Premedication with dexmedetomidine in pediatric patients: a systematic review and meta-analysis

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Premedication is important in pediatric anesthesia. This meta-analysis aimed to investigate the role of dexmedetomidine as a premedicant for pediatric patients.

A systematic literature search was conducted to identify randomized controlled trials comparing dexmedetomidine premedication with midazolam or ketamine premedication or placebo in children. Two reviewers independently performed the study selection, quality assessment and data extraction. The original data were pooled for the meta-analysis with Review Manager 5. The main parameters investigated included satisfactory separation from parents, satisfactory mask induction, postoperative rescue analgesia, emergence agitation and postoperative nausea and vomiting.

Thirteen randomized controlled trials involving 1190 patients were included. When compared with midazolam, premedication with dexmedetomidine resulted in an increase in satisfactory separation from parents (RD = 0.18, 95% CI: 0.06 to 0.30, $p = 0.003$) and a decrease in the use of postoperative rescue analgesia (RD = -0.19, 95% CI: -0.29 to -0.09, $p = 0.0003$). Children treated with dexmedetomidine had a lower heart rate before induction. The incidence of satisfactory mask induction, emergence agitation and PONV did not differ between the groups. Dexmedetomidine was superior in providing satisfactory intravenous cannulation compared to placebo.

This meta-analysis suggests that dexmedetomidine is superior to midazolam premedication because it resulted in enhanced preoperative sedation and decreased postoperative pain. Additional studies are needed to evaluate the dosing schemes and long-term outcomes of dexmedetomidine premedication in pediatric anesthesia.

KEYWORDS: Dexmedetomidine; Premedication; Pediatrics; Children.

INTRODUCTION

At least 60% of pediatric patients experience preoperative anxiety (1). Children may become overly uncooperative at the time of separation from parents, venipuncture, or mask application. Untreated anxiety can lead to difficult induction, increased postoperative pain, greater analgesic requirements, emergence agitation and even postoperative psychological effects and behavioral issues (2-7). Despite the many advances in nonpharmacologic interventions, practitioners still rely on sedative premedicants (8,9).

Midazolam, which causes sedation, anxiolysis and amnesia, is one of the most frequently used premedicants (10-14).

It has additional beneficial properties, such as anticonvulsant activity, rapid onset and a short duration of action and it reduces postoperative vomiting (12,15-18). However, it is far from an ideal premedicant due to its undesirable effects, which include restlessness, paradoxical reactions, cognitive impairment, postoperative behavioral changes and respiratory depression (19-21). Ketamine is another popular premedicant that causes dissociative anesthesia and it has both sedative and analgesic properties (22,23). However, its side effects, such as excessive salivation, nausea and vomiting, nystagmus, hallucination and postoperative psychological disturbances have limited its use (24-26).

Dexmedetomidine is a highly selective α-2 adrenoceptor agonist that provides sedation, anxiolysis and analgesic effects without causing respiratory depression (27). Recently, it has been explored extensively in the pediatric population. Although several randomized controlled trials have focused on dexmedetomidine premedication in children, the sample sizes have been relatively small and differing conclusions have been reported. Thus, the evidence supporting the use of dexmedetomidine is unclear.

This meta-analysis was conducted to investigate the effects of premedication with dexmedetomidine on preoperative sedation, hemodynamic stability, postoperative pain and possible adverse events in pediatric patients.

■ MATERIALS AND METHODS

Search strategy and trial selection

This systematic review of randomized controlled trials was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (28). Two researchers (K.P. and SR.W.) independently searched the following databases up to April 2014: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). The terms used in the search strategy were as follows: 1) dexmedetomidine AND (premedication* OR premedicant* OR preoperative OR pre anesthesia OR pre anaesthesia) AND (child* OR pediatric* OR paediatric*) for the MEDLINE and CENTRAL searches and 2) 'dexmedetomidine'/exp OR dexmedetomidine AND (premedication* OR premedicant* OR preoperative OR preanesthesia OR preanaesthesia) AND (child* OR pediatric* OR paediatric*) for the EMBASE search.

All searches were performed without language or publication date restrictions. The results were collated and deduplicated in Endnote X7 (Thomson Reuters, New York, NY). The titles and abstracts were screened before retrieval of the full articles. Any controversy concerning study selection or data extraction was resolved by consensus with a third reviewer (HF.J.). All three authors read the full texts of all papers and determined which papers should be included or excluded.

Inclusion and exclusion criteria

To be eligible for this meta-analysis, publications were required to meet the following four inclusion criteria: 1) original research comparing premedication with dexmedetomidine to premedication with midazolam or ketamine or placebo as the sole agent administered through noninvasive routes (oral, rectal, intranasal, sublingual and buccal) in pediatric patients undergoing elective procedures; 2) a randomized controlled trial (RCT) study design; 3) disclosure of at least one of the following outcome measures: quality of separation from parents, quality of mask induction, hemodynamic variables, postoperative pain, recovery time, time to discharge from the post-anesthesia care unit (PACU), emergence agitation (EA), postoperative nausea and vomiting (PONV), shivering and other possible untoward events; and 4) availability of the full-text article.

Data extraction and quality assessment

The following data from the included studies were extracted and tabulated by two researchers (K.P. and SR.W.): author, year of publication, sample size, mean age, intervention measure, type of procedure, anesthesia scheme and any outcome that met the inclusion criteria. Corresponding authors were contacted to obtain missing data if necessary. For the trials assessing different premedication doses, the groups were combined to create a single pair-wise comparison (29).

