studies are summarized in Table 1.

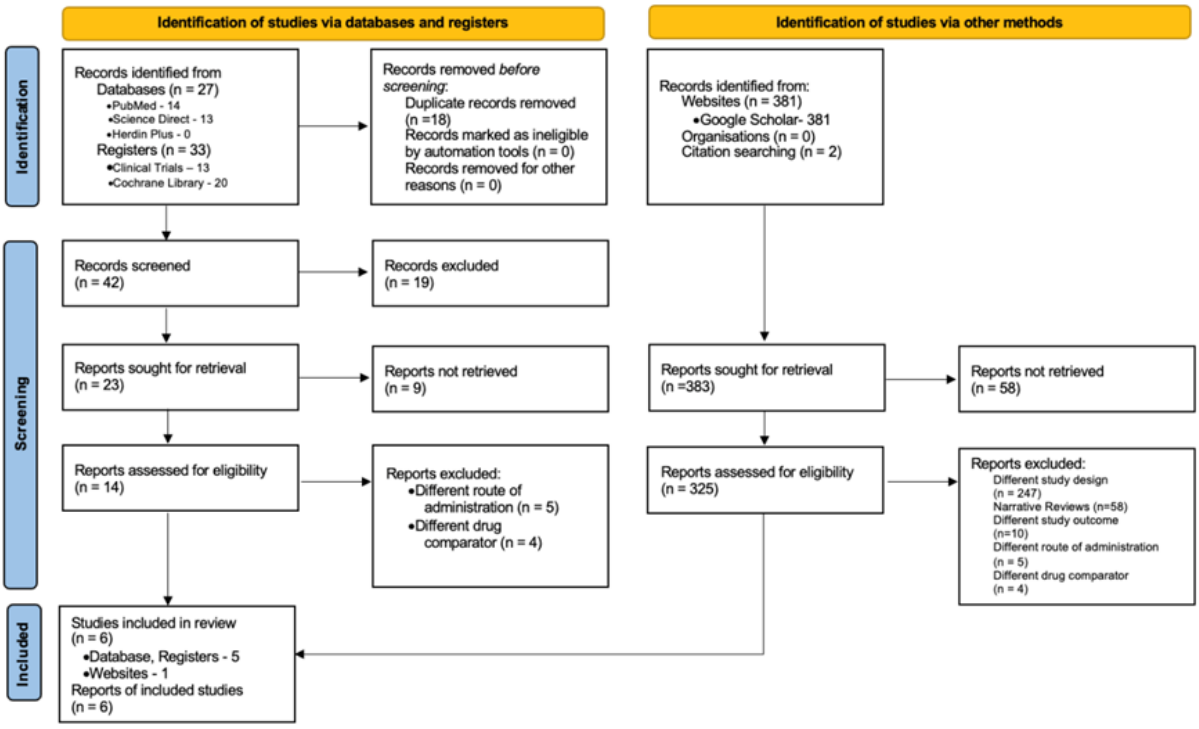
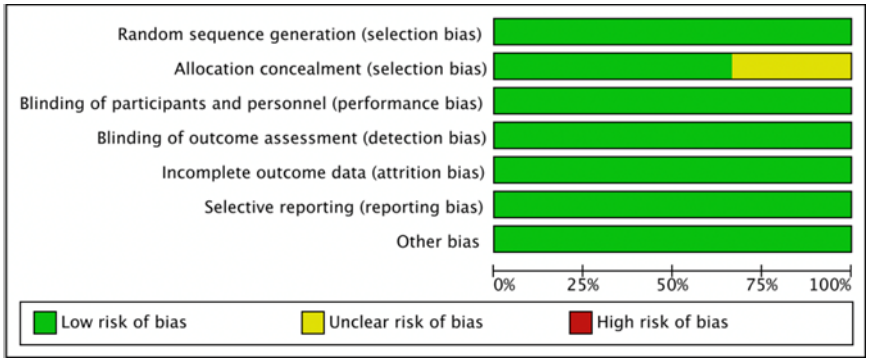


