Abstract

**Background:** Dexmedetomidine (DEX), an \(\alpha_2\)-adrenergic receptor agonist, produces ideal sedation and early postoperative recovery for premedication in paediatric surgery, reducing preoperative anxiety and facilitating smooth induction of anaesthesia. We performed a meta-analysis to compare the effects of DEX and midazolam (MDZ) in paediatric anaesthesia with sevoflurane.

**Methods:** PubMed, Ovid, Web of Science, and Public Health Management Corporation were searched through December 2016 for randomized controlled trials (RCTs) that compared DEX and MDZ in children undergoing sevoflurane anaesthesia. The risk ratio (RR) with 95% incidence interval (95%CI) was used for dichotomous variables.

**Results:** Twelve RCTs involving 422 patients in the DEX group and 448 patients in the MDZ group were included. Patients in the DEX group had a significantly lower incidence of unsatisfactory sedation (RR [95%CI] = 0.71 [0.57–0.89]), unsatisfactory parental separation (RR [95%CI] = 0.56 [0.35–0.87]), and rescue analgesia (RR [95%CI] = 0.52 [0.35–0.77]) than patients in the MDZ group. However, both groups had a similar incidence of unsatisfactory mask acceptance, emergence agitation, and postoperative nausea and vomiting.

**Conclusion:** Compared with MDZ, DEX is beneficial in paediatric anaesthesia with sevoflurane because of its lower incidence of unsatisfactory sedation, parental separation, and rescue analgesia.

**Keywords**

Dexmedetomidine, midazolam, paediatric anaesthesia, sevoflurane, meta-analysis

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Introduction

Paediatric anaesthesia may be accompanied by significant anxiety, uncooperative behaviour, distress, fear, and physical resistance during preoperative preparation, times of parental separation, and invasive diagnostic procedures.\(^1\) Thus, paediatric anaesthesia is always considered a principal challenge for anaesthetists. Sevoflurane is characterized by more rapid onset and offset than other inhaled anaesthetics because of its low solubility in blood, relatively low airway irritation, and stable hemodynamic effects, all of which are ideal for induction and maintenance of anaesthesia in children.\(^2,3\) However, inhaled sevoflurane in paediatric anaesthesia tends to lead to a high occurrence of emergence agitation (EA) or delirium accompanied by restlessness, crying and moaning, agitation or thrashing, and incoherence.\(^4\)

Because of the particularity and arduous work of paediatric anaesthesia, it is necessary to administer premedication using drugs such as dexmedetomidine (DEX) or midazolam (MDZ) for sedation, analgesia, relief of the stress response, and elimination of nervousness, anxiety, and fear. DEX, a highly selective \(\alpha_2\)-receptor agonist with a ratio of affinity between \(\alpha_2\) and \(\alpha_1\) receptors 7.36 times higher that of clonidine,\(^5\) is the most prevalent premedication used in paediatric anaesthesia because of its sedative, analgesic, amnesic, anxiolytic, and sympatholytic properties without respiratory depression.\(^6\) Various studies have demonstrated that DEX more effectively decreases anxiety and sedation, reduces EA, and provides postoperative analgesia than does MDZ in children;\(^7\)\(^-\)\(^10\) however, the definitive effects of DEX versus MDZ in paediatric anaesthesia with sevoflurane remain unclear.

Although some randomized controlled trials (RCTs) have compared the efficacy of DEX versus MDZ in paediatric anaesthesia with sevoflurane, the sample size in all of these trials was too small to provide a definite conclusion. Moreover, some of their results were inconsistent. Therefore, the present meta-analysis was performed to confirm their conclusions using a large sample size.

Methods

Search strategy and process

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.\(^11\) All relevant references that compared the effect of DEX versus MDZ in paediatric anaesthesia with sevoflurane were identified. PubMed, Ovid, Web of Science, and Public Health Management Corporation (updated December 2016) were systematically searched for all articles that may be included. The following search terms were used to identify comparative studies: “dexmedetomidine” or “DEX” or “\(\alpha_2\) receptor agonist,” and “midazolam” or “MD.” The primary references were filtered to include only RCTs or clinical trials involving humans without publication year restrictions but with the published language limited to English. Relevant references were manually searched to identify additional studies.

