Low-Dose Intramuscular Dexmedetomidine as Premedication: A Randomized Controlled Trial

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Data Collection B
Statistical Analysis C
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Background: Dexmedetomidine-induced bradycardia or hypotension has recently attracted considerable attention because of potentially grave consequences, including sinus arrest and refractory cardiogenic shock. A route other than intravenous injection or a low dose may help minimize cardiovascular risks associated with dexmedetomidine. However, few studies have addressed the clinical effects of low-dose intramuscular dexmedetomidine as premedication.

Material/Methods: Forty American Society of Anesthesiologists physical status I adult patients undergoing suspension laryngoscopic surgery were randomized to receive intramuscular dexmedetomidine (1 µg·kg^{-1}) or midazolam (0.02 mg·kg^{-1}) 30 minutes prior to anaesthesia induction. The sedative, hemodynamic, and adjuvant anaesthetic effects of both premedications were assessed.

Results: The levels of sedation (Observer's Assessment of Alertness/Sedation scales) and anxiety (visual analog score) at pre-induction, and the times to eye-opening and extubation, were not different between the groups. The heart rate response following tracheal intubation and extubation, and mean arterial pressure responses after extubation, were attenuated in the dexmedetomidine group compared to the midazolam group. No bradycardia or hypotension was noted in any patients. Propofol target concentrations at intubation and at start and completion of surgery were decreased in the dexmedetomidine group, whereas no difference in respective remifentanil levels was detected.

Conclusions: This study provides further evidence that dexmedetomidine premedication in low dose (1 µg·kg^{-1}) by intramuscular route can induce preoperative sedation and adjuvant anaesthetic effects without clinically significant bradycardia or hypotension.

MeSH Keywords: **Anesthesia, Intravenous • Dexmedetomidine • Laryngoscopy • Premedication**

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Background

The objectives of premedicating a patient before surgery are to relax the patient, improve the effects of the anaesthetic drugs, and prevent adverse effects and complications [1,2]. Dexmedetomidine, a α2-adrenoreceptor agonist well known for its anti-anxiety, sedative, analgesic, anaesthetic-sparing and respiratory-sparing effects [3,4], is a perfect candidate for premedication. Indeed, many studies have been conducted to determine the feasibility of using dexmedetomidine as a premedication [5–10] However, bradycardia and hypotension frequently occurred following the administration of dexmedetomidine in adults. This is particularly the case when high-dose or rapid intravenous (IV) administration is used. It has been reported that an intramuscular (IM) dose over 2 μg·kg^{-1} [5–8,11] or an IV bolus over 1 μg·kg^{-1} [10,12,13] elicited marked decreases in heart rate (HR) and mean arterial blood pressure (MAP). Clinically significant bradycardia, sinus arrest, and refractory cardiogenic shock have been observed in young, healthy subjects with high vagal tone [14–18]

Although the current hemodynamic profile of dexmedetomidine indicates that a low-dose or a different route than the IV route help to minimize the cardiovascular risks [5,11,19], few studies have addressed the clinical effects of low-dose intramuscular dexmedetomidine as premedication. By contrast, most studies using high-dose dexmedetomidine refereed the protocol used in the dose-finding study, which reported that a 2.5 μg·kg^{-1} dose of IM dexmedetomidine was sedative and anxiolytic compared with 0.08 mg·kg^{-1} midazolam. Given the trend in modern anaesthesia toward eliminating routine pre-operative deep sedation [2], we hypothesized that a lower sedative dose of dexmedetomidine could be a promising alternative by minimizing its cardiovascular risks while preserving the adjuvant anaesthetic effects. We therefore conducted this prospective study to investigate the clinical effects of low-dose dexmedetomidine (1 μg·kg^{-1}) by comparing the sedative, hemodynamic, and adjuvant anaesthetic effects with midazolam (0.02 mg·kg^{-1}), the most common premedication, in patients undergoing suspension laryngoscopic surgery under general anaesthesia. We believed that this trial could provide further evidence for the off-label use of dexmedetomidine, specifically the use in low-dose and by intramuscular route, as a premedication for general short-term surgery.

Material and Methods

The Institutional Ethics Committee approved this study in May 2011, and all participants signed a written, informed consent form. Participants eligible for this study were adult patients aged 18–55 years, American Society of Anesthesiologists physical status I, scheduled for elective suspension laryngoscopic surgery of benign vocal fold lesions at the Guangzhou First People's Hospital. The exclusion criteria included patients with neurological deficits, pregnancy, imprisonment, morbid obesity (body mass index ≥30 kg·m^{-2}), preoperative HR <45 beats·min^{-1} (bpm), second- or third-degree AV block, and antihypertensive medication with α-methyldopa, clonidine, or other α2-adrenergic agonists.

