A comparative evaluation of dexmedetomidine and midazolam in pediatric sedation: A meta-analysis of randomized controlled trials with trial sequential analysis

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Abstract

Background: The present study with trial sequential analysis (TSA) was conducted to evaluate comprehensively the efficacy and safety of dexmedetomidine and midazolam in pediatric sedation, and to investigate whether the outcomes achieved the required information size to draw the conclusions.

Methods: PubMed, Embase, and Cochrane Library were searched from inception to October 2019. All randomized controlled trials used dexmedetomidine and midazolam in pediatric sedation were enrolled. Sedative efficacy, postoperative analgesic effect, and incidence of emergence agitation were considered as the co-primary outcomes. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was applied to rate the quality of evidences.

Results: We acquired data from 34 studies involving 2281 pediatric patients. The results indicated that administration of dexmedetomidine was associated with less incidence of emergence agitation (RR = 0.78, with 95% CI [0.65, 0.92]) and more satisfactory sedation at parental separation (RR = 0.31, with 95% CI [0.24, 0.41]) compared to midazolam, and the current sample sizes were sufficient with unnecessary further trials. Two groups did not differ significantly in sedation level at mask induction (RR = 0.86, with 95% CI [0.74, 1.00]). And using of dexmedetomidine was associated with less incidence of postoperative analgesic rescue (RR = 0.57, with 95% CI [0.35, 0.93]), but the number of patients was too few to achieve the required information size and to draw reliable conclusions. Premedication of dexmedetomidine was associated with significant less value of SBP, heart rate, increased incidence of bradycardia, and a lower rate of shivering. And there were no differences about onset of sedation and recovery time between two groups.

Conclusions: Given that more satisfactory sedation at separation from parents and less incidence of emergence agitation, dexmedetomidine is preferred for pediatric sedation. However, compared with midazolam, the superiority of dexmedetomidine
1 | INTRODUCTION

Anxiety and distress developed in pediatric patients during perioperative period bring the challenges for anesthesiologist and pediatric clinicians. Uncooperative physically resistance from children results in increased difficulties in separation from parents, mask application, and induction of anesthesia. It is estimated that up to 60%-70% of children suffered anxiety, anguish, and fear throughout the perioperative period or diagnostic procedures. Sedative premedications can help to reduce the anxiety, minimize the emotional discomforts, ease the parental separation, and smooth the induction of anesthesia. Many premedicants via different routes have been tried in clinical practice.

Compared with other benzodiazepine, midazolam has rapid onset and high metabolic clearance, and its sedative efficacy in pediatric premedication has been demonstrated widely. However, untoward effects including negative postoperative behavioral changes, cognitive impairment, respiratory depression, and insufficient prevention of postoperative emergence agitation have been reported in children premedicated with midazolam, which makes it a less-than-ideal option in pediatric sedation.

As one highly selective $\alpha_2$-adrenoceptor agonist (selectivity ratio for $\alpha_2$-adrenoceptor:$\alpha_1$-adrenoceptor is 1600:1) with sedative and analgesic characteristics, dexmedetomidine provides cooperative and arousable sedation without clouded consciousness and respiratory depression. Owing to these beneficial effects, it has been demonstrated to be a useful pre-anesthesia medication in children. In an effort to evaluate the influences of the two premedications on pediatric perioperative sedation, Pasin et al and Sun et al conducted the relevant meta-analyses with total of 13 randomized trials (1033 patients) and 11 randomized trials (829 patients) which showed a satisfactory sedation profiles of dexmedetomidine premedication. The included items and the sample size of two studies were approximate, and authors also described that available data were still lacking. More evidences with large sample size were required to draw the reliable conclusions.

Therefore, on the basis of combining the latest evidences, the present updated meta-analysis of RCTs was conducted to evaluate comprehensively the effects of two premedicants in pediatric sedation at separation from parents and mask induction, hemodynamic status, and various adverse effects. And the trial sequential analysis (TSA) was also performed to determine whether the findings achieved the required information size to draw the conclusions.