The validity was assessed and scored by two researchers (SR.W. and J.L.) and checked by a third researcher (FH.J.) using the Jadad scale (30,31), which considers the reporting

and adequacy of randomization (2 points), double blinding (2 points) and description of drop-outs (1 points).

Statistical analysis

When outcomes of interest were reported by two or more studies, the included articles were pooled and weighted using Review Manager (version 5.1, 2011; the Nordic Cochrane Center, the Cochrane Collaboration). Categorical outcomes are reported as risk differences (RDs) and 95% confidence intervals (CIs), while continuous outcomes are reported as weighted mean differences (WMDs) and 95% CIs.

Heterogeneity, which was assessed using I^2 statistics, describes the percentage variability in effect estimates (RD or WMD) that is due to heterogeneity rather than sampling error. A random-effect model was used for the analysis. Publication bias was assessed visually with a funnel plot if more than 10 studies were included.

Sensitivity analyses were performed to further test the robustness of the results. These analyses included 1) an assessment of the influence of publication quality (high *versus* low quality) on the results and 2) subgroup analysis according to the different routes of premedication administration.

■ RESULTS

Included trials

A total of 171 of the articles were relevant to the search terms. Screening of the titles and abstracts revealed that 21 studies were potentially eligible for inclusion. After reading the full-text articles, 13 trials (published between 2007 and 2014) involving 1190 participants were finally included in this meta-analysis (32-44) (Table 1). A flow diagram depicting the trial selection process is shown in Figure 1.

Characteristics of the included trials

Table 1 presents the characteristics of the included trials, which were all randomized controlled trials that investigated pediatric patients undergoing different procedures (dental rehabilitation and tooth extraction, lymph node excision, herniorrhaphy, circumcision, bone marrow biopsy and aspiration, adenotonsillectomy and others). The children ranged in age from 2 to 10 years old and most were 4 to 6 years old.

Eleven trials compared dexmedetomidine with midazolam premedication (32-35,37-40,42-44), two compared dexmedetomidine with ketamine (35,36) and three compared dexmedetomidine with a placebo (36,38,41). All trials administered premedication through noninvasive routes, including oral and transmucosal (intranasal, sublingual and buccal) administration, at 30-75 min before commencement of surgery. The dosing scheme for dexmedetomidine was 1-2 µg/kg for transmucosal premedication or 2.5-4 µg/kg for oral premedication. Ten trials used balanced inhalational general anesthesia with sevoflurane or isoflurane and one trial provided sedation with propofol.

Effect of dexmedetomidine *versus* midazolam on separation from parents

Seven trials including 650 patients compared dexmedetomidine *versus* midazolam premedication for satisfactory separation from parents (32,33,35,37,40,42,43). The meta-analysis revealed that more children experienced satisfactory separation following treatment with dexmedetomidine

Table 1 - Characteristics of the included studies.

Study	Intervention time and dosing scheme	N	Age (y)	Procedure	Anesthesia	Jadad score
Linares Segovia 2014	1. Intranasal dexmedetomidine 1 µg/kg (0.5 ml) at 60 min before induction	52	4	Inguinal hernia repair, umbilical hernia repair, circumcision	No details provided	4
	2. Oral midazolam 0.5 mg/kg at 60 min before induction	56	4			
Sheta 2013	1. Intranasal dexmedetomidine 1 µg/kg (1 ml) at 45-60 min before induction	36	3.9	Complete dental rehabilitation	Sevoflurane + N_2O + local anesthesia	5
	2. Intranasal midazolam 0.2 mg/kg (1 ml) at 45-60 min before induction	36	4.2			
Pant 2013	1. Sublingual dexmedetomidine 1.5 µg/kg (undiluted) at 45 min before induction	50	4.5	Inguinal hernia repair, orchidopexy, circumcision	Sevoflurane + N_2O + caudal block	5
	2. Sublingual midazolam 0.25 mg/kg (undiluted) at 20 min before induction	50	2			
Mostafa 2013	1. Intranasal dexmedetomidine 1 µg/kg at 30 min before induction	32	5	Bone marrow biopsy and aspiration	Sevoflurane	3
	2. Intranasal midazolam 0.2 mg/kg at 30 min before induction	32	4.8			
	3. Intranasal ketamine 5 mg/kg at 30 min before induction	32	4.9			
Gyanesh 2013	1. Intranasal dexmedetomidine 1 µg/kg (1 ml) at 60 min before IV cannulation	52	5.1	Magnetic resonance imaging	Propofol (sedation only)	5
	2. Intranasal ketamine 5 mg/kg (1 ml) at 30 min before IV cannulation	52	4.9			
	3. Placebo	46	5			
Akin 2012	1. Intranasal dexmedetomidine 1 µg/kg (1.5 ml) at 45-60 min before induction	45	5	Adenotonsillectomy	Sevoflurane + N_2O	5
	2. Intranasal midazolam 0.2 mg/kg (1.5 ml) at 45-60 min before induction	45	6			
Ozcengiz 2011	1. Oral dexmedetomidine 2.5 µg/kg at 40-45 min before induction	25	5.5	Esophageal dilatation procedures	Sevoflurane + N_2O	4
	2. Oral midazolam 0.5 mg/kg at 40-45 min before induction	25	4.9			
	3. Placebo	25	6.2			
Mountain 2011	1. Oral dexmedetomidine 4 µg/kg at 30 min before entering the operating room	22	4	Dental restoration, tooth extraction	Sevoflurane + N_2O + local anesthesia	4
	2. Oral midazolam 0.5 mg/kg at 30 min before entering the operating room	19	4			
Ghali 2011	1. Intranasal dexmedetomidine 1 µg/kg (0.5 ml) at 60 min before induction	60	8.2	Outpatient adenotonsillectomy	Sevoflurane + N_2O	4
	2. Oral midazolam 0.5 mg/kg at 30 min before induction	60	8.1			
Yuen 2010	1. Intranasal dexmedetomidine 1 µg/kg (0.4 ml) at 30-75 min before IV cannulation	79	4	Elective surgery (no details provided)	No details provided	5
	2. Placebo	21	4			
Talon 2009	1. Intranasal dexmedetomidine 2 µg/kg (atomization) at 30-40 min before induction	50	9.5	Reconstructive surgery	Isoflurane + N_2O	4
	2. Oral midazolam 0.5 mg/kg at 30-40 min before induction	50	10.7			
Yuen 2008	1. Intranasal dexmedetomidine 1 µg/kg (0.4 ml) at 60 min before induction	32	6.1	Orchidopexy, excision of lymph nodes, circumcision	Isoflurane + N_2O + regional anesthesia	5
	2. Intranasal dexmedetomidine 0.5 µg/kg (0.4 ml) at 60 min before induction	32	6.8			
	3. Oral midazolam 0.5 mg/kg at 30 min before induction	32	6.4			
Schmidt 2007	1. Transmucosal dexmedetomidine 1 µg/kg at 45 min before surgery	20	8	Excision of lymph nodes, herniorrhaphy, circumcision	Sevoflurane/isoflurane + N_2O + Regional anesthesia	3
	2. Oral midazolam 0.5 mg/kg at 30 min before induction	22	9			