A research member accomplished randomization by using a computer-generated randomization table. Group allocation was concealed in sealed opaque envelopes that were numbered and opened sequentially after patient consent had been obtained. A nurse who was not involved in any other sections of the study obtained the envelopes and then prepared the premedications by drawing 0.02 mg·kg^{-1} of midazolam (Enhua Pharmaceutical, Jiangsu, China) or 1 μg·kg^{-1} of dexmedetomidine (Hengrui Med, Jiangsu, China) into a 5-mL syringe and diluting it with 2 mL of 0.9% sodium chloride solution. The premedications were administered intramuscularly 30 minutes prior to anaesthesia induction. HR and oxygen saturation were monitored with fiber-optic pulse oximetry during transfer from the ward to the operating room.

When the patients arrived in the operating room, standard monitoring (a 5-lead electrocardiogram, non-invasive blood pressure, and oxygen saturation) and Narcotrend® electroencephalography (software version 4.3; MonitorTechnik, Bad Bramstedt, Germany) were applied and recorded continuously. The Narcotrend monitor was connected to the patient's forehead according to the manufacturer's instructions. Studies comparing Narcotrend and Bispectral Index (BIS®) monitors showed that Narcotrend indices "D0" to "E1" were equivalent to BIS values 56 to 35 [20].

Thirty minutes following the administration of the premedication, induction was achieved in sequence using propofol and remifentanil in a target-controlled infusion (TCI) model. The concentration of propofol was adjusted to achieve an intraoperative Narcotrend index between "D0" and "E1" measured using Diprifusor software (version 2.0, Graseby® 3500 anesthesia pump, Smiths Medical, Watford, UK). The remifentanil infusion was then started at 3.0 ng·mL^{-1}, according to the Minto pharmacokinetic model [21]. Rocuronium 0.6 mg·kg^{-1} was used to facilitate tracheal intubation. The concentrations of anesthetics were adjusted to maintain MAP changes within 25% of baseline values and the target Narcotrend stages. At the end of the surgery, neuromuscular blockade was reversed with the administration of neostigmine and atropine. After the operation, all patients were transferred to the Recovery Room for recovery and were monitored for an extra hour after extubation.

The patients' level of sedation was evaluated on the modified observer's assessment of alertness/sedation (OAA/S) scale (0

= does not respond to deep stimulus; 1 = does not respond to mild prodding or shaking; 2 = responds only after mild prodding or shaking; 3 = responds only after name is called loudly and/or repeatedly; 4 = lethargic response to name spoken in normal tone; 5 = responds readily to name spoken in normal tone) [22] and the visual analog score (VAS, patients were asked to self-evaluate their feelings of anxiety with scores of 0–10, with 0 = absent and 10 = very much). Values of OAA/S, VAS, blood pressure, and HR before pre-medication were used as baselines. Bradycardia was defined as HR<45 bpm, tachycardia as HR>100 bpm, hypertension as a >30% increase from baseline in MAP, and hypotension as a <30% decrease from the baseline in MAP, and respiratory depression as SpO_2 <90% or respiratory rate <8 bpm. Intra-operatively, tachycardia was treated by the administration of esmolol, bradycardia by administration of atropine, and, if persistent (more than 10 seconds), hypertension and hypotension were initially treated by adjusting the remifentanil TCI concentration with an incremental dosage of 0.5 ng·mL^{-1}, by the administration of cardiovascular active reagents. Hemodynamic variables were then allowed to stabilize after any pharmacologic interventions. Post-operatively, pain scoring above 50 on a 0–100 mm visual analogue scale was treated with IV parecoxib 40 mg, and nausea and vomiting were treated with a 4-mg ondansetron IV. On the first post-operative day, follow-up interviews to determine intra-operative recall were conducted by the same observer, who was blinded to the premedication.

Statistical analysis

The following protocol-defined endpoints were mainly evaluated: sedation profiles, intubation and extubation responses, and adjuvant anaesthetic effect. The sample size estimation was based on a previous study [13] that showed that mean the HR value immediately after intubation in patients not treated with dexmedetomidine was 76 bpm, with a standard deviation (SD) of 13 bpm. A 20% reduction in the HR response following intubation was considered clinically relevant and feasible. We calculated that a total sample of 36 subjects (18 subjects in each group) would be required to detect this difference with 80% power at a 2-side 5% significance level. Therefore, the target number of patients to recruit in each group was 20. Continuous data are reported as mean (SD) and analyzed using a 2-sample *t* test. Nonparametric data, such as OAA/S scales, are reported as median (IQR) or numbers and were analyzed with χ^2 and the Mann-Whitney U test. All reported P values are 2-sided.