Figure 1. Flow Diagram of the literature search strategy



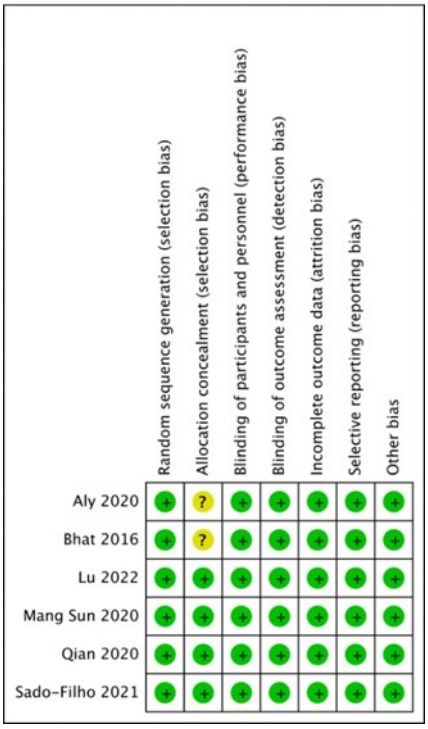


Figure 2. Cochrane Risk of Bias Assessment

Table 1. Characteristics of included studies

Primary Author	Year	N	Type of study	Age , ASA status, type of surgery	Inter-vention (Dose)	Com-parator	Primary Outcome	Secondary Outcome
Aly, A	2020	60	RCT	2-4 yrs. old, ASA I-III, for interven-tional cardi-ac catheter-ization	IN Dex (1mcg/ kg) + Ket (3mg/ kg)	IN Dex (2mcg/ kg)	Sedation success measured by child's behavior during venous cannulation	Onset of sedation, behavior at parental separation, propofol consumption during procedure, recovery time, incidence of postoperative agitation, adverse events
Bhat, R	2016	54	RCT	1-6 yrs. old, ASA I-II, for elective minor sur-gery	IN Dex (1mcg/ kg) + Ket (2mg/ kg)	IN Dex (1 mcg/ kg)	Level of sedation measured via 5 point sedation score	parental separation, mask acceptance, postoperative recovery, incidence of emergence agitation
Mang Sun, MM	2020	60	RCT	1 to 36 mos. old, ASA I-II, for transthorac-ic echocar-diography	IN Dex (2mcg/ kg) + Ket (1mg/ kg)	IN Dex (2mcg/ kg)	Change in hemodynamics (MAP, HR)	sedation success measured via MOAA/S. onset time, wake up time, discharge time, adverse events
Qian, B	2020	66	RCT	3 to 7 yrs. old, ASA I-II, for ton-sillectomy	IN Dex (2mcg/ kg) + Ket (2mg/ kg)	IN Dex (2mcg/ kg)	Sedation level assessed by Modified Observer Assessment of Alertness and Sedation (MOAA/ S) scale	sedation onset time, parental separation anxiety, acceptance of mask induction, emergence time, emergence delirium, postoperative pain intensity, length of PACU stay, adverse events

Table 1. Characteristics of included studies								
Sado-Filho, J	2021	88	RCT	1-7 yrs. old, ASA I-II, for dental restoration	IN Dex (2 mcg/kg) + Ket (1mg/kg)	IN Dex (2.5 mcg/kg)	Sedation success measured by children's behavior using OSUBRS	parental and dentist satisfaction, adverse events, recovery time
Lu, X	2022	60	RCT	1-6 yrs. old, ASA I-II, for lower abdominal or perineal surgery	IN Dex (1mcg/kg) + Ket (0.5mg/kg)	IN Dex (2mcg/kg)	Sedation success measured via Induction Compliance Checklist (ICC) scale	sedation success rate, preoperative anxiety scale score, time of reaching 2 points on the UMSS, parental separation anxiety scale, anesthesiologist satisfaction with induction based on VAS, emergence agitation scale, adverse effects

