Title

A comparison of dexmedetomidine and midazolam for sedation during wisdom teeth extraction

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Short Running Title

Dental sedation with dexmedetomidine vs. midazolam

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Summary

Background

Dexmedetomidine is a highly selective alpha-2 adrenergic agonist that provides sedation, anxiolysis, and analgesia without respiratory depression. This study was performed to determine whether it has any advantage over midazolam for intravenous sedation during dental surgery under local anaesthesia.

Methods

The study was randomized and double-blind. Sixty patients received either dexmedetomidine (up to 1 μg kg^{-1}) or midazolam (up to 5 mg). The drug was infused until the Ramsay Sedation Score reached 4 or the maximum dose had been administered. Intraoperative vital signs and adverse events were recorded. Numerical rating pain scores and analgesic consumption were charted for 3 days after surgery. The pre- and post-operative Mini Mental State Examination (MMSE) scores were compared. Amnesia was assessed by asking patients to recall two pictures shown after sedation.

Results

Sedation was achieved by median [range] doses of 47 μg [25-76] or 0.88 μg kg^{-1} [0.6-1.0] dexmedetomidine, and 3.6 mg [1.9-5.0] or 0.07 mg kg^{-1} [0.017-0.12] midazolam. SpO_2 < 90% occurred in 6 patients (20%) who received dexmedetomidine and 4 patients (13%) who received midazolam ($P = 0.488$). There was no significant difference in respiratory rate. Heart rate and blood pressure were lower in the dexmedetomidine group during surgery. Patients' and surgeons' satisfaction, pain

scores and MMSE scores did not differ significantly between groups. Midazolam was associated with greater amnesia.

Conclusions

Dexmedetomidine produces comparable sedation to midazolam with a lower heart rate and blood pressure but less amnesia. No additional analgesic effect of dexmedetomidine could be demonstrated.

Introduction

Midazolam is commonly used as an intravenous sedative agent for dental procedures. It has a fast onset and rapid recovery, but after repeated administration, prolongation of sedation and hangover effects due to the relatively long half-life of midazolam and its metabolites are possible.[1] Moreover, it depresses the ventilatory response to carbon dioxide and results in respiratory depression.[2,3] Some patients may also develop disinhibition and/or disorientation and not comply with treatment.[4]

Dexmedetomidine is an alpha-2 agonist which acts on adrenoceptors in many tissues including the nervous, cardiovascular and respiratory systems.[5,6] The site of action in the central nervous system is at the locus coeruleus, where it induces electroencephalographic activity similar to natural sleep. The drug also reduces catecholamine secretion, thereby reducing stress and leading to a modest (10-20%) reduction in heart rate and blood pressure, which may be particularly beneficial in patients with cardiovascular disease.[7] Unlike midazolam, dexmedetomidine does not affect the ventilatory response to carbon dioxide.[8,9] In addition to sedation, it also produces analgesia,[10,11] which could potentially alleviate pain after tooth extraction. Such a pharmacodynamic profile may have an advantage over midazolam for dental sedation. Therefore, we conducted this study to compare the sedative effects of dexmedetomidine versus midazolam for third molar surgery under local anaesthesia.

Methods

This was a randomized, double-blind trial and the protocol was approved by our local Institutional Review Board. Eligibility for subject recruitment included all American Society of Anesthesiologists (ASA) physical status I or II patients aged between 18 to 50 years of age, with asymptomatic impacted third molar scheduled for unilateral extraction under local anaesthesia and intravenous sedation. Exclusion criteria included clinical history or electrocardiographic evidence of heart block, ischaemic heart disease, asthma, sleep apnoea syndrome, impaired liver, renal or mental function, alcohol consumption in excess of 28 units per week, and those who regularly used or had known allergy to dexmedetomidine, midazolam, paracetamol or dextropropoxyphene.