Results

Eighty-three Chinese patients were screened for the study between September 2013 and October 2013. Thirty-two patients
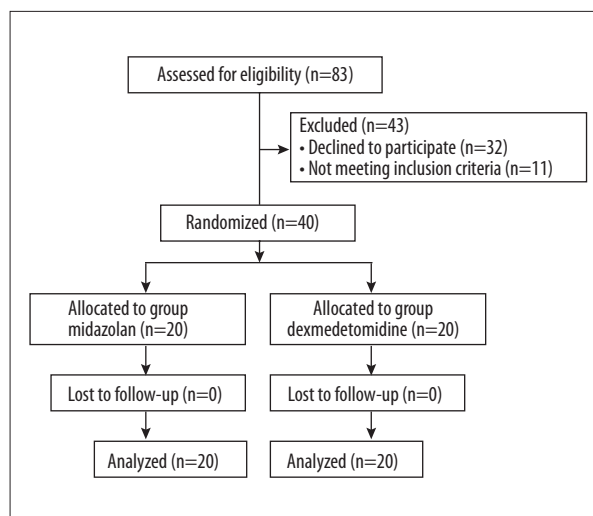

Figure 1. CONSORT flow diagram.

Table 1. Characteristics and surgical data of patients receiving intramuscular midazolam 0.02 mg/kg or dexmedetodine 1 µg·kg^{-1}. Values are mean (SD) or number.

	Midazolam (*n*=20)	Dexmedetomidine (*n*=20)
Age, yrs	51 (8)	53 (7)
Gender, male/female	11/9	13/7
Height, cm	170 (14)	168 (17)
Weight, kg	65 (9)	58 (12)
Duration of anaesthesia, min	31 (9)	28 (11)
Duration of surgery, min	16 (7)	17 (6)

* There were no significant differences between groups.

declined to participate in the study, and 11 patients were excluded because they did not meet the inclusion criteria. Forty patients were randomized to receive 1 of the 2 premedications (Figure 1). The results of all 40 patients were included in the analysis. The patients' characteristics and surgical data are shown in Table 1.

There was no difference in the levels of sedation (OAA/S) and anxiety (VAS) at any recorded time point between the groups (data not shown). HR response following tracheal intubation and extubation, and MAP responses after extubation were attenuated in the dexmedetomidine group compared to the midazolam group by mean (95% CI) 9 (4–14) and 11 (2–21) bpm, and 9 (0–17) mmHg (P=0.003, 0.031 and 0.035), respectively (Figure 2). No cardiac events (bradycardia, hypotension, tachycardia, and hypertension) were noted.
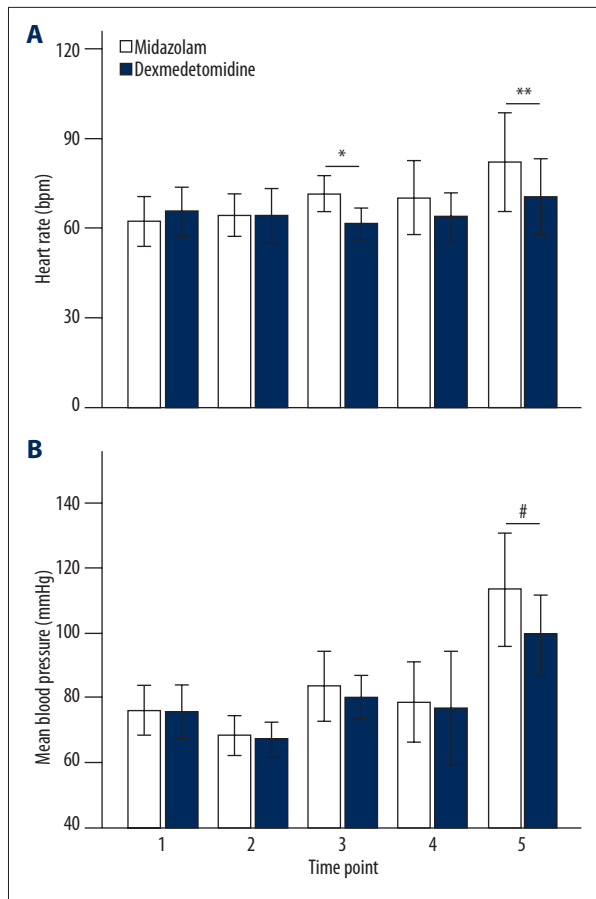
Figure 2. Hemodynamic responses at different time points in patients receiving intramuscular midazolam 0.02 mg/kg or dexmedetomidine 1 µg·kg^{-1}. (**A**) Heart rate response. (**B**) Mean arterial pressure response. Time point 1 represents baseline, 2 at pre-induction, 3 after induction, 4 at eye opening, and 5 after extubation. The bar represents mean (SD). * P=0.003; ** P=0.031; # P=0.035.