2 | MATERIALS AND METHODS

The present meta-analysis was performed in accordance with the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the guidelines described in the Cochrane Handbook.

2.1 | Search strategy

Two independent reviewers (BL and YF) performed the literature search. The databases including PubMed, Embase, and Cochrane Library were searched systematically. The strategies used for searching were including infant, child, adolescent, dexmedetomidine, midazolam, and randomized controlled trial (Appendix S1). Only human studies were involved, and there were no restrictions of language. The final literature search was performed on October 7, 2019.

2.2 | Eligibility criteria

The studies meeting the following criteria were selected for further analysis:

2.2.1 | Participants

The patients were the children (<18 years old) who experienced different surgical and diagnostic procedures.

2.2.2 | Intervention and comparison

Using dexmedetomidine vs midazolam as the premedication (regardless of the route and dose of administration).

2.2.3 | Outcome measures

Given that satisfactory separation from parents and satisfactory induction or facemask compliance with limited postoperative pain and agitation were considered as the ideal characteristics of pediatric sedatives, the co-primary outcomes were as follows: (a) number of patients with satisfactory separation from parents, (b) number of patients with satisfactory induction or mask acceptance, (c) number
| Study (Reference) | Year | Type of surgery/procedure | Patient age (range) & ASA status | Patients enrolled (Gender: F/M, n) | DEX dose, route of administration | MDZ dose, route of administration | Scale used for sedation measurement | Outcomes |
|------------------|------|----------------------------|----------------------------------|----------------------------------|---------------------------------|---------------------------------|-----------------------------------|----------|
| Tobias et al\(^1^4\) | 2004 | Mechanical ventilation | Not mentioned | 30 (10/20) | 1. DEX 0.25: 0.25 μg/kg/h, Infusion; 2. DEX 0.5: 0.5 μg/kg/h, Infusion | 0.1 mg/kg/h, Infusion | 6-points scale | V, VI, VIII, |
| Koroglu et al\(^1^5\) | 2005 | Magnetic resonance imaging procedures | 1-7 y (ASA I-II) | 80 (29/51) | Loading dose 1 μg/kg followed by 0.5 μg/kg/h, Infusion | Loading dose 0.2 mg/kg, Oral | 6-points scale | VII-X |
| Schmidt et al\(^1^6\) | 2007 | Elective ambulatory surgical procedures | 7-12 y (ASA I-II) | 42 (18/24) | 1 μg/kg, Oral transmucosal | 0.5 mg/kg, Oral | 4-point scale | III, VII, VIII, X, |
| Yuen et al\(^1^7\) | 2008 | Elective minor surgery | 2-12 y (ASA I-II) | 96 (7/89) | 1. DEX patients: 50; 2. DEX 1.0 patients: 32; 3. MDZ patients: 32 | 0.5 mg/kg, Oral | 6-points scale | I, II |
| Talon et al\(^1^8\) | 2009 | Elective reconstructive surgery | 1-18 y (Not mentioned) | 100 (47/53) | 2 μg/kg, Intranasal | 0.5 mg/kg, Oral | 6-points scale | I-III |
| Aksu et al\(^1^9\) | 2011 | Electroencephalogram procedures | 6 mo-6 y (ASA I) | 60 (18/42) | 0.5 μg/kg, IV | 0.1 mg/kg, IV | 6-points scale | IV, X |
| Ghali et al\(^2^0\) | 2011 | Elective outpatient adenotonsillectomy surgery | 4-12 y (ASA I) | 120 (58/62) | 1 μg/kg, Intranasal | 0.5 mg/kg, Oral | 6-points scale | I, III, V, VIII, X |
| Mountain et al\(^2^1\) | 2011 | Dental restoration and possible tooth extraction | 1-6 y (ASA I) | 41 (20/21) | 4 μg/kg, Oral | 0.5 mg/kg, Oral | 4-point scale | I, II, IV |
| Özcengiz et al\(^2^2\) | 2011 | Esophageal dilatation procedures | 3-9 y (ASA I-II) | 50 (26/24) | 2.5 μg/kg, Oral | 0.5 mg/kg, Oral | Not mentioned | IV |
| Akin et al\(^2^3\) | 2012 | Elective adenotonsillectomy | 2-9 y (ASA I) | 90 (37/53) | 1 μg/kg, Intranasal | 0.2 mg/kg, Intranasal | 6-points scale | I-IV, XII |