Selection and quality assessment of included studies

Citations selected from the initial search were subsequently screened for eligibility using the follow criteria: (1) all subjects were children undergoing sevoflurane anaesthesia, (2) details of the comparison between the DEX and MDZ groups were included, and (3) the study was designed as an RCT. Conference abstracts and other forms of summary publications were also excluded. In the case of multiple studies apparently
based on the same population, we included only the study with the largest number of participants. The methodological quality of the included RCTs was assessed according to the tool established by the Cochrane Collaboration. This tool was used to examine the following items: (1) description of random sequence generation, (2) allocation concealment, (3) blinding of outcome assessment and participants, (4) incomplete outcome data, and (5) selective reporting. A judgment of unclear, low, or high risk of material bias was executed for each item.9

**Data extraction and sorting**

The eligibility of the included trials was independently assessed by two co-authors (X.-X.W. and Y.-Y.L.). The titles and abstracts of the studies were screened independently by these two authors. Full texts were examined for any trial that appeared qualified. Disagreements and contradictions were resolved by discussion with a third author (J.-F.F.) to attain a consensus. For each study, the following data were collected and sorted: first author; publication year; patient age; American Society of Anesthesiologists physical status; type of surgery; dose, route, and timing of DEX or MDZ administration; incidence of unsatisfactory sedation, parental separation, and mask acceptance; and incidence of postoperative complications involving EA, rescue analgesia, and postoperative nausea and vomiting (PONV).

**Outcome measures**

The primary outcomes in this meta-analysis were the incidences of unsatisfactory sedation, unsatisfactory parental separation, and unsatisfactory mask acceptance. The secondary outcomes were the incidences of postoperative complications involving EA, rescue analgesia, and PONV.

**Statistical analysis**

The statistical analysis of all included RCTs was performed using Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark). Pooled estimates of risk ratio (RRs) with corresponding 95% confidence intervals (95%CIs) were calculated for dichotomous data using the Mantel–Haenszel method. The I-square ($I^2$) test was conducted to estimate heterogeneity; if heterogeneity was present at $I^2 > 50\%$, a random-effects model was selected; otherwise, a fixed-effects model was used according to the Cochrane Review guidelines. Potential publication bias was assessed using a funnel plot. Point estimates of RR were considered statistically significant when $P < 0.05$.

**Results**

**Literature search**

In total, 451 references were identified. Among them, 140 were duplicates. After excluding 231 irrelevant studies, 60 studies involving adults, and 8 RCTs without sevoflurane anaesthesia, the remaining 12 RCTs were included (Figure 1).1,4,13–22 These 12 RCTs included 454 patients in the DEX group and 480 patients in the MDZ group. Clinical heterogeneity was mostly derived from the type of surgery and the dose, route, and timing of drug administration (Table 1). Two routes of DEX administration were used: intranasal in five trials1,13,16,17,19 and oral in seven trials.4,14,15,18,20–22 DEX was administered at different doses: $\leq 2 \mu g/kg$ in nine trials,1,13,15–17,19–22 $2.5 \mu g/kg$ in one trial,4 and $4 \mu g/kg$ in two studies.14,18 The route and dose of MDZ administration also varied among the RCTs (Table 1). Yuen et al.22 compared 0.5- and 1.0-μg/kg doses of DEX with MDZ.

As shown in Figure 2, a risk of bias remained in some studies. A funnel plot was employed to evaluate publication bias with respect to unsatisfactory sedation. Only one RCT showed evident publication bias based
Quantitative data analysis

Primary outcomes. Unsatisfactory sedation was reported in all included studies.\textsuperscript{1,4,13–22} Low heterogeneity was present between the studies ($I^2 = 5\%$). The incidence of unsatisfactory sedation in the DEX group was significantly lower than that in the MDZ group (RR [95\%CI] = 0.71[0.57–0.89], $P = 0.003$) (Figure 4(a)). Similarly, the incidence of unsatisfactory parental
Table 1. General characteristics of included studies.