Figure 3. Predicted effect-site concentrations of anaesthetics after intramuscular midazolam 0.02 mg/kg or dexmedetomidine 1 µg·kg^{-1}. (**A**) propofol, (**B**) remifentanil. Time point 1 represents at induction, 2 at start of surgery, 3 at completion of surgery, 4 at eye opening, and 5 at extubation. TCI = target-controlled infusion. The bar represents mean (SD). * P=0.021; ** P=0.016.

Propofol TCI concentrations at intubation and at start and completion of surgery were decreased in the dexmedetomidine patients by 0.48 (0.05–0.92), 0.26 (–0.16–0.70), and 0.41 (–0.09–0.91) µg·mL^{-1}, P=0.021, 0.125, and 0.016, respectively. Respective remifentanil TCI levels were similar between the groups. Dexmedetomidine did not induce difference in propofol and remifentanil plasma concentrations at eye opening by 0.21 (–0.03–0.46) µg·mL^{-1} and 0.08 (–0.01–0.17) ng·mL^{-1}, P=0.05 and 0.10, respectively; and at extubation by 0.15 (–0.01–0.30) µg·mL^{-1} and 0.07 (–0.01–0.15) ng·mL^{-1}, P=0.32 and 0.21, respectively (Figure 3).

Dexmedetomidine did not induce difference in times to eye opening and to extubation by 0.7 (–3.0–4.4) and 3.8 (–2.1–9.8) min, P=0.58 and 0.31, respectively. Pain episodes requiring treatment were reported in 2 patients in the midazolam group and in 2 patients in the dexmedetomidine group (P=1.0).
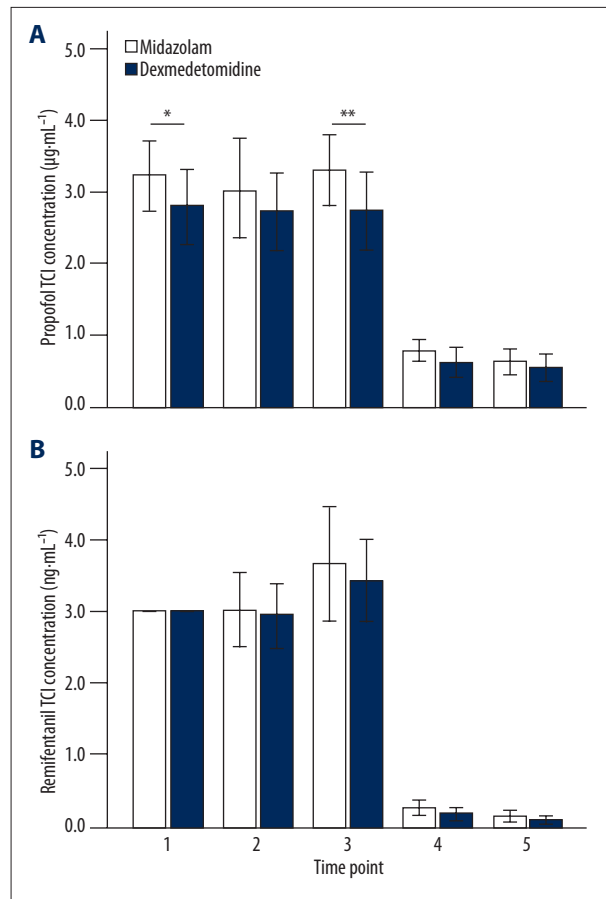
Postoperative nausea and vomiting requiring medication were noted in 3 midazolam patients and 1 dexmedetomidine patient (P=0.65). Postoperative shivering, respiratory depression, and intra-operative awareness were not recorded.

