Systematic Review and Meta-Analysis

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The comparison of dexmedetomidine and ketamine for pediatric dental surgery

A meta-analysis of randomized controlled studies

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Abstract

Introduction: Dexmedetomidine and ketamine are used for the sedation of pediatric dental surgery. We conduct a systematic review and meta-analysis to compare the sedation of dexmedetomidine and ketamine for pediatric dental surgery.

Methods: PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched. Randomized controlled trials (RCTs) assessing the influence of dexmedetomidine versus ketamine on pediatric dental surgery are included. Two investigators independently have searched articles, extracted data, and assessed the quality of included studies. This meta-analysis is performed using the random-effect model.

Results: Four RCTs involving 163 children are included in the meta-analysis. Compared with ketamine for pediatric dental surgery, dexmedetomidine results in comparable sedation level (very low quality, 2 RCTs, n = 40; Std. MD = −0.26; 95% CI = −0.74 to 0.23; $P = .31$), intraoperative analgesia scores (very low quality, 2 RCTs, n = 98; Std. MD = 0.17; 95% CI = −0.23 to 0.57; $P = .40$), postoperative analgesia scores (very low quality, 2 RCTs, n = 98; Std. MD = 0.23; 95% CI = −0.17 to 0.62; $P = .27$), DBP (very low quality, 3 RCTs, n = 123; Std. MD = −0.38; 95% CI = −1.04 to 0.27; $P = .25$) and SpO_2 (very low quality, 3 RCTs, n = 123; Std. MD = 0.24; 95% CI = −0.20 to 0.69; $P = .28$), but significantly decreases heart rate (very low quality, 3 RCTs, n = 123; Std. MD = −1.51; 95% CI = −2.75 to −0.27; $P = .02$) and SBP (very low quality, 3 RCTs, n = 123; Std. MD = −0.62; 95% CI = −1.16 to −0.08; $P = .02$), longer recovery time (very low quality, 3 RCTs, n = 138; Std. MD = 1.74; 95% CI = 0.23 to 3.25; $P = .02$).

Conclusions: Dexmedetomidine and ketamine have similar sedation, analgesia scores, and hemodynamic balance, but very low quality of the evidence (GRADE) is revealed in this meta-analysis.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials.

Keywords: dexmedetomidine, ketamine, meta-analysis, pediatric dental surgery, sedation

1. Introduction

Pain, fear, anxiety, and anger are the main emotional components when treating a child by a pedodontist.[1–3] Some behavioral (non-pharmacologic) management procedures (e.g., tell-show-do, positive reinforcement, and controlled expectations) should be conducted in the most fearful and uncooperative children.[4,5] Pharmacological methods have emerged as an important approach to augment child cooperativeness and provide quality dental care. Pharmacological sedation in pedodontics is performed in order to transform the patient's behavior to a level that allows employing behavior management techniques.[5–7]

Dexmedetomidine is known as a potent, highly selective α-2 adrenoceptor agonist, and can inhibit sympathetic activity by activating the receptors in the central nervous system.[8,9] It results in a reduction in blood pressure and heart rate, sedation, and anxiolysis in dose-dependent way, with no respiratory depression.[10,11] Dexmedetomidine has been extensively studied in dental surgery.[12–14] Ketamine, a phencyclidine derivative can produce a state of sedation, anesthesia, immobility, analgesia, and amnesia through blocking n-methyl d-aspartate receptors.[15]

Although much research has been conducted on different sedation drugs in children, a "golden" sedation drug has yet to be discovered.[16] We, therefore, conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to compare the efficacy of dexmedetomidine versus ketamine for the sedation of pediatric dental surgery.

2. Materials and methods

Ethical approval and patient consent are not required since this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[17]

2.1. Search strategy and study selection

Two investigators have independently searched the following databases (inception to June 2018): PubMed, Embase, and the Cochrane Register of Controlled Trials. The electronic search strategy is performed using the following keywords: dexmedetomidine, and ketamine, and dental. We also have checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

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The authors declare no conflict of interest.

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The following inclusive selection criteria are applied:

(i) population: children undergoing dental surgery;
(ii) intervention: dexmedetomidine;
(iii) comparison: ketamine; and
(iv) study design: RCT.