(RD = 0.18, 95% CI: 0.06 to 0.30, $p = 0.003$) (Figure 2). Subgroup analysis showed that RD = 0.10 (95% CI: -0.12 to 0.31) for intranasal dexmedetomidine *versus* intranasal midazolam and RD = 0.24 (95% CI: 0.10 to 0.38) for intranasal dexmedetomidine *versus* oral midazolam. However, there was significant heterogeneity among the pooled studies ($I^2 = 73\%$).

Effect of dexmedetomidine *versus* midazolam on mask induction

Six trials including 475 patients compared satisfactory mask induction in children treated with dexmedetomidine *versus* midazolam (32,33,37,39,42,43). The meta-analysis showed that there was no significant difference between the groups (RD = -0.01, 95% CI: -0.16 to 0.14, $p = 0.88$) (Figure 3). The subgroup analysis revealed that RD = -0.00 (95% CI: -0.44 to 0.43) for intranasal dexmedetomidine *versus* intranasal midazolam and RD = 0.01 (95% CI: -0.19 to 0.21) for intranasal dexmedetomidine *versus* oral midazolam. This analysis was influenced by heterogeneity ($I^2 = 75\%$).

Effects of dexmedetomidine *versus* midazolam on heart rate (HR), systolic blood pressure (SBP) and oxygen saturation (SpO$_2$) before induction

Two trials including 162 patients compared HR before induction in children treated with dexmedetomidine *versus* midazolam (40,44). The meta-analysis revealed that the HR before induction was significantly lower in the children treated with dexmedetomidine (WMD = -15.49 beats/min, 95% CI: -25.13 to -5.86 beats/min, $p = 0.002$). This analysis was influenced by heterogeneity ($I^2 = 74\%$).

Two trials including 184 patients compared systolic blood pressure (SBP) before induction in children treated with dexmedetomidine *versus* midazolam (35,40). There was no significant difference between the groups (WMD = -7.13 mmHg, 95% CI: -19.02 to 4.75 mmHg, $p = 0.24$). This analysis was influenced by heterogeneity ($I^2 = 99\%$).

Two trials including 184 patients compared SpO$_2$ before induction in children treated with dexmedetomidine *versus* midazolam (35,40). The meta-analysis showed that there was no significant difference between the groups (WMD = 0.27%, 95% CI: -0.21 to 0.74%, $p = 0.27$). Additionally, no significant heterogeneity was observed ($I^2 = 0\%$).

Effects of dexmedetomidine *versus* midazolam on recovery time and time to discharge from the PACU

Three trials including 204 patients compared the recovery times of children treated with dexmedetomidine *versus* midazolam (33,37,44). There was no significant difference between the groups (WMD = -0.45 min, 95% CI: -1.26 to 0.35 min, $p = 0.27$) and no significant heterogeneity was observed ($I^2 = 0\%$).

Three trials including 234 patients compared the time to discharge from the PACU for children treated with dexmedetomidine *versus* midazolam (33,40,44). There was no significant difference between the groups (WMD = 0.45 min, 95% CI: -2.33 to 3.23 min, $p = 0.75$). This analysis was influenced by heterogeneity ($I^2 = 62\%$).

Effect of dexmedetomidine *versus* midazolam on postoperative rescue analgesia

Five trials including 417 patients compared dexmedetomidine with midazolam premedication for postoperative rescue analgesia (33,37,40,42,44). Meta-analysis revealed that fewer children needed rescue analgesia when they were treated with dexmedetomidine (RD = -0.19, 95% CI: -0.29 to -0.09, $p = 0.0003$) (Figure 4). The subgroup analysis showed that RD = -0.20 (95% CI: -0.33 to -0.06) for intranasal dexmedetomidine *versus* intranasal midazolam and RD = -0.11 (95% CI: -0.22 to -0.01) for intranasal dexmedetomidine *versus* oral midazolam. This analysis was influenced by heterogeneity ($I^2 = 36\%$); however, no significant heterogeneity ($I^2 = 0\%$) was detected in the subgroup analysis.