| Author        | Age (y) | ASA | Type of surgery                      | DEX dose | MDZ dose | Route/timing of DEX         | Route/timing of MDZ | Sedation/anxiety scores |
|---------------|---------|-----|--------------------------------------|----------|----------|-----------------------------|----------------------|--------------------------|
| Akin, 2012    | 2–9     | I   | ADT                                  | 1.0 μg/kg| 0.2 mg/kg| Intranasal 45–60 min        | Intranasal 45–60 min| Modified observer's assessment |
| Arora, 2014   | 1–4     | I–II| Urogenital surgery                   | 4.0 μg/kg| 0.5 mg/kg| Oral 60 min                 | Oral 30 min         | 4-point scale             |
| Faritus, 2015 | 2–12    | I–II| On-pump heart surgery                | 2.0 μg/kg| 0.5 mg/kg| Oral 45 min                 | Oral 45 min         | Ramsay                   |
| Ghali, 2011   | 4–12    | I–II| ADT                                  | 1.0 μg/kg| 0.5 mg/kg| Intranasal 60 min           | Oral 30 min         | MOAA/S mYPAS              |
| Hosokaw, 2010 | 1/12–12 | I–II| Cardiac surgery                      | 0.6 μg/kg| 0.5 mg/kg| Intranasal 30 min           | Intranasal 30 min   | Ramsay                   |
| Mountain, 2011| 1–6     | I–II| Dental surgery                        | 4.0 μg/kg| 0.5 mg/kg| Oral 45 min                 | Oral 45 min         | 4-point scale             |
| Ozcengiz, 2011| 3–9     | I–II| Oesophageal dilatation               | 2.5 μg/kg| 0.5 mg/kg| Oral 45 min                 | Oral 45 min         | Emergence agitation       |
| Pant, 2014    | 1–12    | I–II| Inguinal hernia repair, orchidopexy, | 1.5 μg/kg| 0.25 mg/kg| Intranasal >45 min          | Intranasal >20 min  | MOAA/S                    |
|               |         |     | circumcision                          |          |          |                             |                      |                          |
| Savla, 2013   | 1–6     | I–II| Short elective surgery               | 2.0 μg/kg| 0.5 mg/kg| Oral 30 min                 | Intranasal 30 min   | Ramsay                   |
| Schmidt, 2007 | 7–12    | I–II| Ambulatory surgery                    | 1.0 μg/kg| 0.5 mg/kg| Oral 45 min                 | Oral 30 min         | STAIC STAI                |
| Sheta, 2013   | 3–6     | I–II| Dental surgery                        | 1.0 μg/kg| 0.5 mg/kg| Intranasal 45–60 min        | Intranasal 45–60 min| 4-point scale             |
| Yuen, 2008    | 2–12    | I–II| Minor surgery                         | 0.5 or 1.0 μg/kg | 0.5 mg/kg | Oral 30 min | Oral 30 min | MOAA/S |

ASA, American Society of Anesthesiologists physical status; DEX, dexmedetomidine; MDZ, midazolam; ADT, adenotonsillectomy; MOAA/S, modified from the observer assessment of alertness and sedation scale; mYPAS, modified Yale preoperative anxiety scale; STAIC, State-Trait Anxiety Inventory for Children; STAI, State-Trait Anxiety Inventory for Adults.
separation\textsuperscript{1,13,14,16,18,19,22} was significantly lower in the DEX than MDZ group (RR [95\% CI] = 0.56 [0.35–0.87], \( P = 0.01 \)) with high heterogeneity (\( I^2 = 74\% , \ P < 0.001 \)) (Figure 4(b)). However, the patients in the two groups had a similar incidence of unsatisfactory mask acceptance (Figure 4(c)).\textsuperscript{1,13,14,18–20}

\textbf{Secondary outcomes.} Four RCTs\textsuperscript{1,4,13,17} reported the incidence of sevoflurane-related EA by comparison of the DEX and MDZ groups (Figure 5(a)). The incidence of rescue analgesia was significantly lower in the DEX than MDZ group (RR [95\% CI] = 0.52 [0.35–0.77]; \( P = 0.001 \)) (Figure 5(b)). However, there was no significant difference in the prevalence of PONV\textsuperscript{1,13,17} between the two groups (Figure 5(c)).

\textbf{Discussion}
This meta-analysis included 12 RCTs that compared the pharmacological effect of DEX versus MDZ in children undergoing...
anaesthesia with sevoflurane. The results suggest that DEX is associated with a significantly lower incidence of unsatisfactory sedation, parental separation, and rescue analgesia than is MDZ.

Various drugs have been used for premedication to eliminate the adverse events associated with sevoflurane-inhaled anaesthesia in children. Oral MDZ was historically used as a common preanaesthetic medication because it effectively reduced anxiety and allowed for uneventful parental separation in children undergoing induction of anaesthesia without impacting the recovery time. Oral MDZ has since been substituted with other drugs, such as the $\alpha_2$-agonists clonidine and DEX, for premedication in children.