| Aydogan et al\(^2^4\) | 2013 | Scoliosis surgery | 12-18 y (ASA I-II) | 32 (15/17) | 0.4 μg/kg/h, Infusion | 0.1 mg/kg/h, Infusion | Richmond Agitation Sedation Scale | IV, XI |
| Study (Reference) | Year | Type of surgery/procedure | Patient age (range) & ASA status | Patients enrolled (Gender: F/M, n) | DEX dose, route of administration | MDZ dose, route of administration | Scale used for sedation measurement | Outcomes |
|-------------------|------|---------------------------|----------------------------------|-----------------------------------|---------------------------------|---------------------------------|-----------------------------------|----------|
| Bhadla et al²⁵    | 2013 | Ophthalmic day-care surgery | 5-12 y (ASA I-II)               | 60 (21/39)                        | 0.4 μg/kg, IV                   | 0.05 mg/kg, IV                  | 5-points scale                    | I, II, IV, V, VIII, XIII          |
| Sheta et al²⁶     | 2013 | Complete dental rehabilitation | 3-6 y (ASA I-II)               | 72 (41/31)                        | 1 μg/kg, Intranasal             | 0.2 mg/kg, Intranasal           | 4-point scale                     | I-IV, IX, X, XII, XIII            |
| Arora et al²⁷     | 2014 | Elective urogenital surgical procedures | 1-4 y (ASA I-II)   | 56 (4/52)                         | 4 μg/kg, Oral                   | 0.5 mg/kg, Oral                 | 4-point scale                     | I, II                                   |
| Pant et al²⁸      | 2014 | Inguinal hernia repair, orchidopexy, or circumcision | 1-12 y (ASA I-II) | 100 (12/88)                       | 1.5 μg/kg, Sublingually         | 0.25 mg/kg, Sublingually        | 6-point scale                     | I, II                                   |
| Savla et al²⁹     | 2014 | Short elective surgical procedure | 1-6 y (ASA I-II)   | 34 (2/32)                         | 2 μg/kg, Intranasal             | 0.5 mg/kg, Intranasal           | 6-point scale                     | II                                      |
| Linares Segovia et al³⁰ | 2014 | Elective surgery | 2-12 y (ASA I)               | 108 (52/56)                       | 1 μg/kg, Intranasal             | 0.5 mg/kg, Oral                 | N/A                                | II, IV                                 |
| Surendar et al³¹  | 2014 | Dental treatment | 4-14 y (ASA I)               | 63 (N/A)                          | 1. DEX 1.0 patients: 21         | 0.5 mg/kg, Intranasal           | 5-points scale                    | V, VI, VIII-X                      |
| Hojjat et al³²    | 2015 | Computed tomography scan procedures | 2-12 y (Not mentioned) | 100 (44/56)                       | 2 μg/kg, IV                     | 0.05 mg/kg, IV                  | 6-point scale                     | IV                                      |
| Faritus et al³³   | 2015 | Surgery for congenital heart disease | 2-12 y (Not mentioned) | 60 (28/32)                        | 2 μg/kg, Oral                   | 0.5 mg/kg, Oral                 | 6-point scale                     | II, V, VI, VIII                    |
| Singla et al³⁴    | 2015 | Elective surgery | 3-10 y (ASA I)               | 60 (29/31)                        | 1 μg/kg, Intranasal             | 0.5 mg/kg, Intranasal           | 6-point scale                     | I, II, V, VIII                     |
| Abdelaziz et al³⁵ | 2016 | Elective strabismus surgery | 1-7 y (ASA I-II) | 66 (32/34)                        | 1 μg/kg, Intranasal             | 0.1 mg/kg, Intranasal           | N/A                                | III, IV, XII                       |
| Ghai et al³⁶      | 2016 | Computed tomography scan procedures | 1-6 y (ASA I-II) | 59 (36/23)                        | 2.5 μg/kg, Intranasal           | 0.5 mg/kg, Oral                 | 6-point scale                     | I                                      |