2.2. Data extraction and outcome measures

We have used a piloted data-extraction sheet, which covers the following information: first author, number of patients, age, male, weight, and detail methods in 2 groups. Data are extracted independently by 2 investigators, and discrepancies are resolved by consensus. We have contacted the corresponding author to obtain the data when necessary. No simplifications and assumptions are made.

The primary outcome is sedation level. Secondary outcomes include intraoperative analgesia, postoperative analgesia, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), SpO_2, and recovery time.

2.3. Risk of bias in individual studies

Risk of bias was assessed by 2 authors independently via using Cochrane risk of bias tool which includes 7 criteria (rating: low, unclear, or high risk of bias): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Discrepancies are rechecked with a third reviewer and consensus is obtained by discussion.[18]

2.4. Statistical analysis

We have estimated standard mean differences (Std. MDs) with 95% confidence intervals (CIs) for continuous outcomes (sedation level, intraoperative analgesia, postoperative analgesia, heart rate, SBP, DBP, SpO_2, and recovery time) [19,20]. A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity.[21] Whenever significant heterogeneity is present, we search for potential sources of heterogeneity. Sensitivity analysis is performed to detect the influence of a single study on the overall estimate via omitting 1 study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias is not assessed. Results are considered statistically significant for $P < .05$. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

2.5. Quality of evidence

The quality of evidence for each outcome is evaluated based on the methodological quality and the confidence in the results, and it is assessed by GRADE recommendations as high quality, moderate quality, low quality, or very low quality.[22]

3. Results

3.1. Literature search, study characteristics, and quality assessment

A detailed flowchart of the search and selection results is shown in Figure 1. 471 potentially relevant articles are identified

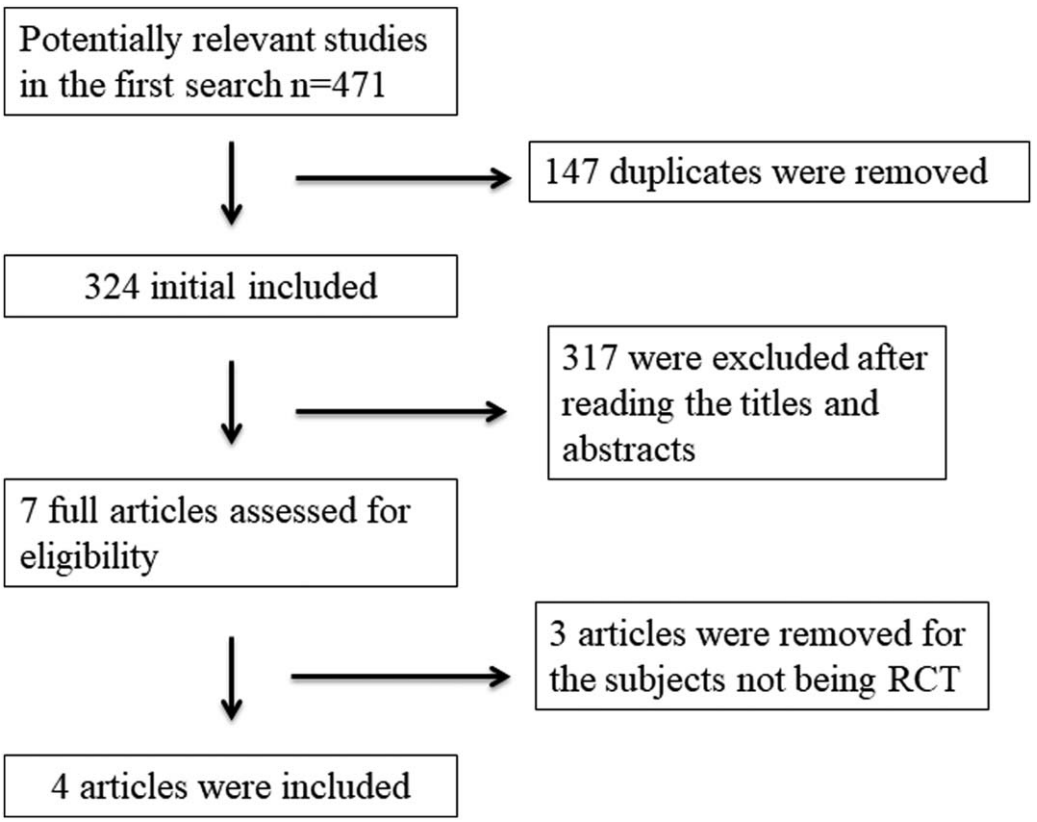

Figure 1. Flow diagram of study searching and selection process.