After obtaining written informed consent, patients' demographic data were collected and a baseline Mini Mental State Examination (MMSE) was performed.[12] Patients were then randomly allocated to receive dexmedetomidine (Group D) or midazolam (Group M) for intravenous sedation. A computer generated random sequence, based on blocks of 4 was used for the drug allocation and was prepared by the statistician who was unaware of the clinical nature of the study. The sedation drug was prepared by an anaesthesiologist who did not participate in patient management or data collection. Either dexmedetomidine 1 μg kg^{-1} (Group D) or midazolam 5 mg (Group M) was mixed with normal saline to a total volume of 20 mL and this was given to the attending anaesthesiologist for administration. Both preparations were clear solutions and, thus, patients, all medical and nursing staff and data collectors were blind to the allocated drug.

On arrival at the operating theatre, a 22-gauge intravenous cannula was inserted. Heart rate, blood pressure, respiratory rate and oxygen saturation (S/5 Anesthesia Monitor, Datex-Ohmeda, WI, USA) were recorded every 2 minutes during infusion of the study drug and thereafter at 5-minute intervals from the time of commencing surgery to the end of recovery. The 20 mL solution of study drug was infused over 10 minutes at a constant rate. During this period, the patients were assessed every minute using the Ramsay Sedation Score (RSS, Appendix 1).[13] The infusion was stopped either when the RSS reached 4 or the full 20 mL (dexmedetomidine 1 μg kg^{-1} or midazolam 5 mg) had been given, whichever was earlier. Following the drug infusion and prior to surgery, 2 pictures were shown to the patients and they were asked to remember their contents.

Inferior alveolar nerve block was achieved by infiltrating 2% lignocaine with 1 in 80,000 adrenaline. Patients were then asked to grade the pain resulting from the infiltration of local anaesthesia using a numerical rating scale (NRS) where 0 corresponds to no pain and 10 is the worst pain imaginable. Unilateral wisdom tooth extraction was then performed in the usual manner without any further study interventions or intended sedative drug supplementation. Inadequate analgesia was treated with infiltration of local anaesthetic into the surgical site. If the oxygen saturation decreased to less than 90%, surgery was stopped and the instruments removed from the patient's mouth. The patient was prompted to take deep breaths and oxygen therapy was administered via nasal cannulae. Surgery resumed when oxygen saturation was restored to 90% or above. Upon completion of surgery, patients were transferred to the recovery room and monitored for 30 minutes. They were then

transferred back to the general ward if fully conscious and the vital signs including heart rate, blood pressure and oxygen saturation were stable.

Following arrival of the patients in the ward, heart rate, blood pressure, oxygen saturation and NRS pain scores were assessed hourly for 4 hours. Patients were prescribed 2 analgesic tablets, each containing paracetamol 320 mg and dextropropoxyphene 32.5 mg (Dolpocetmol, Synco Limited, Hong Kong, China), on an as required basis to a maximum of 4 times daily. Two hours after surgery, RSS was charted and a second MMSE was performed. After that, patients were asked whether they were relaxed during the operation (yes or no) and to grade their overall satisfaction with the procedure using NRS (0 being least satisfied and 10 being most satisfied). They were asked to choose the type of anaesthetic technique they would prefer if undergoing a similar operation in the future (local anaesthesia with sedation like this time, or general anaesthesia or local anaesthesia with no sedation). To test for amnesia, patients were asked if they were aware of certain events during surgery (infiltration of local anaesthetic, use of burs, tooth extraction and suturing), and to identify the pictures shown immediately after the infusion of the sedation drug from a panel of 12 pictures. Patients were discharged from hospital the next day as is usual in this hospital. The oral analgesic regimen described above was prescribed for 3 days upon discharge.

The chief dental surgeon was asked to grade the surgical conditions in a 4-point scale (good, fair, poor, very poor) and grade their satisfaction with sedation using NRS (0 being least satisfied and 10 being most satisfied). Adverse events were recorded for 3 days postoperatively.

