

Comparison of dexmedetomidine with midazolam for dental surgery

A systematic review and meta-analysis

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Abstract

Introduction: Dexmedetomidine and midazolam have become important approaches for the sedation of dental surgery. However, the comparison of these 2 drugs for the sedation of dental surgery has not been well established. We conduct a systematic review and meta-analysis to evaluate the efficacy of dexmedetomidine versus midazolam for dental surgery.

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

Results: Five RCTs and 420 patients are included in the meta-analysis. Compared with midazolam intervention for dental surgery, dexmedetomidine intervention has similar lowest SpO₂, lowest heart rate and lowest systolic blood pressure, duration of surgery, and total volume of local anesthetic, but is associated with stable and reduced lowest diastolic blood pressure.

Conclusions: Similar benefits of dexmedetomidine and midazolam intervention are observed for the sedation of dental surgery in terms of SpO₂, heart rate, systolic blood pressure, and the volume of local anesthetic, but dexmedetomidine may result in more stable diastolic blood pressure.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials, SMD = standard mean difference.

Keywords: dental surgery, dexmedetomidine, meta-analysis, midazolam, randomized controlled trials

1. Introduction

Dental surgery has become a common practice in clinical work, mainly including dental implantation, teeth extraction, and repair.^[1–3] For instance, surgical removal of third molars is one of the most commonly performed procedures by oral surgeons, and generally causes stress and fear affecting patient physiology. It is necessary to minimize anxiety and discomfort during the surgical

procedure in order to increase patient satisfaction after surgery.^[4] The sedation in dental surgery can result in the reduction in pain and anxiety, good cooperation, and patients' satisfaction.^[5–7]

Although various agents have been used for dental surgery, the ideal agent and regimen remain to be unestablished. Dexmedetomidine is a potent, highly selective α -2 adrenoceptor agonist with high selectivity for the α -2 and its action actions rely on postsynaptic α -2 adrenoceptors that activate the G proteins with good sensitivity to pertussis toxin. Activation of these receptors in the central nervous system results in the reduction in blood pressure and heart rate, decreased arousal, sedation, and anxiolysis because of the inhibition of sympathetic activity.^[8] Midazolam is a derivative of benzodiazepine, and is reported to reduce anxiety effectively without producing cardiorespiratory instability.^[9] It can lead to reliable sedation, desirable anterograde amnesic properties, good operating conditions, patient satisfaction, but is associated with delayed recovery and psychomotor function, impairment of memory, and adverse respiratory effects.^[10–12]

Dexmedetomidine may prove to be a better sedative drug for dental sedation than midazolam because of its analgesic property, shorter recovery profile, and less cognitive impairment and respiratory depression.^[13] However, the use of dexmedetomidine intervention versus midazolam intervention for the sedation of dental surgery has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting.^[4,14–16] Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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RCTs to evaluate the sedation of dexmedetomidine intervention versus midazolam intervention in patients with dental surgery.

2. Materials and methods

Ethical approval and patient consent are not required, as 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 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).^[17]

2.1. Search strategy and study selection

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

The following inclusive selection criteria are applied: population: patients (age ≥ 18 years old) with dental surgery; intervention: dexmedetomidine treatment; comparison: midazolam treatment; and study design: RCT. The exclusion criteria include acute rhinitis, upper respiratory tract infection, allergies to midazolam or dexmedetomidine, heart block, ischemic heart disease, or asthma.

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,

female, body mass index, 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 lowest plasma oxygen saturation (SpO_2). Secondary outcomes include lowest heart rate, lowest systolic blood pressure, lowest diastolic blood pressure, duration of surgery, and total volume of local anesthetic.

2.3. Quality assessment in individual studies

The Jadad Scale is used to evaluate the methodological quality of each RCT included in this meta-analysis.^[18] This scale consists of 3 evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts, and withdrawals (0–1 points). One point would be allocated to each element if they have been mentioned in article, and another 1 point would be given if the methods of randomization and/or blinding had been appropriately described. If the methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then 1 point was deducted. The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3 , the study is thought to be of high quality.^[19]

2.4. Statistical analysis

We have estimated standard mean differences (Std. MDs) with 95% confidence intervals (95% CIs) for continuous outcomes (lowest SpO_2 , lowest heart rate, lowest systolic blood pressure, lowest diastolic blood pressure, duration of surgery, and total