Effects of dexmedetomidine *versus* midazolam on EA and PONV

Five trials including 346 patients compared dexmedetomidine with midazolam premedication for EA treatment (33,37-39,42). There was no significant difference between the groups (RD = -0.03, 95% CI: -0.10 to 0.04, $p = 0.36$) (Figure 5). Subgroup analysis showed that RD = -0.05 (95% CI: -0.16 to 0.06) for intranasal dexmedetomidine *versus* intranasal midazolam and RD = -0.03 (95% CI: -0.17 to 0.10) for oral dexmedetomidine *versus* oral midazolam. This analysis was influenced by heterogeneity ($I^2 = 42\%$)

Three trials including 226 patients compared dexmedetomidine with midazolam premedication for PONV treatment (33,35,37). The meta-analysis showed that there was no significant difference between the groups (RD = -0.01, 95% CI: -0.06 to 0.04, $p = 0.83$) (Figure 6) and no significant heterogeneity was detected ($I^2 = 0\%$).

Dexmedetomidine *versus* ketamine

None of the data illustrating the effects of dexmedetomidine *versus* ketamine could be pooled because similar outcomes were not reported by any two trials (35,36).

Effect of dexmedetomidine *versus* placebo on intravenous cannulation

Two trials including 198 patients compared satisfactory intravenous cannulation in patients treated with dexmedetomidine *versus* placebo (36,41). The meta-analysis revealed that more children had satisfactory intravenous cannulation following treatment with dexmedetomidine (RD = -0.48, 95% CI: -0.92 to -0.04, $p = 0.03$). However, this analysis was significantly influenced by heterogeneity ($I^2 = 91\%$).

■ DISCUSSION

The current meta-analysis revealed that dexmedetomidine premedication of pediatric patients resulted in more satisfactory separation from parents and a reduced need for postoperative rescue analgesia compared with midazolam. The dexmedetomidine-premedicated children had lower HRs before induction.

Although premedication is often applied, the ideal agent and the best route of administration remain unclear (45). Oral premedication is the most widely used route; however, it results in low bioavailability (46,47). Rectal application is often painful and medications administered in this way may be easily expelled from the rectum in young children and can be problematic for use in older children. Intramuscular premedication has also been used, but it is invasive and should be avoided if possible. Transmucosal routes, including intranasal, sublingual and buccal administration, have been shown to be effective because of the rich mucosal blood supply and because administration via these routes
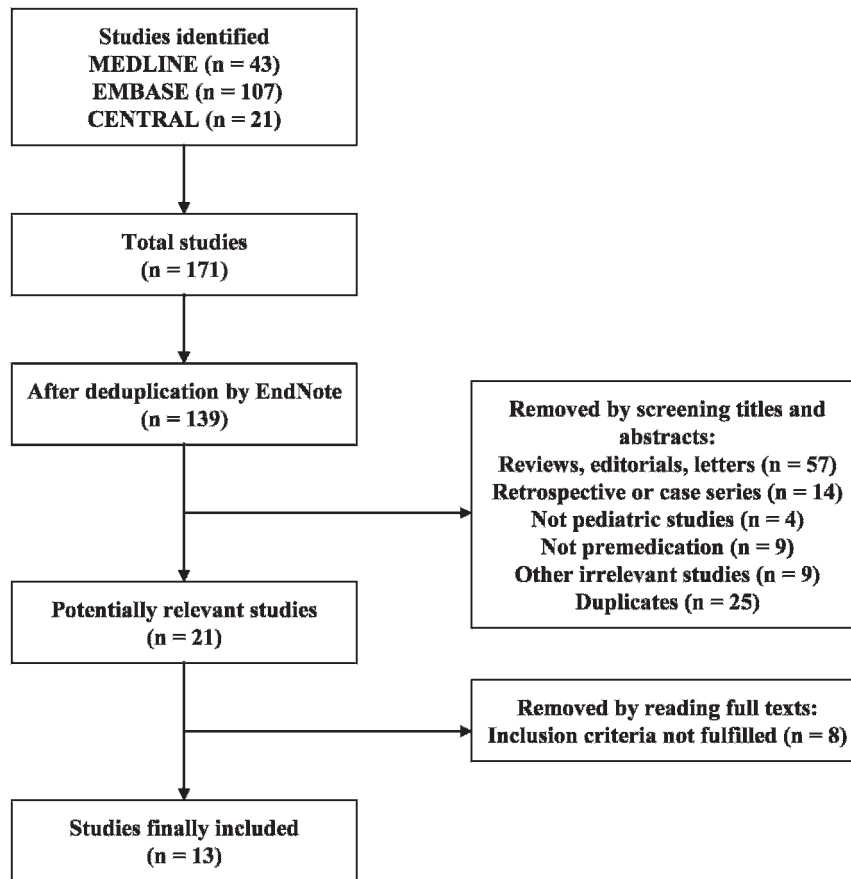
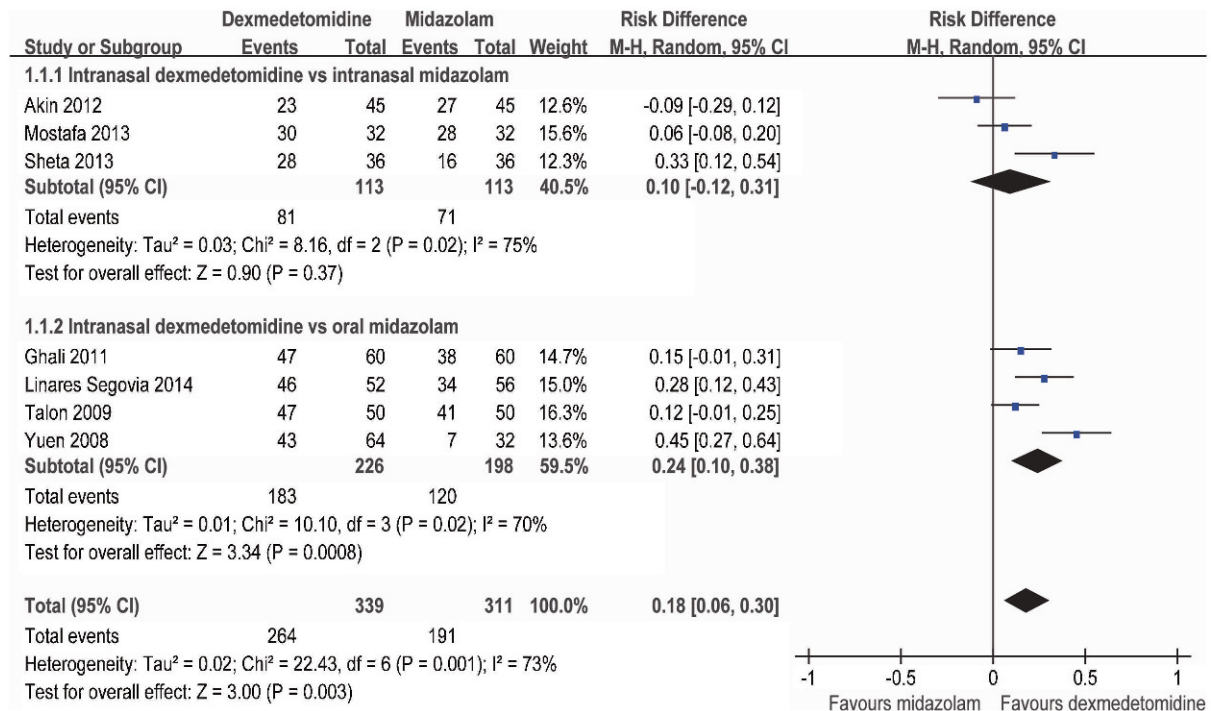**Figure 1 -** Flow chart of retrieved, excluded and included trials.