The primary outcome measure of this study was patients' satisfaction scores using NRS from 0 to 10. Sample size calculation was based on a population standard deviation of 1.1, two-sided level of significance at 0.05, and power of test at 0.90.[14] To detect a difference in satisfaction score of 1 between groups, a total of 60 patients were recruited. An intention-to-treat model was adopted and all recruited patients were included in the data analysis. Statistical analysis was performed using SPSS 14.0 for Windows (SPSS Inc., IL, USA). Perioperative vital signs were plotted into graphs using GraphPad Prism 4.03 (GraphPad Software Inc., CA, USA) and the mean areas under curve (during study drug infusion, surgery, recovery and in the ward) were compared between groups using Student's t test. Patients' and surgeons' satisfaction scores, NRS pain scores and analgesic consumption, and difference in pre- and post-operative MMSE scores were compared using Mann-Whitney U test. All categorical data were analyzed using χ^2 test. Time to first analgesic use was compared using log-rank test in Kaplan-Meier survival analysis.

Results

Sixty patients were recruited. All of them underwent their planned surgical procedure and received the allocated study drug. No assigned patients dropped out of the study. The patient characteristics and operation data were similar between the two groups (Table 1). Sedation was achieved by median [range] dose of 47 µg [25-76] or 0.88 µg kg^{-1} [0.6-1.0] dexmedetomidine in Group D, or 3.6 mg [1.9-5.0] or 0.07 mg kg^{-1} [0.017-0.12] midazolam in Group M. Twenty three (77%) Group D patients and 24 (80%) Group M patients reached the sedation end point (RSS = 4) before or at the time when the maximum dose of study drug was infused. All patients in Group D and 28 patients (93%) in Group M had a RSS of 3 or above at the end of the study drug infusion. Surgery was very difficult in one patient who developed moderate aggressive behaviour after receiving midazolam (RSS = 1). No more midazolam was given and the procedure could still be completed after repeated reassurance. Another was fully awake, but calm (RSS = 2) despite the maximum dose of midazolam. One patient in Group M, who had reached RSS 4 after initial infusion, became anxious 30 minutes after surgery started and required a further 1 mg bolus dose of midazolam.

All baseline vital signs were similar between groups ($P > 0.05$, Fig. 1a-b). Heart rate decreased significantly after dexmedetomidine infusion and remained lower than Group M during the surgical and recovery periods ($P < 0.001$). While respiratory rates were similar between groups, oxygen saturation was lower in Group M during drug infusion ($P = 0.003$), but lower in Group D during surgery ($P = 0.03$). Oxygen desaturation (oxygen saturation lower than 90%) occurred in 6 patients (20%) who

received dexmedetomidine and 4 patients (13%) who received midazolam ($P = 0.488$). Oxygen saturations rapidly returned to normal upon treatment.

Intraoperative anxiety levels, patients' and surgeons' satisfaction scores were similar between groups and most would choose the same intravenous sedation for a similar procedure in the future (Table 2). Surgeons graded the surgical conditions as good in 29 patients (96%) in Group D and 25 patients (83%) in Group M ($P = 0.193$). The main reason of dissatisfaction was patient movement during the procedure. Amnesia was more profound in patients receiving midazolam (Table 3). After 30 minutes of recovery, 13 patients (43%) in Group D and 18 patients (60%) in Group M reached RSS of 2. All the patients were cardiovascularly stable in the recovery room. Both groups had a similar difference in MMSE scores before and at two hours after surgery ($P = 0.716$).

NRS pain scores during local anaesthetic infiltration, in the ward and at 3 days postoperatively were similar ($P > 0.05$, Fig. 2). Median time to first oral analgesic use (187 minutes in Group D versus 185 minutes in Group M, $P = 0.903$) and analgesic consumption during the first 3 days after surgery ($P > 0.05$, Fig. 3) were also similar between groups. Within 3 days postoperatively, both groups had 7 patients (23%) reporting dizziness, while nausea and vomiting occurred in 3 patients (10%) in Group D and 2 patients (7%) in Group M.