(Continues)
| Study (Reference) | Year | Type of surgery/procedure | Patient age (range) & ASA status | Patients enrolled (Gender: F/M, n) | DEX dose, route of administration | MDZ dose, route of administration | Scale used for sedation measurement | Outcomes |
|-------------------|------|---------------------------|---------------------------------|----------------------------------|---------------------------------|---------------------------------|-----------------------------------|----------|
| Jambure et al⁷⁷    | 2016 | Cardiac catheterization for diagnostic/therapeutic procedures | 2-10 y (ASA I-II) | 61 (15/46) | 2 μg/kg, Intranasal | 0.5 mg/kg, Oral | 6-point scale | IX, XI |
| Jannu et al⁸⁸     | 2016 | Elective, minor, lower abdominal surgeries | 1-7 y (ASA I-II) | 60 (32/28) | 4 μg/kg, Oral | 0.75 mg/kg, Oral | 4-point scale | IV, IX, |
| Gupta et al⁹⁹     | 2017 | Elective brain magnetic resonance imaging | 1-8 y (ASA I-II) | 60 (26/34) | 1 μg/kg, Intranasal | 0.2 mg/kg, Intranasal | 6-point scale | I, II |
| Prabhu et al⁰⁰    | 2017 | Elective surgery | 1-10 y (ASA I-II) | 90 (35/55) | 4 μg/kg, Oral | 0.5 mg/kg, Oral | N/A | II-IV, X |
| Kumar et al⁴¹     | 2017 | Abdominal surgery | 2-12 y (ASA I-II) | 60 (26/34) | 1 μg/kg, Intranasal | 0.5 mg/kg, Oral | 6-point scale | I, II |
| Kumari et al⁴²     | 2017 | Ophthalmic surgery | 4-12 y (ASA I) | 60 (25/35) | 4 μg/kg, Oral | 0.5 mg/kg, Oral | 3-point scale | I, II |
| Li et al⁴³        | 2017 | Selective primary repair for tetralogy of Fallot | 5-28 mo (Not mentioned) | 38 (N/A) | 5 μg/kg, Oral | 0.5 mg/kg, Oral | 5-points scale | I, II, IX |
| Surana et al⁴⁴    | 2017 | Cleft palate surgery | 6 mo-12 y (ASA I) | 60 (30/30) | Loading dose 1 μg/kg followed by 0.5 μg/kg/h, Infusion | 0.05 mg/kg, IV | N/A | III, XI |
| Abdel-Ghaffar et al⁴⁵ | 2018 | Bone marrow aspiration and biopsy | 3-7 y (ASA I-II) | 60 (31/29) | 2 μg/kg, Inhalation | 0.2 mg/kg, Inhalation | 5-points scale | I, II, IV, XII |
| Sajid et al⁴⁶     | 2019 | Elective herniotomy | 1-6 y (ASA I) | 80 (32/48) | 4 μg/kg, Oral | 0.5 mg/kg, Oral | 5-points scale | I, II, IV, XI, |
| Sathyamoorthy et al⁴⁷ | 2019 | Dental procedures | 5-18 y (Not mentioned) | 73 (23/50) | 0.2 μg/kg, Intranasal | 0.5 mg/kg, Oral | 5-points scale | I, II |

Note: I—Number of patients with satisfactory separation from parents; II—Number of patients with satisfactory induction or mask acceptance; III—Incidence of postoperative pain needed analgesics rescue; IV—Incidence of emergence agitation; V—Hemodynamic status (SBP); VI—Hemodynamic status (DBP); VII—Hemodynamic status (MAP); VIII—Hemodynamic status (HR); IX—Onset of sedation; X—Recovery time; XI—Incidence of adverse events (Bradycardia); XII—Incidence of adverse events (Nauseas and vomiting); XIII—Incidence of adverse events (Shivering).