Of the six studies [20-25], five had available data on sedation success. There were a total of 319 patients with 159 in the intranasal dexmedetomidine – ketamine group and 160 in the intranasal dexmedetomidine group. Forest plot depicted as Figure 3 showed no difference in sedation success among patients premedicated with intranasal dexmedetomidine and ketamine as compared to intranasal dexmedetomidine alone (RR = 1.05; 95%CI = 0.97,1.13; P = 0.27, I^2 = 20%). As to sedation onset time, only two studies had available data. As depicted in figure 4, patients given a combination of intranasal dexmedetomidine and ketamine had faster sedation onset time compared to dexmedetomidine given alone (WMD = -7.17; 95%CI = -12.44, -1.89; P=0.008). Though substantial heterogeneity was noted to be significant (□2 = 7.56, I^2 = 87%, P=0.006), subgroup analysis was not performed due to the number of involved studies.

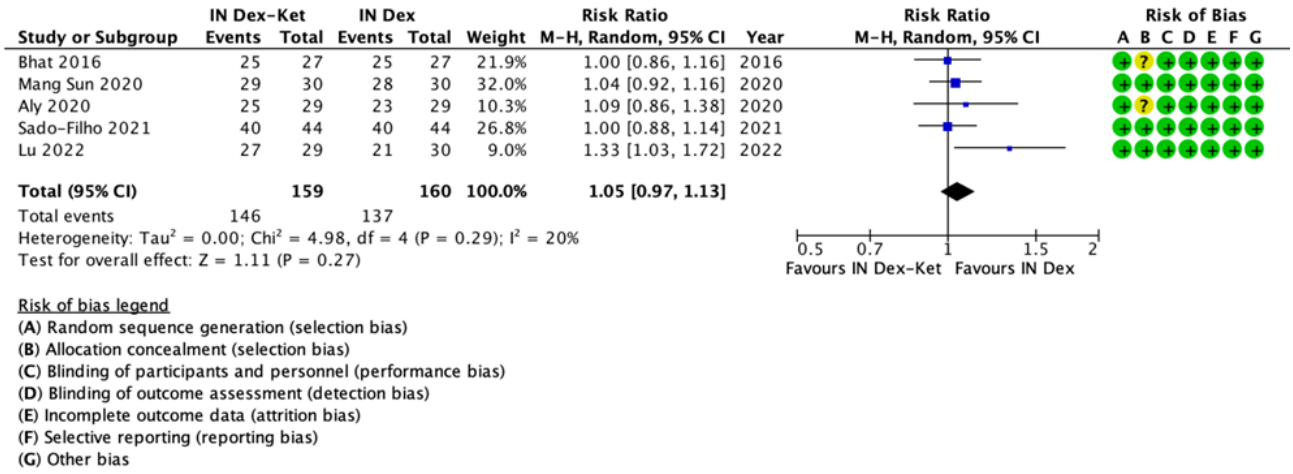


Figure 3. Incidence of sedation success