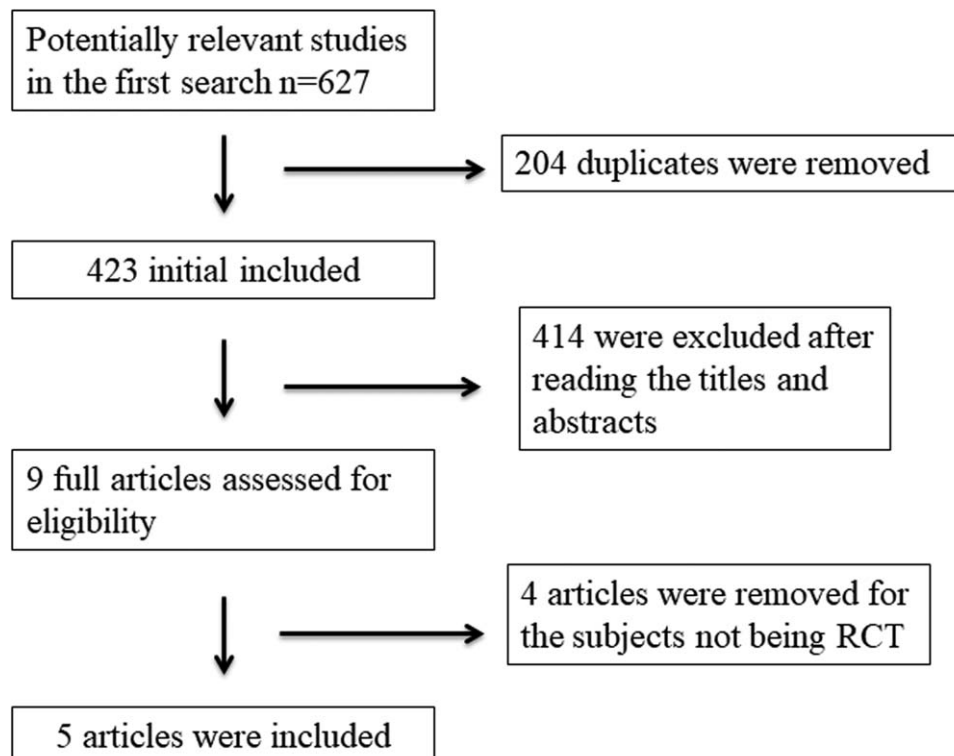


Figure 1. Flow diagram of study searching and selection process.

Table 1
Characteristics of included studies.

No.	Ref.	Dexmedetomidine group				Midazolam group				Surgery	Jada scores			
		Age, yr	Female (n)	Body weight, kg	Body mass index, kg/m ²	Number	Age, yr	Female (n)	Body weight, kg			Body mass index, kg/m ²	Methods	
1	Hiwarkar et al ^[4]	18-60	11	—	—	20	18-60	11	—	—	Intranasal dexmedetomidine sedation (1.5 µg/kg)	Intranasal midazolam sedation (0.2 mg/kg)	Surgical removal of bilaterally impacted mandibular third molars under local anesthesia	5
2	Peng et al ^[4]	43.9±14.2	5	59.1±15.8	23.0±3.9	10	46.0±13.4	3	55.8±11.1	23.2±3.3	Intravenous dexmedetomidine 2 µg/kg/h in the first 10 min, and subsequent 0.5 µg/kg/h and fentanyl (1.0 µg/kg) and dexmedetomidine (1.0 µg/kg/h) until the end of the surgery	Intravenous midazolam 0.03 mg/kg in the first 10 min, and 0.01 mg/kg in each 30 min	Dental implantation	3
3	Li et al ^[5]	41.61±9.82	11	61.12±8.63	—	30	43.34±8.43	12	59.20±7.73	—	Dexmedetomidine (1.0 µg/kg) in 20 mL of normal saline for 10 min and then a continuous infusion of dexmedetomidine (1.0 µg/kg/h) until the end of the surgery	Midazolam (0.05 mg/kg) and fentanyl (0.001 mg/kg) in 20 mL of normal saline for 10 min, followed by a continuous infusion of midazolam (0.05 mg/kg/h) until the end of the surgery	Dental implantation	4
4	Yu et al ^[6]	32±13.6	12	56.7±8.5	—	30	34.7±13.4	11	57.8±9.5	—	Dexmedetomidine (0.5 mg/kg) and fentanyl (1 mg/kg) in 20 mL of normal saline for 10 min, and then a continuous infusion of dexmedetomidine (0.5 mg/kg/h) until the end of the surgery	Midazolam (0.05 mg/kg) and fentanyl (1 mg/kg) in 20 ml of normal saline for 10 min, followed by a continuous infusion of midazolam (0.05 mg/kg/h) until the end of the surgery	Tooth extraction	4
5	Fan et al ^[3]	26 (7)	11	62 (14)	22 (4)	30	29 (9)	7	65 (9)	23 (3)	An infusion of 0.1 µg/kg/min dexmedetomidine until the adequate sedation	A loading infusion of 0.005 mg/kg/min midazolam until the adequate sedation	Third molar and dental implant surgery	4