Figure 2 - Meta-analysis of satisfactory separation from parents in children treated with dexmedetomidine *vs.* midazolam.
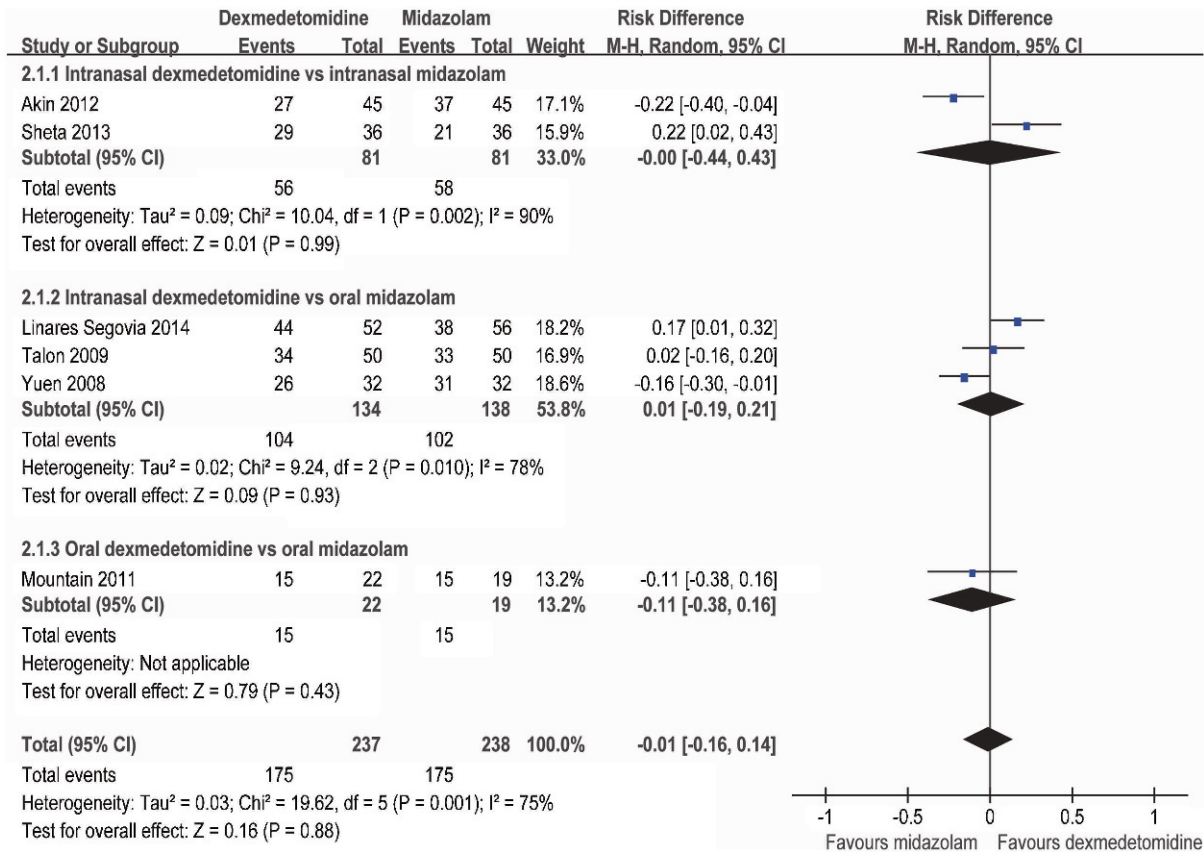
Figure 3 - Meta-analysis of satisfactory mask induction in children treated with dexmedetomidine *vs.* midazolam.