Abbreviations: ASA, American Society of Anesthesiologist physical status; DBP, Diastolic blood pressure; DEX, Dexmedetomidine; HR, Heart rate; MAP, Mean arterial pressure; MDZ, Midazolam; SBP, Systolic blood pressure.
of patients requiring postoperative analgesics rescue, and (d) incidence of emergency agitation. The general hemodynamic parameters, onset of sedation, and recovery time between two groups were considered as the secondary outcomes. The incidence of adverse events, including shivering, bradycardia, nausea, and vomiting, were also analyzed.

2.2.4 Study design

Randomized controlled trials with no language limitations.

2.3 Literature screening, data extraction, and assessment of the risk of bias

Two reviewers (BL and YF) conducted the literature searching and data extraction independently, and then they cross-checked with each other. After removing the duplicates from different databases, those obviously irrelevant records were excluded by titles and abstracts reviewing. The full texts of the remaining studies were obtained and perused. And then, the relevant articles were identified. To collect the general characteristics of enrolled studies, a table was designed and filled by us (Table 1). In accordance with Cochrane Collaboration tool for assessing risk of bias in randomized trials, two reviewers (BL and YF) independently evaluated the methodological quality which includes the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Any disagreements were resolved by discussion among all authors.

2.4 Grading the quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used to assess the quality of evidence and strength of recommendations. The quality of all primary and secondary outcomes was independently assessed by two reviewers (BL and YF). On the basis of risk of bias, inconsistency, indirectness, imprecision, and publication bias, the quality was classified as high, moderate, low, or very low. And GRADE profiler (version 3.6) software was used.

2.5 Statistical analysis

Statistical analyses were done with Review Manager 5.0 software (The Cochrane Collaboration). The risk ratio (RR) with 95% confidence interval (CI) and the Mantel-Haenszel method (fixed or random models) were used to analyze dichotomous data. For continuous data, standardized mean difference (SMD) was chosen for the estimation. The I-squared ($I^2$) test was chosen to weigh the impact of heterogeneity on the results. If significant heterogeneity (present at $I^2 > 50\%$) emerged, the sensitivity analysis was performed by omitting each study individually, and the random effects model was chosen; otherwise, the fixed-effects model was applied. Publication bias was evaluated by using Begg’s test when approximate ten studies or more were included in meta-analysis. A $P$ value < .05 was considered statistically significant.

2.6 Trial sequential analysis

The sparse data and the repetitive significance testing with new studies updating may result in type-1 errors (false-positive outcomes) and type-2 errors (false-negative outcomes) of meta-analyses. Trial sequential analysis (TSA), which controlled the $P$ value and widened the confidence intervals, can adjust the statistical threshold to decrease or eliminate the risk from type-1 and type-2 errors, and can estimate the required information size and trial sequential monitoring boundaries. The cumulative Z curve entering the futility area or crossing the trial sequential monitoring boundary may indicate that the present evidences of intervention effects are at a sufficient level, and further trials will be unnecessary. On the contrary, evidences are insufficient to arrive at the conclusion if Z curve does not cross any boundaries or reach the required information size. The type-I error ($\alpha$) and power were set as 0.05 and 0.80, respectively. For the same outcome, all relevant trials would be involved in analysis, and the results would not be affected by the order of their entry. The proportional reduction in the rate of bad events in clinical trials suggested 52% relative risk reduction in analysis of patients number with satisfactory separation from parents, 22% relative risk reduction in analysis of patients number with requiring postoperative analgesics rescue, and 69% relative risk reduction in analysis of incidence of emergency agitation. And the TSA was performed by the use of Trial Sequential Analysis Viewer Software (version 0.9.5.10 beta; http://www.ctu.dk/tsa).