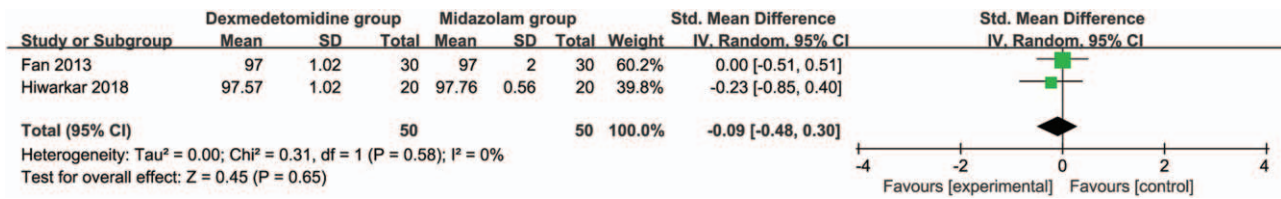


Figure 2. Forest plot for the meta-analysis of lowest SpO₂ (%).

volume of local anesthetic). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the *I*² statistic, and *I*² > 50% indicates significant heterogeneity.^[20] 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 one study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias is not assessed. Results are considered as statistically significant for *P* < .05. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

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. Six hundred twenty-seven potentially relevant articles are identified initially. Finally, 5 RCTs that meet our inclusion criteria are included in the meta-analysis.^[4,13–16]

The main characteristics of the 5 included RCTs are presented in Table 1. The 5 studies are published between 2013 and 2018, and sample sizes range from 20 to 60 with a total of 420. Three RCTs report the sole use of dexmedetomidine or midazolam,^[4,13,14] and the remaining 2 RCTs report the combination of dexmedetomidine (or midazolam) with fentanyl.^[15,16] The methods of drugs include intravenous and intranasal approaches in included RCTs, and the dental surgeries include dental implantation and tooth extraction.

Among the 5 RCTs, 2 studies have reported lowest SpO₂, and lowest heart rate,^[4,13] 3 studies have reported lowest systolic blood pressure, and lowest diastolic blood pressure,^[4,13,14] 2 studies have reported duration of surgery,^[14–16] and 2 studies have reported total volume of local anesthetic.^[14,15] Jadad scores of the 5 included studies vary from 3 to 5, and all 5 studies are considered to be high-quality ones according to quality assessment.

3.2. Primary outcome: lowest SpO₂

These outcome data are analyzed with the random-effects model; the pooled estimate of the 2 included RCTs suggested that dexmedetomidine intervention and midazolam treatment show similar lowest SpO₂ for dental surgery (Std. MD = -0.09; 95% CI = -0.48 to 0.30; *P* = .65), with no heterogeneity among the studies (*I*² = 0%, heterogeneity *P* = .58, Fig. 2).

3.3. Sensitivity analysis

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

3.4. Secondary outcomes

There is no significant difference of lowest heart rate (Std. MD = -0.14; 95% CI = -1.23 to 0.95; *P* = .80; Fig. 3) and lowest systolic blood pressure (Std. MD = -0.39; 95% CI = -1.15 to 0.37; *P* = .32; Fig. 4) between dexmedetomidine intervention and midazolam intervention for dental surgery. However, dexmedetomidine intervention is associated with reduced lowest diastolic blood pressure compared with midazolam intervention for dental surgery (Std. MD = -0.58; 95% CI = -0.95 to -0.22; *P* = .002; Fig. 5). In addition, compared with midazolam treatment for dental surgery, dexmedetomidine intervention has no substantial impact on duration of surgery (Std. MD = -0.05; 95% CI = -0.39 to 0.28; *P* = .75; Fig. 6) and total volume of local anesthetic (Std. MD = -0.13; 95% CI = -0.67 to 0.41; *P* = .63; Fig. 7).