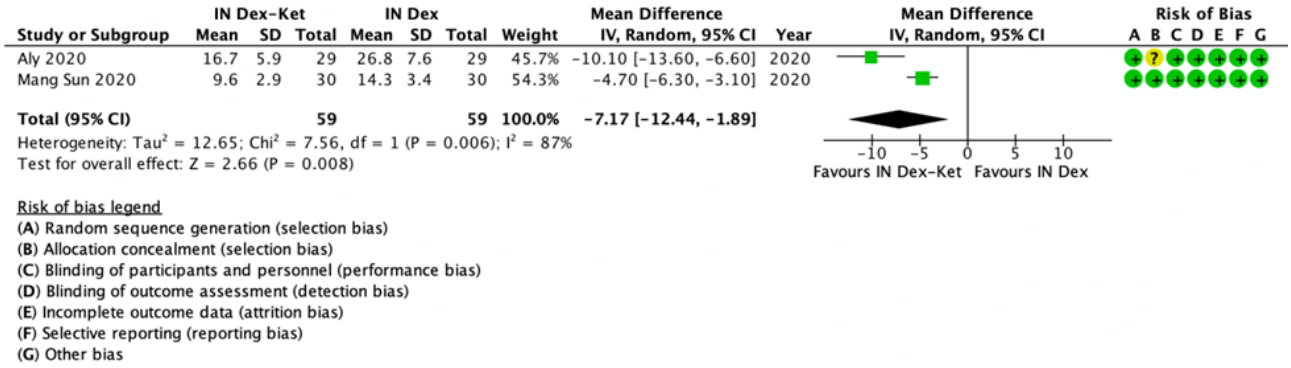


Figure 4. Sedation onset time

Satisfactory sedation at patient separation was reported in only 2 randomized controlled trials utilizing the Patient Separation Anxiety Score (PSAS). The study found no differences in satisfactory sedation at parent separation between intranasal dexmedetomidine and ketamine and dexmedetomidine alone (RR = 1.06; 95%CI = 0.97,1.15; P = 0.19) (Figure 5A). Similar to satisfactory sedation at parent separation, sedation status at mask induction was assessed using a 4 point Mask Acceptance Scale (MAS). Synthesis of data revealed patients premedicated with a combination of intranasal dexmedetomidine and ketamine were significantly sedated at mask induction as compared to those given dexmedetomidine alone (RR = 0.71; 95%CI = 0.53, 0.94; P = 0.02) (Figure 5B).

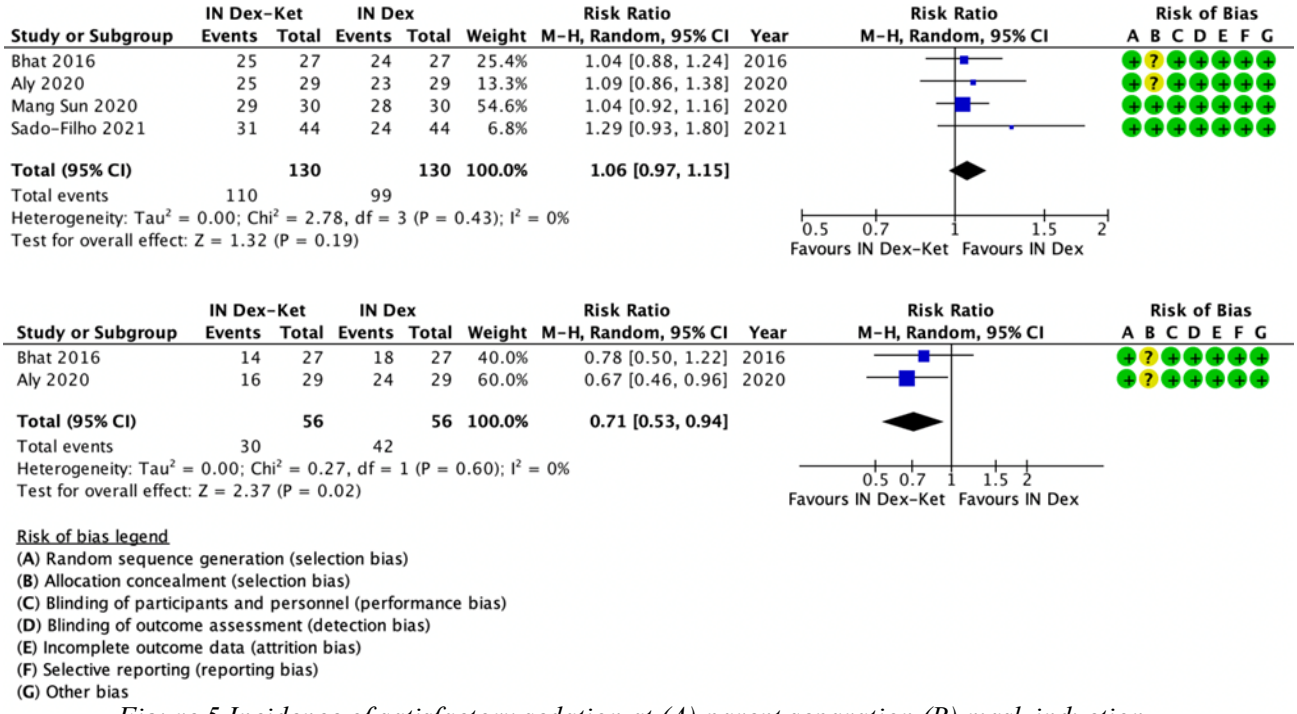


Figure 5 Incidence of satisfactory sedation at (A) parent separation (B) mask induction