allows for the bypass of first-pass metabolism. Moreover, compliance with nasal sedation is easier to achieve than compliance with oral sedation in young children (48). In this meta-analysis, all included trials administered premedication through noninvasive routes, including oral and transmucosal (intranasal, sublingual, or buccal) routes.

The pharmacokinetics of midazolam administration has been well studied. When given orally, its acceptability by children is only 70% due to poor palatability (49). Intranasal administration of this medication is effective; however, it may cause nasal irritation (12). Midazolam results in rapid sedation and most of the included studies in this meta-analysis administered intranasal or oral midazolam at 30 min before induction or surgery. Dexmedetomidine, on the other hand, is colorless, odorless and tasteless and several studies have investigated its pharmacokinetics in children (50-54). Oral administration of dexmedetomidine also results in poor bioavailability. Although intranasal premedication with midazolam causes nasal irritation, none of the children treated with dexmedetomidine showed signs of nasal irritation (33). Intranasal dexmedetomidine is commonly administered 45-60 min before induction of surgery because of the relatively slow onset of maximal sedation.

This meta-analysis revealed that dexmedetomidine was superior to midazolam in producing satisfactory sedation in children separated from their parents. The subgroup analysis showed that premedication with intranasal dexmedetomidine seemed to be more effective than premedication with oral midazolam. Oral premedication is associated with

low and variable bioavailability, which may lead to under-dosage. This fact may explain the reduced effectiveness of oral midazolam. Notably, larger volumes of intranasally administered drugs may be swallowed before there is sufficient time for absorption, leading to reduced bioavailability (33). However, the intranasal drug volumes differed among the studies (range, 0.3 to 1.5 ml). This finding may have contributed to the discrepancies among the included studies and may have introduced bias.

The superiority of dexmedetomidine over midazolam vanished at the time of mask application. Unlike conventional sedatives, the site of action of dexmedetomidine is the central nervous system, primarily the locus coeruleus, in which it induces sedation that parallels natural sleep (55). Therefore, it is not surprising that external stimulation facilitates arousal. However, clonidine, which is another α-2 adrenoceptor agonist, was found to be superior to midazolam in providing acceptable levels of sedation during induction in another meta-analysis (56).

Compared with midazolam premedication, dexmedetomidine premedication reduced the HR during the preoperative sedation period after induction. The children in both groups maintained similar normal SpO_2 values. Dexmedetomidine can decrease sympathetic outflow by decreasing plasma epinephrine and norepinephrine levels, thus leading to decreases in HR and BP (57,58). Additionally, it has been shown to have minimal effects on respiration (59,60), which is its key advantage over other sedative medications.

The most frequently reported adverse events associated with dexmedetomidine treatment are hypotension and
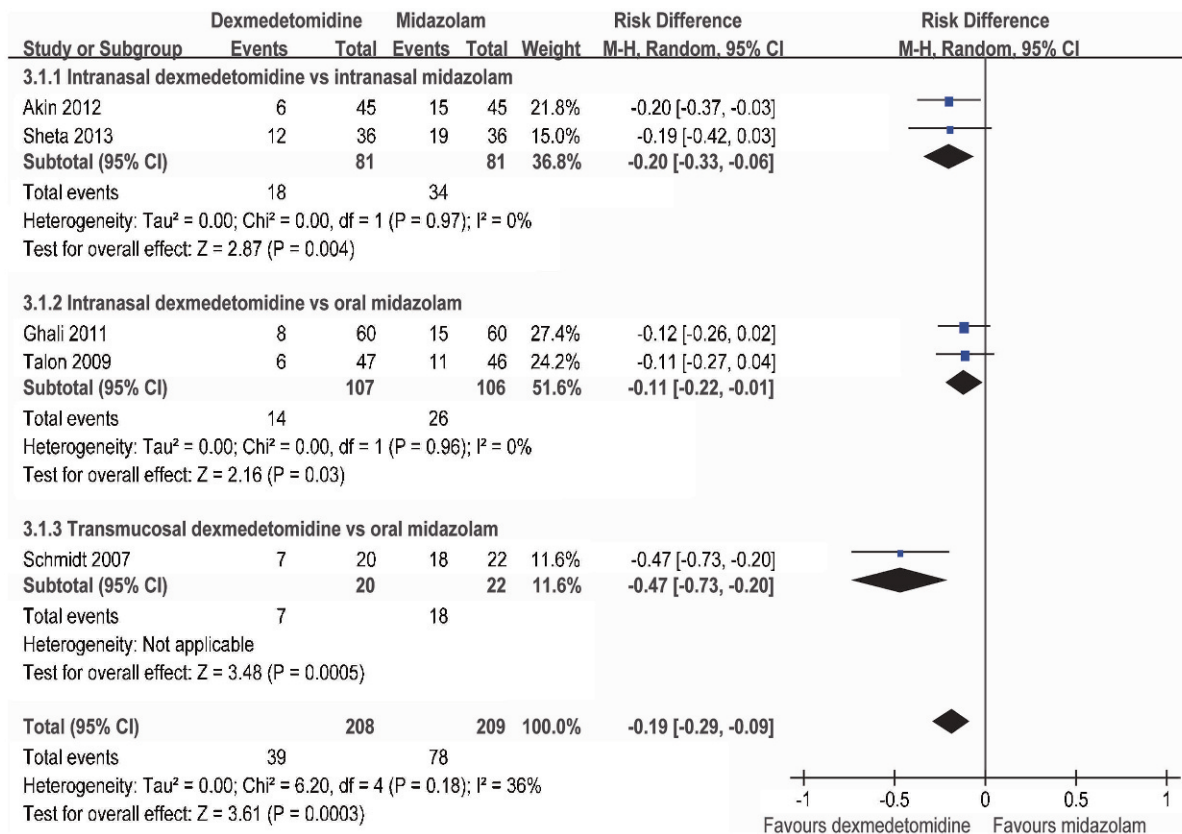
Figure 4 - Meta-analysis of postoperative rescue analgesia in children treated with dexmedetomidine *vs.* midazolam.