4. Discussion

Every surgical procedure may lead to apprehension and anxiety, and good sedation is effective to reduce pain and anxiety for improved patient cooperation and satisfaction.^[21–25] The comparative evaluation of midazolam and dexmedetomidine is conducted by the intravenous or intranasal route. One study compares intravenous propofol with fentanyl and midazolam

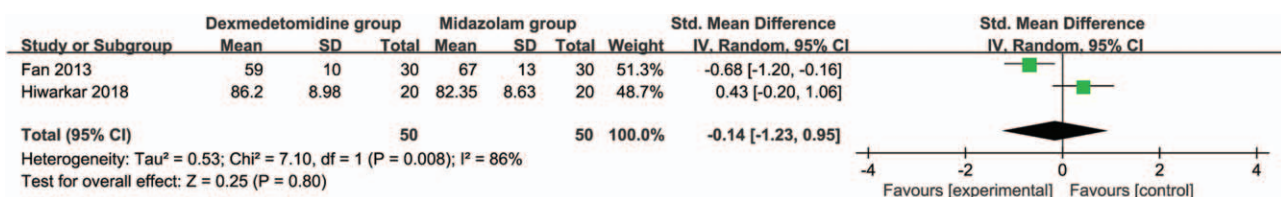


Figure 3. Forest plot for the meta-analysis of lowest heart rate (bpm).

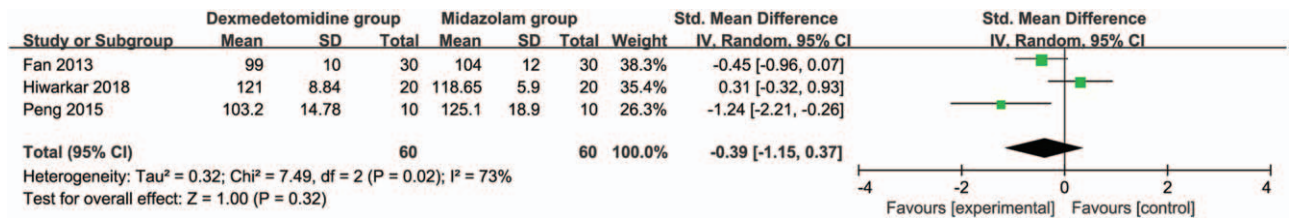


Figure 4. Forest plot for the meta-analysis of lowest systolic blood pressure (mm Hg).

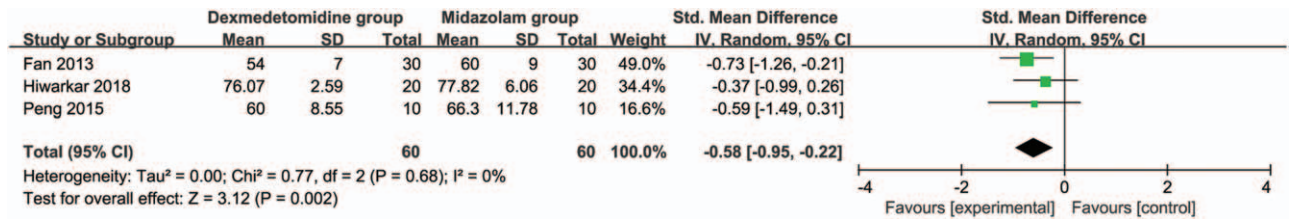


Figure 5. Forest plot for the meta-analysis of lowest diastolic blood pressure (mm Hg).

with fentanyl for third molar surgery and finds no significant reduction in vital parameters (SpO₂, pulse rate, and blood pressure). Cardiovascular parameters maintain stable throughout induction, maintenance, and recovery in these groups, and fentanyl may increase the sedative effects of both drugs.^[26] Intravenous dexmedetomidine and midazolam are reported to produce comparable sedation levels for dental implant surgery determined sedation levels.^[16,27,28]

Previous studies report no significant reduction in plasma SpO₂ in patients undergoing minor surgical procedures using midazolam and dexmedetomidine, and all patients maintain SpO₂ above 90%.^[27-29] However, one study involving 57 subjects

reveals that combination using midazolam and fentanyl for third molar surgery leads to periods of apnea greater than 20 seconds in 2 subjects who can breath after stimulation and require no assisted ventilation.^[26] All included RCTs report no apnea, and our meta-analysis conclude comparable impact on SpO₂ between dexmedetomidine and midazolam for dental midazolam.