initially. Finally, 4 RCTs that meet our inclusion criteria are included in the meta-analysis.[1,5,23,24]

The main characteristics of the 4 included RCTs are presented in Table 1. The 4 studies are published between 2014 and 2016, and sample sizes range from 25 to 56 with a total of 163. There are oral and intranasal approaches for 2 drugs. The doses of dexmedetomidine range from 1 μg/kg to 5 μg/kg, and the doses of ketamine are about 2 to 8 mg/kg.

Among the 4 RCTs, 2 studies have reported sedation level,[5,23] 2 studies have reported intraoperative analgesia and postoperative analgesia,[1,24] 3 studies have reported heart rate, SBP, DBP, and SpO_2,[1,5,24] and 3 studies have reported recovery time.[1,23,24] The details for risk of bias tool are shown in Figure 2. Randomized sequence generation, allocation concealment, blinding and outcome data are conducted adequately in most studies. GRADE evidence is represented by summary of findings tables (Table 2).

3.2. Primary outcome: sedation level

This outcome data is analyzed with the random-effects model, and the pooled estimate of the 2 included RCTs suggested that there is no statistical difference of sedation level between dexmedetomidine and ketamine for pediatric dental surgery (very low quality, 2 RCTs, n = 40; Std. MD = −0.26; 95% CI = −0.74 to 0.23; $P = .31$), with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $P = .31$, Fig. 3).

3.3. Sensitivity analysis

No heterogeneity is observed among the included studies for the sedation level. Thus, we do not perform sensitivity analysis by omitting 1 study in each turn to detect the source of heterogeneity.

3.4. Secondary outcomes

Compared to ketamine for pediatric dental surgery, dexmedetomidine shows no significant impact on intraoperative analgesia scores (very low quality, 2 RCTs, n = 98; Std. MD = 0.17; 95% CI = −0.23 to 0.57; $P = .40$; Fig. 4), postoperative analgesia scores (very low quality, 2 RCTs, n = 98; Std. MD = 0.23; 95% CI = −0.17 to 0.62; $P = .27$; Fig. 5), but is associated with remarkably decreased heart rate (very low quality, 3 RCTs, n = 123; Std. MD = −1.51; 95% CI = −2.75 to −0.27; $P = .02$; Fig. 6) and SBP (very low quality, 3 RCTs, n = 123; Std. MD = −0.62; 95% CI = −1.16 to −0.08; $P = .02$; Fig. 7). No significant difference is found in DBP (very low quality, 3 RCTs, n = 123; Std. MD = −0.38; 95% CI = −1.04 to 0.27; $P = .25$; Fig. 8) and SpO_2 (very low quality, 3 RCTs, n = 123; Std. MD = 0.24; 95% CI = −0.20 to 0.69; $P = .28$; Fig. 9) between 2 groups. In addition, dexmedetomidine results in longer recovery time than ketamine for pediatric dental surgery (very low quality, 3 RCTs, n = 138; Std. MD = 1.74; 95% CI = 0.23–3.25; $P = .02$; Fig. 10).

4. Discussion

Unlike conventional GABAergic sedative drugs (e.g., midazolam), dexmedetomidine acts in the locus coeruleus of the central nervous system and produces the electroencephalogram activity resembling natural sleep. Patients become easily orientated and cooperative.[11,25–28] One study compares the intranasal dexmedetomidine (1 μg/kg), ketamine (5 mg/kg), and placebo (saline) in

Table 1

Characteristics of included studies.