3 RESULTS

3.1 Literature search results

A total of 440 relevant items were identified initially. One hundred eighty-four of them were excluded by duplicate removal, and 165 were excluded by reviewing the title and abstract. In these 165 excluded items, 69 were the protocols or registered trials (still recruiting or not), two were animal researches, 42 were studies performed in adult patients, 33 were unrelated reviews or meeting abstracts, and three were similar systematic reviews published in 2014 and in 2015. A total of 57 items were excluded by full-text reviewing, 54 of them were owing to the inappropriate comparisons, two of them reported the uncorrelated outcomes or the outcomes with inappropriate format, and the full
text of the rest one cannot be gained after contacting the authors. Finally, 34 studies were selected in the consequent analysis. The identification procedure of eligible items is described in Figure S1.

3.2 | Basic characteristics of enrolled studies

These included studies were published from 2004 to 2019 (33 in English and one in Chinese) and were enrolled a total of 2281 pediatric patients (ages ranged from 6 months to 18 years). The primary outcomes “the number of patients with satisfactory separation from parents” and “the number of patients with satisfactory induction or mask acceptance” were reported separately in 18 studies and in 20 studies. And the primary adverse events “the incidence of postoperative pain needed analgesics rescue” and “the incidence of emergence agitation” were mentioned in eight studies and in 14 studies. The secondary outcomes including general hemodynamic parameters (systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate), onset of sedation, recovery time, and the incidences of various adverse events (shivering, bradycardia, nausea, and vomiting) were also reported in different studies. The main characteristics of these enrolled studies were summarized in Table 1.

3.3 | Risk of bias assessment

In accordance with the Cochrane Collaboration tool for assessing risk of bias, we evaluated the mentioned-above items. A total of 65% (22/34) studies performed an adequate method of random sequence generation, and 12 studies reported allocation concealment with detailed descriptions (using opaque, sealed envelopes). Twenty-five studies described the blinding procedure of participants and personnel, and 25 studies mentioned the blinding procedure of outcome assessment. A total of eight studies were high-quality studies with low risk of bias in all items. The detail of risk of bias assessment was shown in Figure S2.

3.4 | Primary outcome 1: the number of patients with satisfactory separation from parents

Eighteen studies with 1285 patients were enrolled. The $I^2$ of 90% indicated substantial heterogeneity, but the source could not be clearly attributed to a single study by performing the sensitivity analysis; thus, the random effects model was used. The premedication of dexmedetomidine was associated with more satisfactory separation from parents compared to midazolam (81.36% vs 60.96%, RR = 0.78, with 95% CI [0.65, 0.92], $P = .004$, $I^2 = 90$%; Figure 1A). Although cumulative Z curves did not reach the required information size, the results of TSA indicated that the curves crossed both the conventional boundary and the trial sequential monitoring boundary. The level of evidence about the intervention effect was sufficient with unnecessary further trials (Figure 3A). Publication bias was detected in analysis by using of Begg’s test ($P = .006$; Figure 4A). Therefore, in order to estimate and adjust for the number and outcomes of missing studies, we performed Duval’s trim and fill method. And the results from sensitivity analyses of trim and fill method (no new studies added) revealed that the result was reliable.

3.5 | Primary outcome 2: the number of patients with satisfactory induction or mask acceptance

A total of twenty studies with 1398 patients were analyzed. The $I^2$ of 76% demonstrated that significant heterogeneity was existed. However, in sensitivity analysis, all attempts to reduce the value of $I^2$ to below 50% by excluding one single study were not successful. Therefore, random effects model was used. The using of dexmedetomidine was associated with higher rate of satisfactory induction or satisfactory mask acceptance compared to midazolam, but no significant differences were observed between two groups (71.11% vs 61.88%, RR = 0.86, with 95% CI [0.74, 1.00], $P = .06$, $I^2 = 76$%; Figure 1B). The TSA indicated that cumulative Z curves did not cross any of the boundaries, and the current number of patients was too few to achieve the required information size (2112 patients). The further evidences with large sample size are required (Figure 3B). Begg’s ($P = .381$) test suggested that publication bias was not found (Figure 4B).