bradycardia (61). Its hemodynamic effects are well known following intravenous infusion (there is a higher risk of bradycardia in patients receiving a rapid bolus and a lower risk in those receiving a continuous infusion). However, these side effects are seldom observed following non-intravenous administration. Yuen et al. (43) have shown that intranasal dexmedetomidine premedication decreases HR by 11% after administration of 0.5 µg/kg and by 16% after administration of 1 µg/kg compared with their respective baseline values within 60 min. Another study (41) has found that the maximum reduction in SBP is 13.2% at 60 min and the maximum reduction in HR is 14.9% at 75 min after administration of 1 µg/kg intranasal dexmedetomidine premedication. None of the included trials reported significant hypotension or bradycardia requiring treatment in either group during the study period.

Dexmedetomidine has been demonstrated to effectively reduce opioid requirements and to potentiate analgesia (61-63). The current meta-analysis reported the same outcome: the patients treated with dexmedetomidine required less postoperative rescue analgesia. Furthermore, the subgroup analyses demonstrated that the routes of premedication may not have influenced the superiority of dexmedetomidine over midazolam. Thus, the use of dexmedetomidine can provide additional analgesic benefits for pediatric patients following premedication.

Emergence agitation, which is a frequent phenomenon in children recovering from general anesthesia, creates a challenging situation (64). Various factors, including pain, preoperative anxiety, personal temperament, type of surgical procedure performed and type of anesthetic may

contribute to its occurrence (38). Compared with placebo, both dexmedetomidine and midazolam have been shown to reduce EA in children following administration of sevoflurane anesthesia (38). This meta-analysis showed that there was no difference in the incidence of EA between the dexmedetomidine and midazolam groups. Additionally, dexmedetomidine had no overall preventive effect on PONV compared with midazolam. However, no details pertaining to perioperative antiemetic prophylaxis were provided for either group; thus, the evidence supporting this comparison is unclear.

This meta-analysis also compared premedication with dexmedetomidine to placebo. Only two trials focusing on satisfactory intravenous cannulation were included and our analysis was influenced by a high level of heterogeneity. The results of the comparison of dexmedetomidine *versus* ketamine premedication could not be pooled using meta-analysis due to the limited available data. Ketamine, which may induce adverse cardiostimulatory effects and postoperative delirium, is currently used less frequently as a sole premedicant. Some studies have shown that the combination of ketamine with other drugs for premedication results in satisfactory sedation and a reduction in side effects (65-67). Because this meta-analysis was not designed to explore the combination of different premedicants, these studies were not included.