		Dexmedetomidine group					Ketamine group				
No.	Author	Number	Age, yr	Male, n	Weight, kg	Methods	Number	Age, yr	Male, n	Weight, kg	Methods
1	Malhotra 2016	13	4.60 ± 1.99	–	15.62 ± 4.21	Intranasal dexmedetomidine at 1 μg/kg	12	4.60 ± 1.99	–	15.62 ± 4.21	0.4 mL intranasal placebo (normal saline) followed at 30 min by oral administration of midazolam 0.5 mg/kg and 5 mg/kg ketamine mixed in 30 mL mango juice
2	Zanaty 2015	20	3.55 ± 0.97	29	17.38 ± 1.95	Premedication with nebulized dexmedetomidine (2 μg/kg) by A standard hospital jet nebulizer via a mouthpiece	20	3.37 ± 0.72	33	16.88 ± 1.49	Premedication with nebulized ketamine (2 mg/kg) by a standard hospital jet nebulizer via a mouthpiece
3	Surendar 2014	21	7.24 ± 2.36	–	17.71 ± 5.36	Intranasal dexmedetomidine 1.5 μg/kg	21	6.71 ± 2.31	–	16.52 ± 3.87	Intranasal ketamine 5 mg/kg
4	Singh 2014	28	6.82 ± 2.22	14	16.61 ± 4.92	Oral dexmedetomidine 5 μg/kg	28	6.54 ± 1.79	14	16.89 ± 4.33	Oral ketamine 8 mg/kg

Table 2

XXX.

Dexmedetomidine group versus Ketamine group for pediatric dental surgery

Patient or population: patients with pediatric dental surgery
Settings:
Intervention: Dexmedetomidine group versus Ketamine group

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Dexmedetomidine group versus Ketamine group	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
sedation level		The mean sedation level in the intervention groups was **0.26 standard deviations lower** (0.74 lower to 0.23 higher)		65 (2 studies)	⊕⊖⊖⊖ very low[1,2]	SMD -0.26 (-0.74 to 0.23)
Intra operative analgesia (score)		The mean intra operative analgesia (score) in the intervention groups was **0.17 standard deviations higher** (0.23 lower to 0.57 higher)		98 (2 studies)	⊕⊖⊖⊖ very low[2,3,4]	SMD 0.17 (-0.23 to 0.57)
Post operative analgesia (score)		The mean post operative analgesia (score) in the intervention groups was **0.23 standard deviations higher** (0.17 lower to 0.62 higher)		98 (2 studies)	⊕⊖⊖⊖ very low[2,3,4]	SMD 0.23 (-0.17 to 0.62)
Hear rate (beats/min)		The mean hear rate (beats/min) in the intervention groups was **1.51 standard deviations lower** (2.75 to 0.27 lower)		123 (3 studies)	⊕⊖⊖⊖ very low[1,2,3,4,5]	SMD -1.51 (-2.75 to -0.27)
SBP		The mean sbp in the intervention groups was **0.62 standard deviations lower** (1.16 to 0.08 lower)		123 (3 studies)	⊕⊖⊖⊖ very low[1,2,3,4,5]	SMD -0.62 (-1.16 to -0.08)
DBP		The mean dbp in the intervention groups was **0.38 standard deviations lower** (1.04 lower to 0.27 higher)		123 (3 studies)	⊕⊖⊖⊖ very low[1,2,3,4,5]	SMD -0.38 (-1.04 to 0.27)
SpO2,%		The mean spo2,% in the intervention groups was **0.24 standard deviations higher** (0.2 lower to 0.69 higher)		123 (3 studies)	⊕⊖⊖⊖ very low[1,2,3,4]	SMD 0.24 (-0.2 to 0.69)
Recovery time (min)		The mean recovery time (min) in the intervention groups was **1.74 standard deviations higher** (0.23 to 3.25 higher)		138 (3 studies)	⊕⊖⊖⊖ very low[2,3,4,5]	SMD 1.74 (0.23 to 3.25)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The study conducted by Malhotra has performance bias and attrition bias.
[2] The sample size is less than 400.
[3] The study conducted by Singh has reporting bias.
[4] The study conducted by Surendar has performance bias.
[5] high heterogeneity.