Many studies emphasize that after using dexmedetomidine and midazolam, intraoperative heart rate remains stable without evidence of bradycardia or tachycardia in dental surgery compared to that preoperatively.^[30-32] In addition, no statistical and clinically significant change of blood pressure from mean baseline value is found in 2 studies.^[26,29] In contrast, some other

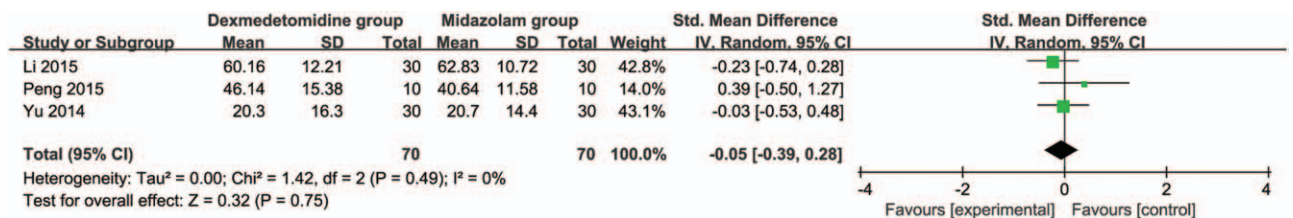


Figure 6. Forest plot for the meta-analysis of duration of surgery (min).

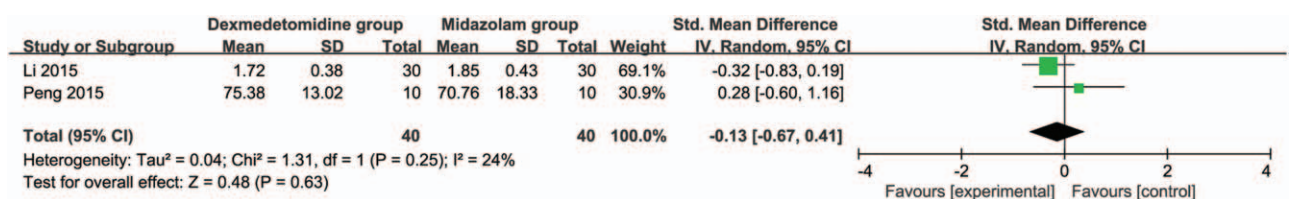


Figure 7. Forest plot for the meta-analysis of total volume of local anesthetic.

trials report mean blood pressure, including systolic blood pressure and diastolic blood pressure, has the tendency of achieving lower values than the baseline values for dexmedetomidine, and remain clinically.^[13,27] Stable change of blood pressure and heart rate after the use of dexmedetomidine and midazolam is revealed in our meta-analysis, but dexmedetomidine intervention produce lower diastolic blood pressure compared with midazolam intervention. In addition, duration of surgery and total volume of local anesthetic have no statistical difference between these 2 drugs in our meta-analysis.

Amnesia is a common characteristic of dexmedetomidine and midazolam. In one included RCT, 30% patients (n=6) have total amnesia, 70% patients (n=14) with partial amnesia for midazolam intervention. Although 20% patients (n=4) have total amnesia, rest 80% patients (n=16) with partial amnesia. Most of the patients suffer from partial amnesia in both the groups.^[4] The midazolam (or in combination with) remifentanyl for patient-controlled sedation during operations on third molars is found to produce a better level of amnesia.^[29,31]

This meta-analysis has several potential limitations that should be taken into account. First, our analysis is based on only 5 RCTs, and all of them have a relatively small sample size (n<100). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples, and more RCTs with large sample size are required to explore this issue. Next, although there is no significant heterogeneity in this meta-analysis, different methods of dexmedetomidine and midazolam may have an influence on the pooling result. These 2 drugs are used solely or in combination with fentanyl, and their approaches include intravenous and intranasal methods. Finally, some important indexes (eg, sedative levels, patient satisfaction, and recovery time) cannot undergo the meta-analysis based on current limited data from included RCTs and more studies should explore these indexes.

5. Conclusion

Dexmedetomidine and midazolam intervention provide comparable benefits for dental surgery with regard to SpO₂, heart rate, systolic blood pressure, and the volume of local anesthetic, but dexmedetomidine may be preferred because of the more stable diastolic blood pressure.

Author contributions

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