3.6 | Primary outcome 3: the number of patients requiring postoperative analgesics rescue

It was reported in eight studies with 640 patients. Patients who received dexmedetomidine experienced significantly lower incidence of postoperative analgesics rescue than patients who received midazolam (22.88% vs 34.58%, RR = 0.57, with 95% CI [0.35, 0.93], $P = .02$, $I^2 = 67$% (Figure 2A). The sensitivity analysis indicated that the substantial heterogeneity ($I^2 = 67$%) was attributable to the Talon et al study. Heterogeneity was resolved ($I^2 = 0$%) by removing this study, and the summary estimate was unchanged essentially (14.13% vs 29.89%, RR = 0.47, 95% CI [0.34, 0.66], $P < .00001$). The TSA showed that cumulative Z curves crossed the conventional boundary for benefit but did not cross both trial sequential monitoring boundary and required information size. It might reveal a possible false-positive effect of dexmedetomidine in reducing the incidence of postoperative severe pain compared to midazolam. The further trials to achieve the firm evidences are necessary (Figure 3C). Begg’s test ($P = .711$) indicated that publication bias was not found in the analysis (Figure 4C).

3.7 | Primary outcome 4: the incidence of emergence agitation

The emergence agitation was mentioned in 14 studies with 969 patients. Emergence agitation was significantly
**FIGURE 1** Effects of dexmedetomidine vs midazolam in number of patients with satisfactory separation from parents and in number of patients with satisfactory induction or mask acceptance. A, Forest plot depicting the meta-analysis for the outcome "number of patients with satisfactory separation from parents"; B, Forest plot depicting the meta-analysis for the outcome "number of patients with satisfactory induction or mask acceptance"
infrequent in patients in dexmedetomidine group compared with the midazolam group (10.54% vs 34.23%, RR = 0.31, with 95% CI [0.24, 0.41], P < .00001, I² = 42%; Figure 2B). Given that the value of I² was 42%, the fixed-effects model was used. The outcome of TSA demonstrated that the cumulative Z curves crossed the conventional boundary, trial sequential monitoring boundary, and the required information size (calculated as 218). It suggested that the answer of such clinical question was definitively clear and the sample size of patients was enough. Further studies are unlikely to change the conclusions and are unnecessary (Figure 3D). After Begg’s test (P = .827), no publication bias was found in the analysis (Figure 4D).

### 3.8 Secondary outcomes

All secondary outcomes involving hemodynamic parameters, onset of sedation, recovery time, and incidence of different adverse effects were clarified in Table 2. The details about general hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were reported separately in six studies,\(^{14,20,25,31,33,34}\) three studies,\(^{14,31,33}\) two studies,\(^{15,16}\) and eight studies.\(^{14-16,20,25,31,33,34}\) The results indicated that the using of dexmedetomidine was associated with significant less value of SBP (SMD = 0.99, with 95% CI

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**FIGURE 2** Effects of dexmedetomidine vs midazolam in number of patients requiring postoperative analgesics rescue and in incidence of emergence agitation. A, Forest plot depicting the meta-analysis for the outcome “number of patients requiring postoperative analgesics rescue”; B, Forest plot depicting the meta-analysis for the outcome “incidence of emergence agitation.”
The difference of onset of sedation between two groups was not significant (SMD = −0.26, with 95% CI [−2.04, 1.52], P = .78, I² = 98%), which was inconsistent with the previous outcome from the similar systematic review. It might be resulted from the different sample sizes. And we also found two groups did not differ significantly in recovery time.

The analysis of various adverse events exhibited that the patients in dexmedetomidine group suffered increased incidence of bradycardia, and experienced lower rate of shivering. The incidence of postoperative nausea or vomiting was not different between two groups. However, the reports about the incidence of the adverse events were relatively scarce.

### 3.9 Quality of the evidence

We used GRADE approach to grading the level of each outcome in present study. Although the results from risk of bias assessment part indicated that the quality of trials design was reasonable, the GRADE summary of findings table demonstrated that the overall level of current evidence in our meta-analysis was moderate or low, which might be resulted from the inconsistency issue and, particularly, the limited number of events (Table S1).