DEX, a highly selective $\alpha_2$-agonist with sedative and analgesic functions, is an effective adjuvant medication that can be given before anaesthetic induction in children without inducing respiratory or hemodynamic effects. Children with DEX-induced sedation are characterized as cooperative and semi-arousable, in contrast to the indistinct consciousness induced by MDZ or propofol via the $\gamma$-aminobutyric acid receptor. DEX was recently recommended as an anxiolytic and sedative medication for use in the intensive care unit and during procedural sedation. Like MDZ, DEX may be associated with satisfactory parental separation because of ideal sedation. One study showed that children who received DEX before induction had a lower incidence of unsatisfactory sedation and parental separation, which is consistent with our results.

Sevoflurane, an inhaled anaesthetic with a fragrant and fruity smell, creates fewer airway stimuli and has a prompt onset and offset without hemodynamic effects. Thus, it is often considered to be the preferred inhaled anaesthetic for procedures that range from outpatient procedures to elective surgery. However, increasing evidence has shown that sevoflurane for anaesthesia in

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Figure 3. Funnel plot for incidence of unsatisfactory sedation to assess publication bias. RR: risk ratio.
children is associated with a high incidence of EA.\textsuperscript{4,25} Singh et al.\textsuperscript{26} compared the incidence of EA among isoflurane, desflurane, and sevoflurane in children and found that sevoflurane was associated with a higher incidence of EA. DEX was recently associated with a lower incidence of postoperative EA than placebo in children undergoing general anaesthesia, especially with sevoflurane.\textsuperscript{12,27–30} However, the present findings do not prove that DEX effectively prevents the occurrence of postoperative sevoflurane-associated EA.

Compared with other premedications, DEX has potential analgesic properties and is opioid-sparing. The analgesia may be concentrated on the alleviation of inflammatory and oxidation reactions,\textsuperscript{31} activation of central $\alpha_2$-adrenergic receptors in the locus coeruleus,\textsuperscript{32} sedation, and prevention

![Figure 4. Forest plot for primary outcomes: incidence of unsatisfactory (a) sedation, (b) parental separation, and (c) mask acceptance during induction between the dexmedetomidine and midazolam groups. M-H: Mantel–Haenszel method; 95%CI: 95% confidence interval.](image-url)
of EA. Consistent with other studies, our results also prove that DEX favours reduction in the need for rescue analgesia during anaesthesia.

Moreover, DEX is associated with a shorter stay in the post-anaesthesia care unit following sevoflurane anaesthesia in paediatric patients. Some trials have shown that premedication with DEX in children clearly reduces the incidence of EA, improves sedation and parental separation, and shortens the stay in the post-anaesthesia care unit compared with other sedatives such as midazolam or propofol. Our results are in accordance with their findings.

Compared with previous meta-analyses, our study has some different findings. This is the first study to analyse the most recent RCTs of only children (<12 years of age) undergoing general anaesthesia with sevoflurane. We comprehensively compared DEX and MDZ with respect to the quality of recovery, including the incidence of unsatisfactory sedation, parental separation, and mask acceptance as well as the incidence of postoperative complications such as EA, rescue analgesia, and PONV.

Our findings should be interpreted with caution because of the limitations in this meta-analysis. Although 12 RCTs were included, the sample size of the included studies was small. Moreover, fewer than 12 studies were included in some outcome analyses. Therefore, more RCTs with larger sample sizes are needed to confirm
our findings. Second, the patients underwent different types of surgery and received different doses of DEX or MDZ, which may also limit the reliability of our findings. However, a subgroup analysis based on different types of surgery or different doses of drugs was unable to be performed because of the small sample size and lack of original data.

In conclusion, premedication with DEX significantly promotes the recovery quality during sevoflurane-inhaled anaesthesia in paediatric patients, reducing unsatisfactory sedation and parental separation and the need for rescue analgesia compared with MDZ.

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Authors’ contributions
Dr. J.-F. Feng designed the study; Drs. X.-X. Wang, Y.-Y. Lu, and D.-G. Pang checked the data and statistical analysis; Drs. W. Peng and J.-L. Mo wrote the manuscript; and Dr. J.-F. Feng reviewed the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests
The authors declare that there is no conflict of interest.

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