150 children between 1 and 10 years to facilitate propofol administration for a magnetic resonance imaging. The results reveal fewer children withdrew or fought against the procedure in the 2 treatment groups whose premedication has equal efficacy.[29] Our meta-analysis has included 4 RCTs involving 163 children, and the results demonstrate that dexmedetomidine and ketamine have comparable sedation level, intraoperative analgesia, postoperative analgesia scores, DBP, and SpO_2 for pediatric dental surgery, but dexmedetomidine premedication leads to decreased heart rate, SBP and increased recovery time. The hemodynamics is well balanced in 2 groups.

Oral administration is widely accepted as efficacious, economic, and convenient among all routes of conscious sedation. Intranasal site is highly vascularized and very permeable for drug administration in order to ensure rapid absorption into systemic circulation. The administration of the drugs is well tolerated, effective, and fast acting.[30] Nebulized dexmedetomidine administration can provide rapid drug absorption through nasal, respiratory, and buccal mucosa, and allow bioavailability of 65% through nasal mucosa and 82% through buccal mucosa.[31,32]

Oral administration may be difficult in uncooperative children. An atomized spray of drug results in maximizing surface area coverage with a thin layer of drug, less drug loss to the oropharynx, higher cerebrospinal fluid levels, better patient acceptability, and improved clinical effectiveness than oral administration.[33] One RCT compares effects of nebulized dexmedetomidine versus nebulized ketamine and their combination on mask induction and satisfactory sedation in children undergoing dental surgeries. The results find that nebulized combination of low-dose ketamine and dexmedetomidine has more satisfactory sedation and provide a smoother induction of general anesthesia, more rapid recovery than ketamine or dexmedetomidine alone.[23] In addition, all included RCTs have reported no serious adverse events.[1,5,23,24]

This meta-analysis has several potential limitations that should be taken into account. First, our analysis is based on only 4 RCTs, and all of them have a small sample size ($n < 100$). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Although there is no significant heterogeneity in this meta-analysis, different doses and approaches of drugs may have an influence on the pooling results. Next, more RCTs should be conducted to explore the combination of dexmedetomidine and ketamine on the sedation of pediatric dental surgery. Finally, some unpublished and missing data may lead bias to the pooled effect.

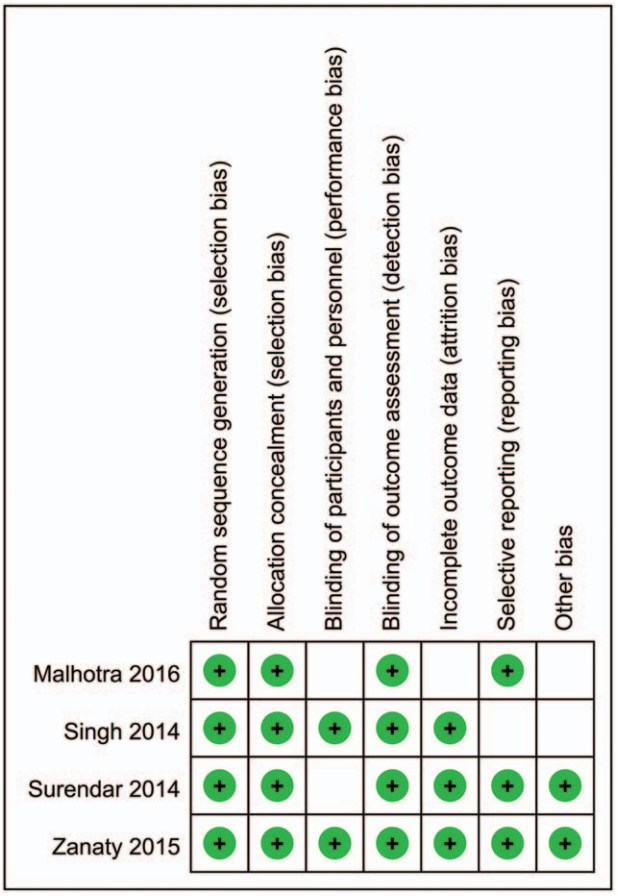

Figure 2. Assessment for risk of bias.