Four trials reported the recovery time from premedication administration, however only 2 studies fulfilled this study's operational definition. Patients premedicated with intranasal dexmedetomidine and ketamine had faster recovery time compared to those given dexmedetomidine alone, however was not statistically significant (WMD = -0.84; 95% CI = -2.15,0.48; P=0.21; I^2 = 0%) (Figure 6).

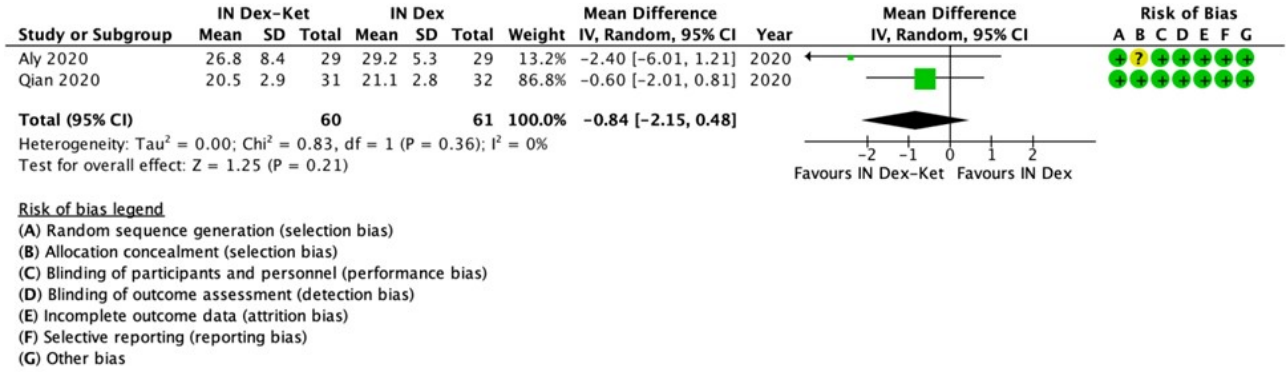
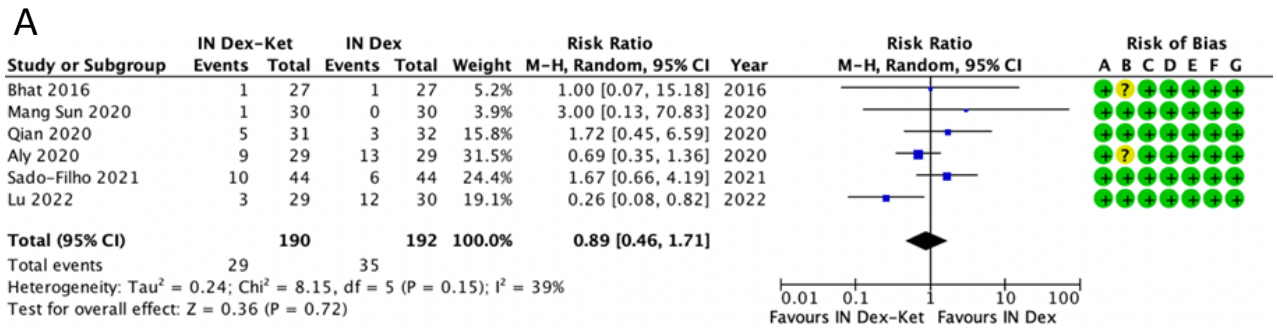