Discussion

Although dexmedetomidine has a good tolerance profile in children[23], trials using high-dose dexmedetomidine (an IM dose over 2 µg·kg^{-1} or an IV dose over 1 µg·kg^{-1}) in adults showed that the cardiovascular and sympatholytic effects of this reagent could offset any potential benefits [14–18] The main finding of this study is that a low dose (1 µg·kg^{-1}) of IM dexmedetomidine as a premedication produced beneficial results without increasing risk of bradycardia and hypotension.

The dose of dexmedetomidine premedication administered in the present study (1 μg·kg⁻¹) was based on a dose-response study in which the selected dose resulted in a deeper sedative effect than a dose of 0.5 μg·kg⁻¹ did, and a less significant decrease in HR than the dose of 1.5 μg·kg⁻¹ did [24]. Our results revealed that the selected dose was sedative and anxiolytic compared to 0.02 mg·kg⁻¹ midazolam. This finding confirmed the study by Virkkila et al. [24], which showed that, in eye surgery patients, premedication with exactly the same 2 regimens used in our study facilitated clinically similar and feasible preoperative sedation and anxiolysis. In addition, the effects of dexmedetomidine were of longer duration than those of midazolam. For example, Mattila et al. [25] reported that the maximal vigilance impairment in healthy volunteers was slightly greater after the administration of 0.08 mg·kg⁻¹ IM midazolam than after dexmedetomidine 1.2 μg·kg⁻¹, but the effect of the latter persisted up to 6 hours after administration. Although we did not find longer sedation, we did record a much smoother extubation in the dexmedetomidine patients.

Suspension laryngoscopy can cause an intense nociceptive stimulus that dramatically increases HR and MAP [13,26], which is similar to the response to intubation and is associated with the release of large amounts of catecholamines [27]. A α2-adrenergic agonist may have the potential to moderate sympathetic response during these procedures. In an earlier study, oral clonidine (the archetypal α2 agent) premedication blunted hypertensive response following tracheal intubation and endoscopy in patients undergoing microlaryngoscopy and bronchoscopy [28]. Recently, dexmedetomidine was shown to provide ideal conditions for laryngoscopy and bronchoscopy [29]. A more recent investigation by our group found that a single dose of dexmedetomidine infusion improved peri-operative hemodynamic stability in a similar cohort of patients [13]. The mechanism is thought to involve decreased plasma catecholamine concentrations in clonidine-[27,30] or dexmedetomidine-[31,32] premedicated patients, although the catecholamine response was not measured in this study. Combining dexmedetomidine and remifentanil accomplished superior efficacy in blunting the responses to tracheal intubation and extubation to standard premedication in our microlaryngoscopy patients.

It is known that hypotension and bradycardia are the most prominent possible adverse effects of a α2 agent. However, these cardiovascular effects, which are usually associated with high-dose intravenous dexmedetomidine, probably can be avoided by using a slower infusion or a different route of injection [31]. Indeed, dose-range studies of IM dexmedetomidine [19,24] have demonstrated that a dose of 1–1.2 μg·kg⁻¹ or lower was not associated with significant hemodynamic changes, whereas a single dose in 1.5–2.4 μg·kg⁻¹ induced significant decreases in both HR and MAP. We thus applied

a relatively low dose (1 μg·kg⁻¹) by a different route (IM) for sedation. Our findings indicate that a low dose of IM dexmedetomidine is preferable not only for minimal risk of cardiovascular side effects but for efficient pre-anaesthetic sedation. Interestingly, a recently published trail [33] using exactly the same dose by exactly the same route as in our study also reported dexmedetomidine-premedicated patients had more stable intraoperative hemodynamics.

However, until the hemodynamic stability of low-dose IM dexmedetomidine is demonstrated in a large-scale multicenter trial, it seems prudent to monitor carefully for potential adverse effects in all treated patients. Other limitations of our study include the relatively good health of the patients enrolled and the calculated plasma concentrations via target-controlled infusion.

Conclusions

This study provides plausible evidence supporting dexmedetomidine premedication, which in low dose (1 μg·kg⁻¹) by IM route can induce preoperative sedation and adjuvant anaesthetic effects without clinically significant bradycardia or hypotension, and thus shows promising premedication effects that warrant further investigation.

Statement

This report describes a prospective randomized clinical trial. This study was conducted with written informed consent from the study subjects. The author states that every item in the CONSORT checklist is included in the report. Registration: Clinical Trials number NCT01937611. IRB contact information: the Ethics' Committee of Guangzhou First Municipal People's Hospital.

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