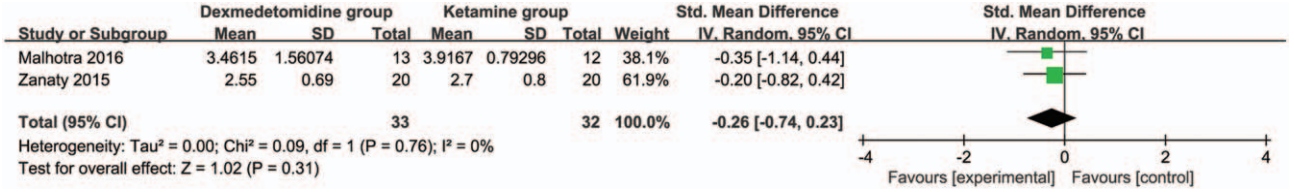

Figure 3. Forest plot for the meta-analysis of sedation level.

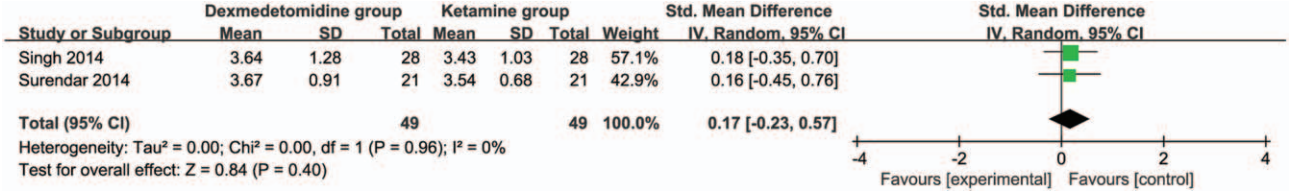

Figure 4. Forest plot for the meta-analysis of intraoperative analgesia (score).

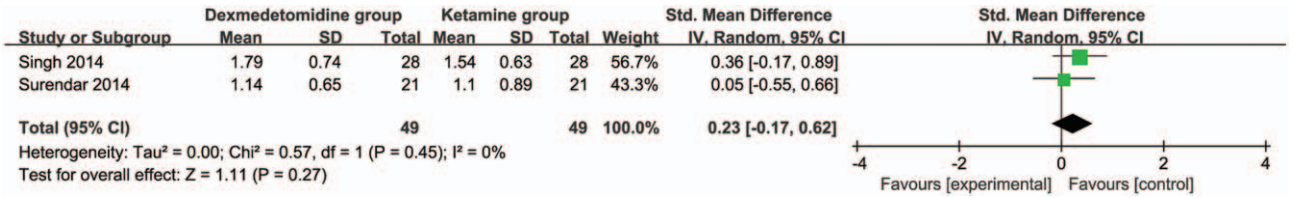

Figure 5. Forest plot for the meta-analysis of postoperative analgesia (score).

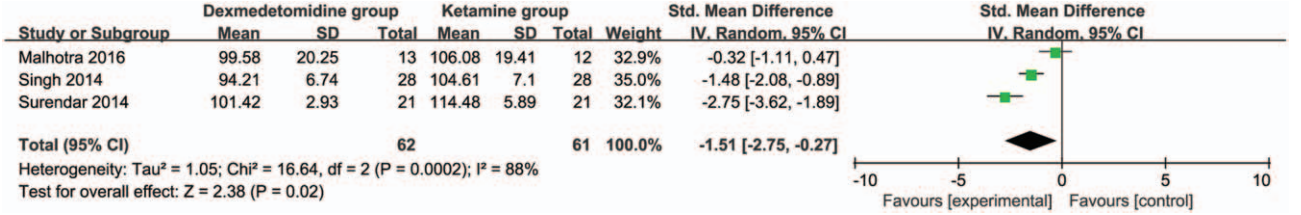

Figure 6. Forest plot for the meta-analysis of heart rate (beats/min).