Figure 6. Recovery time

All six of the studies revealed the incidence of adverse effects of a combination of intranasal dexmedetomidine and ketamine as premedication as compared to intranasal dexmedetomidine alone. The forest plot in Figure 7A shows there is no difference on the likelihood of adverse events between intranasal dexmedetomidine and intranasal dexmedetomidine and ketamine given in combination (RR = 0.89; 95%CI = 0.46, 1.7; P=0.72; I^2 = 39%). A subgroup analysis of the different adverse effects associated with dexmedetomidine and ketamine use are shown in Figure 7B. There were no observed differences among both study groups as to the incidence of emergence agitation with the use of a combination of dexmedetomidine and ketamine (RR = 0.57; 95%CI = 0.22, 1.48; P=0.25; I^2=12%), and occurrence of postoperative nausea and vomiting (RR = 2.21; 95%CI = 0.51; 9.61; P = 0.29; I2=0%). All of the six included studies in the meta-analysis, noted no occurrence of bradycardia, hypoxemia, hypotension and nasal irritation, among all the study participants.



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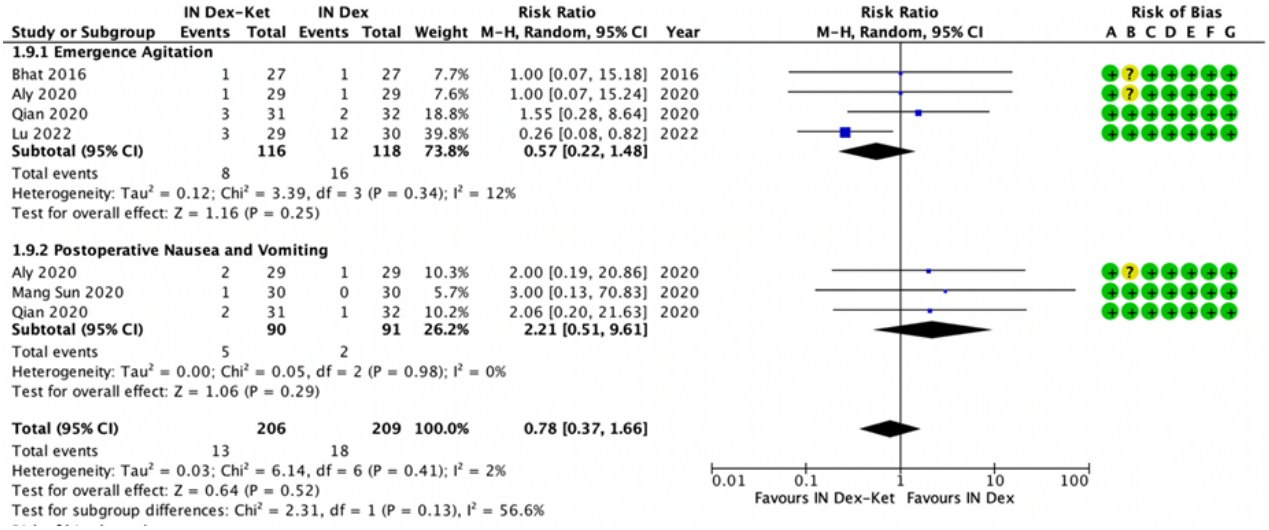

Figure 7. (A) Incidence of Adverse Events (B) Subgroup Analysis of Adverse Event

DISCUSSION

This meta-analysis showed that premedication for pediatric patients via the intranasal administration of a combination of ketamine and dexmedetomidine is as safe and efficacious as intranasal dexmedetomidine alone. Patients who were administered the combination drug achieved faster sedation onset time and smoother inhalational induction than intranasal dexmedetomidine alone without significantly prolonging recovery time or increasing clinically relevant adverse events.