Limitations

This meta-analysis had some limitations. First, the sample sizes of all the included trials were relatively small and the methodological quality was variable. Second, differences in
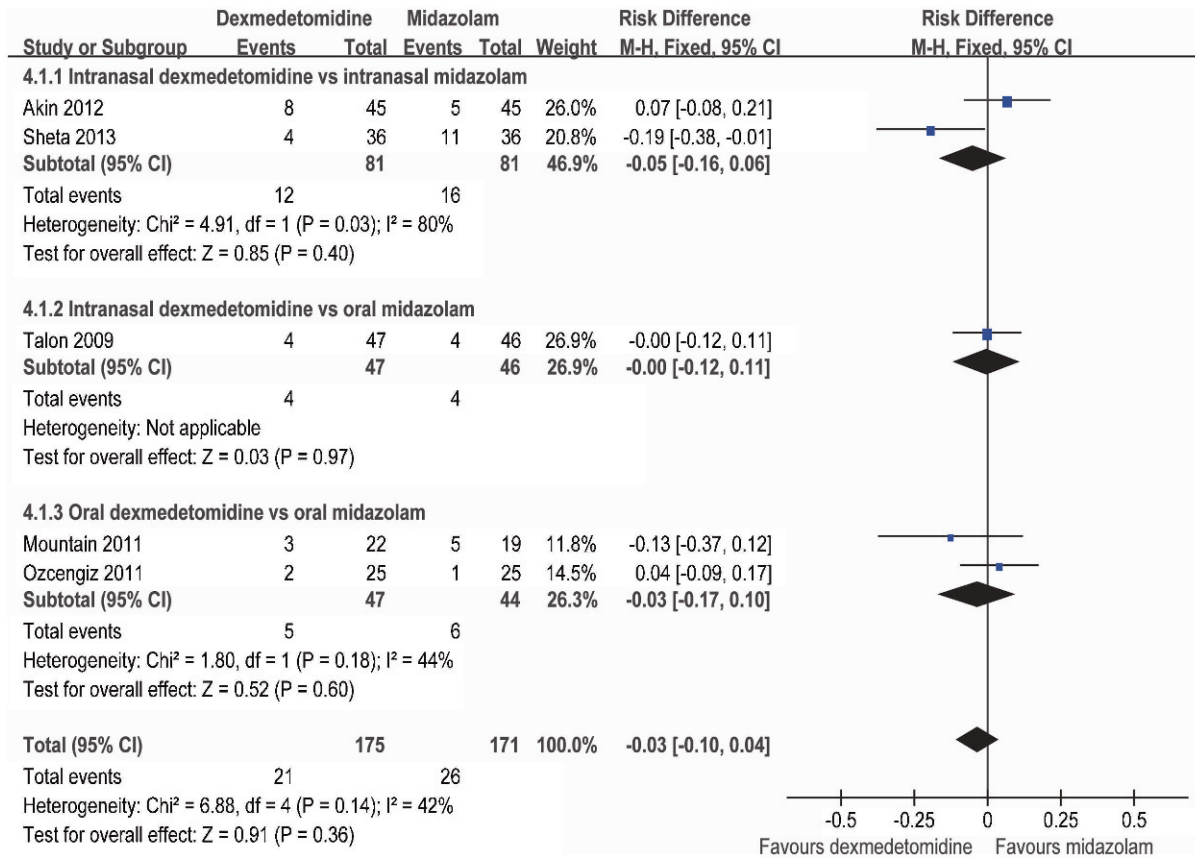
Figure 5 - Meta-analysis of EA in children treated with dexmedetomidine *vs.* midazolam. EA: emergence agitation.

age may have influenced some of the results because the pharmacokinetics and pharmacodynamics between younger and older children vary. Third, the various routes of premedication may have also introduced bias. Fourth, significant heterogeneity was observed in some of the analyses (separation from parents, mask induction, HR and SBP before induction, time to discharge from the PACU and satisfactory intravenous cannulation); therefore, the results should be assessed with caution. Fifth, publication bias may have affected the precision of some of the outcomes because positive results are more likely to be published than negative results; hence, our results may have been overestimated. Finally, although considerable clinical data have been reported, dexmedetomidine is not approved for use in children in any country. Thus, its use in children is considered 'off-label' and exercising caution in its administration to at-risk patients is warranted.

■ CONCLUSIONS

This meta-analysis provides evidence that dexmedetomidine is superior to midazolam premedication in promoting
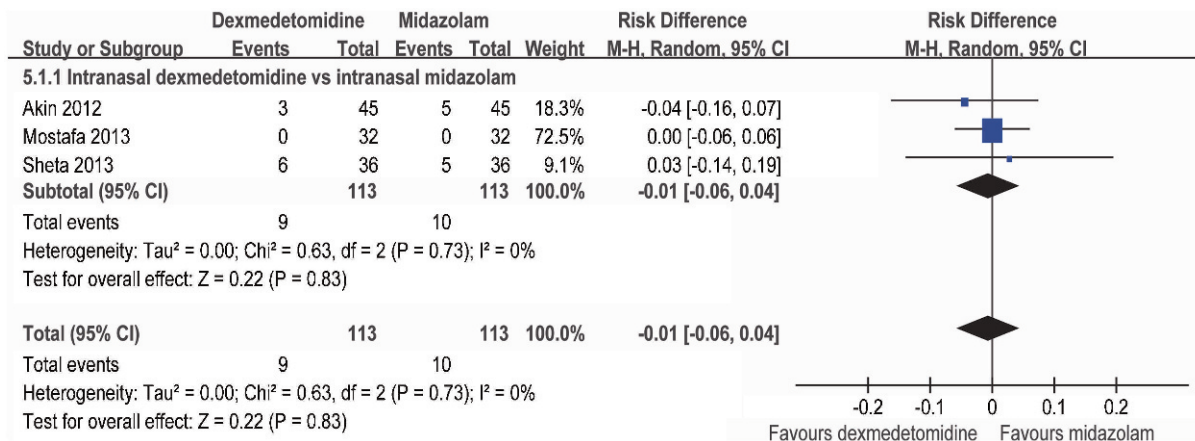

Figure 6 - Meta-analysis of PONV in children treated with dexmedetomidine *vs.* midazolam. PONV: postoperative nausea and vomiting.

preoperative sedation and decreasing postoperative pain. Further studies are needed to evaluate the dosing schemes and long-term outcomes of preoperative dexmedetomidine administration in pediatric anesthesia.

◼ AUTHOR CONTRIBUTIONS

Peng K and Wu SR independently searched the following databases up to April 2014: MEDLINE, EMBASE and CENTRAL. Any controversy concerning study selection or data extraction was resolved by consensus with Ji FH. Peng K, Wu SR and Ji FH read the full texts of all papers and determined which papers should be included or excluded. Peng K and Wu SR extracted and tabulated all relevant data from the included studies. Validity was assessed and scored by Wu SR and Li J, and checked by Ji FH.

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