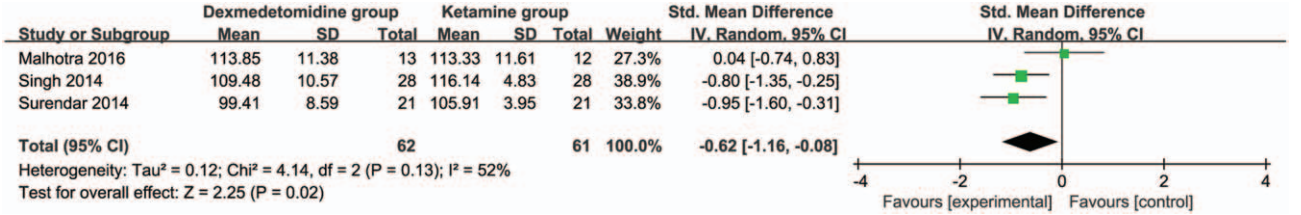

Figure 7. Forest plot for the meta-analysis of SBP (mmHg).

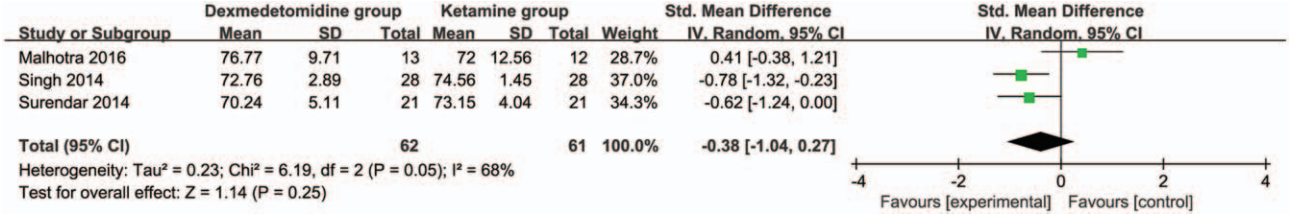

Figure 8. Forest plot for the meta-analysis of DBP (mmHg).

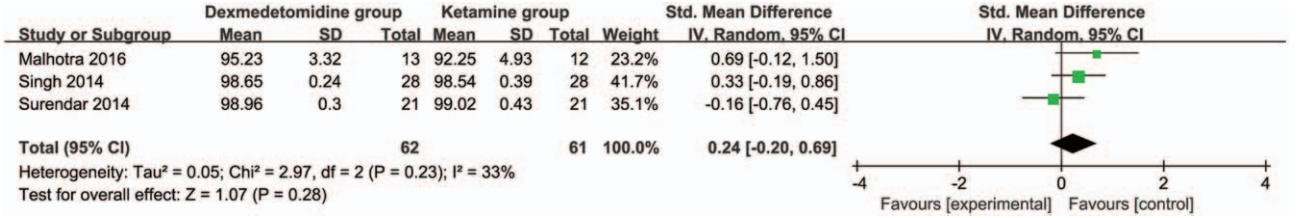

Figure 9. Forest plot for the meta-analysis of SpO_2 (%).

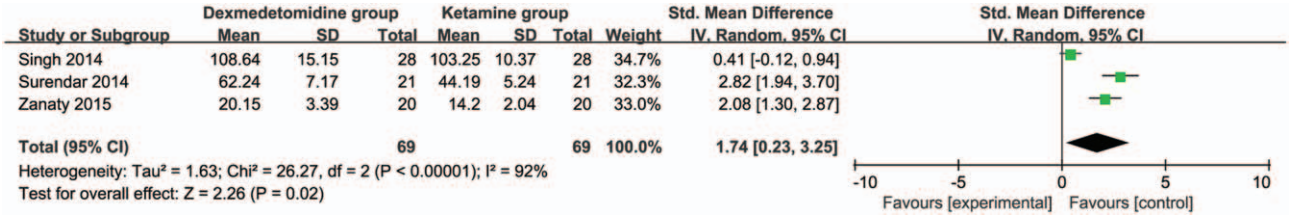

Figure 10. Forest plot for the meta-analysis of recovery time (min).

5. Conclusion

Dexmedetomidine and ketamine provide comparable sedation for pediatric dental surgery, but this study has very low-GRADE quality.

Author contributions

Conceptualization: Zhifang Luo.
Formal analysis: Zhifang Luo.
Methodology: Zhifang Luo.

Software: Jin Qiu.
Supervision: Jin Qiu.
Writing – original draft: Jin Qiu.
Writing – review & editing: Jin Qiu.

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