Dexmedetomidine has been advocated as an alternative premedication in the field of pediatric anesthesia, given its sedative properties paralleling those of natural sleep, analgesia, and an anesthetic sparing effect with minimal respiratory depression [26,27]. As it leads to sympatholysis, it attenuates the cardiovascular and metabolic response in in response to surgical trauma. Despite its robust benefits, attention should be paid to the hemodynamic effects of the drug, among which, depending on dose administered and age group result in bradycardia and either hypotension (low doses with effect on presynaptic a2-a that generate vasodilation) or hypertension (use of high doses that activate postsynaptic a2-b receptors generating vasoconstriction) [28]. Yuen et al's studies on intranasal dexmedetomidine on the pediatric population reveal dexmedetomidine at a dose of 1 to 1.5 mcg/kg produced sedation in 45-60 minutes with median onset time of sedation 25 minutes and peaks in 90-105 minutes, with bioavailability as high as 82% [29,30].

Ketamine at subanesthetic doses, in addition to its ability to provide nearly all the requirements of anesthesia namely analgesia, immobility, amnesia and hypnosis, also has the beneficial qualities of producing bronchodilation, the ability to maintain airway reflexes and the sympathetic nervous system tone. When given intranasally among children it is safe and fast acting with sedation onset time after approximately 5-10 minutes and peak plasma concentration within 18± 13 minutes [31-33]. Ketamine interacts with multiple binding areas, including NMDA and non-NMDA glutamate receptors; nicotinic, muscarinic, cholinergic, adrenergic and opioid receptors. Due to its adrenergic effect, it leads to tachycardia, increasing cardiac output and blood pressure except in cases of catecholamine depletion, when it can cause a negative inotropic effect. Other potentially worrying effects are sialorrhea, nausea and psychomimetic effects [34-36].

When used together, dexmedetomidine can limit tachycardia, hypertension, salivation and restlessness on ketamine awakening. While the latter can prevent dexmedetomidine induced hypotension and bradycardia, in addition to speeding up the onset of sedation and maintaining airway patency. Several studies have shown similar results of increased sedation success, translatable to decreased parental separation anxiety and increased mask acceptance on induction with use of intranasal dexmedetomidine combined with ketamine. Yang et al did a retrospective analysis on the use of dexmedetomidine 2 mcg/kg combined with ketamine 1mg/kg intranasally for procedural sedation with a success rate of 93% [17]. Zanaty et al. compared nebulized ketamine, nebulized dexmedetomidine and their combination and reported more satisfactory sedation at venipuncture when combining the two drugs than using either drug alone [37]. Similarly, Qiao reported that adding oral ketamine 3 mg/ kg to intranasal dexemedetomidine 2mcg/kg resulted in successful sedation at venous cannulation in 80.5% of patients given the combination drug 30 minutes prior to eye surgery as compared to dexmedetomidine (47%) alone [38].

Of the studies included in this meta-analysis, only 2 had relevant study values on sedation onset time, coincidentally involving children diagnosed with acyanotic congenital heart disease (CHD). Though the rapid onset of action via the intranasal route is attributed to direct nose to brain delivery by bypassing the blood-brain barrier via the olfactory and trigeminal nerve pathways, a third route is via a peripheral pathway, where drugs enter the systemic circulation via vascular absorption and subsequently cross the blood-brain barrier [39]. The study populations on RCTs done by Aly and Mang Sun et al., could explain faster sedation onset as the shunting of blood among children with CHD affects drug pharmacokinetics [21,25]. In patients whose lesions are characterized by left to right shunting and increased pulmonary

pulmonary blood flow, drug reaches the brain at the same time as it would if no shunt existed. In lesions with right to left shunting, where systemic venous blood bypasses the pulmonary circulation, the drug reaches the brain sooner than predicted [40]. In part, the age of the patient population of both studies done by Aly (2.9±0.8 yrs old) and Mang Sun et al (10.6 ± 8.05 months old) may also explain the difference in sedation onset time as children do not follow a simple linear growth process with drug distribution dependent upon body composition. Lipophilic drugs, as with dexmedetomidine and ketamine, have a relatively larger volume of distribution in infants compared with older children owing to their higher comparative levels of fat (22.4% at 12 months vs 13% at 15 years) [41].