### 4 DISCUSSION

Pediatric sedation is always served as one of conundrums during diagnostic and surgical procedures, such area changes rapid and engenders several debates among the anesthesiologists and pediatric specialists. For instance, the optimal premedication between dexmedetomidine and midazolam for pediatric sedation also remains controversial. Although relevant meta-analyses published during 2014-2015 seemed to validate the superiority of dexmedetomidine both in providing sedative effects and in alleviating adverse events compared to midazolam, the recent published studies with inconsistent conclusions prompted us to update the analysis (eg, Abdel-Ghaffar et al suggested that no significant differences were found in sedative level at parental separation between two groups; Sajid et al and Sathyamoorthy et al showed that sedative level at mask induction of children in two groups was approximately similar). Compared with the previous
In order to thoroughly evaluate the efficacy and safety of paediatric sedation, we conducted meta-analyses and added the latest evidence from the literature. In addition, we performed trial sequential analysis (TSA) to determine whether the required information size was met to draw conclusions about the primary outcomes. The GRADE methodology was employed to assess the quality of the available evidence.

Our analysis revealed that patients who received dexmedetomidine as premedication had a lower incidence of postoperative pain and emergence agitation compared to those who received midazolam. This result supports the potential analgesic effects of alpha-2 agonists.

The TSA results indicated that the current sample size was adequate to draw conclusions about the incidence of emergence agitation without the need for further studies. However, there was a possibility of a false-positive result in the dexmedetomidine group for reducing postoperative severe pain, as the cumulative Z curves only crossed the conventional boundary for benefit.

The analysis also showed that patients who received dexmedetomidine had a greater number of satisfactory separations from parents post-premedication compared to those who received midazolam. However, the TSA results did not verify the superiority of dexmedetomidine in producing satisfactory sedation during mask induction.

The combination of sedative studies with expanded sample sizes demonstrated that the difference in onset time between dexmedetomidine and midazolam was not significant. Moreover, the summary of new evidences indicated that no difference was found in recovery time between the two groups.

Notably, the use of dexmedetomidine was associated with a significant reduction in systolic blood pressure and heart rate, but it was also linked to an increased risk of bradycardia. These findings suggest that the biphasic effects of dexmedetomidine might be derived from its unique properties.
α2-adrenoceptor. It enhanced the blood pressure temporarily as the transient vasoconstrictive effects in peripheral vasculature and then lowered the arterial pressure with decreasing sympathetic outflow.51 Even though, some researchers still regarded the dexmedetomidine as one appropriate sedative option for pediatric patients, in consideration of great hemodynamic changes could be resolved by decelerating the rate of administration.52,53

The secondary outcomes about different adverse events suggested that incidence of shivering was lower in patients received dexmedetomidine compared to midazolam. And no difference was found in occurrence rate of postoperative nausea and vomiting between two groups. However, owing to extremely limited sample size, the above data were not enough to draw a definitive and reliable conclusion. This was one of the limitations in present study. Hence, the focus in future should be moved on the evaluation of safety in using dexmedetomidine and midazolam as premedication in children.

Furthermore, the widespread moderate or low quality in outcomes evaluated by GRADE approach resulted from inconsistency (high heterogeneity) and imprecision (lack of events number). Heterogeneity might be originated from different types of procedures, administration routes, and premedication doses. The sensitivity analysis performed by us discovered one trial which brought the significant heterogeneity in evaluation of patients requiring postoperative analgesics rescue, and then, we verified the reliability of conclusion by omitting it. And the other significant heterogeneity among studies led us to use random effects models for meta-analysis.

### 5 | CONCLUSION

In conclusion, the current evidences suggest that dexmedetomidine is the preferred choice for pediatric patients than midazolam owing to its more satisfactory sedation at separation from parents and less incidence of emergence agitation. However, the superiority of using dexmedetomidine as premedication in providing adequate sedation at mask induction and postoperative analgesic effects compared to midazolam has not yet been defined. Additionally, to obtain firm evidences about the effects of dexmedetomidine vs midazolam on hemodynamic parameters and the safety of two premedicants, more high-quality trials are required. And the exploration of the optimal dose range and ideal route of using dexmedetomidine should also be considered in future.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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