Increased sedation success at mask induction in patients premedicated with a combination of intranasal dexmedetomidine and ketamine may be attributed to the higher dose of ketamine used in the involved RCTs study population. In this meta-analysis, included studies assessing mask acceptance score involved patients who underwent procedures where greater patient stimulation is expected namely interventional cardiac catheterization, minor surgery and tonsillectomy. This may explain the choice of larger ketamine dose, as several studies support though dexmedetomidine is effective as a sole premedicant, the application of a face mask or attempts at venipuncture have resulted in patients waking and resulting in difficulties with anesthesia induction [42].

The faster recovery time of children in the dexmedetomidine-ketamine group is noteworthy, though had no statistical significance in the study. Dexmedetomidine has a rapid distribution phase with a distribution half-life of six minutes. In children under 2 years of age, the volume of distribution in the stable phase is high indicating that higher doses are required to obtain the stable phase; but its elimination half-life is prolonged, which can lead to high drug accumulation over time [21]. The use of ketamine as an adjunct, decreases the dose of dexmedetomidine necessary to produce its sedative effects. The difference impacts scheduling, efficiency and finances especially in the office -based or outpatient setting. Though the efficacy of the two sedative regimens in managing the patient's behavior is similar, a single drug which can provide satisfactory and better length of recovery is desirable for the patient and the institution.

The incidence of adverse events are decreased when children are premedicated with a combination of dexmedetomidine and ketamine, though the synthesis of studies revealed no significant differences among study groups. Emergence agitation (EA) with sevoflurane has been found in 18-80% of patients in previous studies [36]. Emergence Agitation after inhalational anesthesia, as was done on all 4 studies who included this outcome in this meta-analysis, can be due to inadequate pain relief,

preoperative anxiety, the type of postoperative environment and type of surgery. Ketamine, used solely, has been associated with dysphoria and hallucinations too. A study by Kim et al found that low dose infusion of dexmedetomidine reduces EA after desflurane anesthesia [43]. This may explain the negligible risk of EA among patients premedicated with a combination of dexmedetomidine and ketamine. The likelihood of PONV is decreased due to the potentially anti-emetic effect of dexmedetomidine as a-2 receptors are found in gastric and intestinal mucosa, although this outcome requires further investigation [44,45]. The absence of hemodynamic instability (bradycardia, hypotension) and hypoxemia in all the included studies may well be explained by the complementary effects of dexmedetomidine and ketamine. Those results are in accordance with the results of Tammam who used a combination of intramuscular dexmedetomidine and ketamine and Qiao et al, who used a combination of intranasal dexmedetomidine and oral ketamine [30].

There are some limitations of the present study. First, clinical heterogeneity among studies such as premedication dose, type of procedure, comorbidities and different age ranges were identified. Varying measurements and scales precluded further synthesis of data, which was compounded by the small number of patients in this study, significantly affecting weight and outcomes. The intervention effects of small clinical trials with incomplete allocation concealment are at risk of being overestimated. Although all the studies in the meta-analysis used a random allocation method and objectively measured outcome date, caution is needed when interpreting these results.

No local studies on dexmedetomidine or ketamine premedication in children were found on literature search, understandably due to the absence of FDA approval among the pediatric population for the former. With increasing use though off-label and its safety and efficacy established as evidenced by numerous studies, in future, once approved by requisite authorities, high quality RCTs, favorably those with large sample sizes are still needed to evaluate the safety of a combination of intranasal dexmedetomidine and ketamine premedication.

Conclusion

This meta-analysis demonstrates that premedication via intranasal administration of a combination of ketamine and dexmedetomidine is as safe as intranasal dexmedetomidine alone. The combination of dexmedetomidine and ketamine achieved faster sedation onset time and smoother inhalational induction than intranasal dexmedetomidine alone without increasing clinically relevant adverse events. Prudence in selection of patient population and procedure type should be exercised in application of drug doses due to the paucity of data to standardize such intervention.

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