Discussion

Significant pharmacogenetic differences exist in sedative drug response resulting in a large variation in dose requirements.[15][16] Studies shows there is a wide range of midazolam blood levels associated with adequate sedation.[1] Titration is obviously important in order to reduce the risk of over sedation and was part of the protocol of this study. The median dose required to achieve adequate sedation was 0.88 µg kg^{-1} for dexmedetomidine and 0.07 mg kg^{-1} for midazolam. Unilateral third molar extraction is usually a short 30-minute procedure and, therefore, we did not plan to give a supplemental intraoperative bolus or maintenance infusion of the study drugs. All patients receiving dexmedetomidine reached RSS of 3 or above immediately after the infusion, whereas 2 patients receiving midazolam did not, which infers that the safe maximum dose of midazolam we had set was insufficient for some patients, such as the one who was still fully alert despite the infusion of 5 mg midazolam. Midazolam is well known to sometimes cause patient restlessness and disinhibition instead of sedation and this has been referred to as a paradoxical reaction.[4] Surgery will then become extremely difficult, and patients may even require flumazenil for reversal.[17] One of our patients, who had RSS of 1 after sedation, became agitated after midazolam administration and we suspected this condition. We did not give extra midazolam because this can exacerbate the problem. This patient could not recall this incident postoperatively.

Dexmedetomidine causes an increase in arterial pressure upon rapid bolus infusion.[18][19] This is due to direct effects on vascular alpha-1 receptors. In our study, this was minimized by slower infusion of dexmedetomidine but the time to sedation end point

would be longer. Dexmedetomidine then exhibits a modest decrease in blood pressure, heart rate and cardiac output.[18 19] There was no cardiovascular instability requiring intervention in all study patients, suggesting both drugs to be safe in this situation. In fact the effects of alpha-2 agonists on the cardiovascular system may be protective in high risk patients.[20] Midazolam also needs to be given reasonably slowly as it has a relatively slow time to peak effect.[2 21] Midazolam can cause respiratory depression[22] while dexmedetomidine does not.[8 9] However, whilst respiratory rate did not differ significantly between the two groups, oxygen desaturation ($SaO_2 < 90\%$) did occur in both groups. Both drugs reduce muscle tone potentially leading to upper airway obstruction and, within the dose range that produces moderate sedation, this may be more important than respiratory depression .[8] For the patients' safety, we started intervention as soon as such events occurred, and all patients responded to verbal stimulus and low flow oxygen therapy.

Pain on local anaesthetic infiltration can be a stressful experience and pain after dental surgery may be considerable.[23] Alpha-2 receptors are abundant in the dorsal horn of the spinal cord where they are involved in pain modulation. The analgesic properties of dexmedetomidine have been demonstrated in healthy volunteer studies,[11 24] but there is some controversy over this in clinical practice.[25] When it is used preoperatively or intraoperatively, the analgesic consumption can be reduced, without lowering the pain scores.[26-28] In our study, pain during the infiltration of local anaesthetic was moderate to severe in both groups (mean NRS pain score over 5). The NRS pain scores recorded postoperatively from the first hour to the third day were also similar. Furthermore, there was no difference in the time of first oral analgesic taken and daily oral analgesic consumption, suggesting no preemptive analgesic effect.

Sedation with midazolam has been reported to reduce pain after dental surgery when compared with placebo,[29] but we felt it was not ethical to have a placebo control group in this study.

Amnesia may or may not be an advantage to patients. Some may wish to avoid the recall of what may be perceived as the unpleasant experience of dental surgery, but many patients do not like this memory loss. It is well known that midazolam has a potent anterograde amnesic effect. Hall and colleagues have also demonstrated impairment of memory and psychomotor performance with dexmedetomidine infusion.[11] In the present study, more than half of the patients receiving dexmedetomidine remembered the pictures shown at the end of sedation drug infusion, but only 2 patients receiving midazolam did so. However, the amnesic effect of midazolam rapidly diminished with time and a comparable number of patients in both groups could remember the surgical procedures. A few patients who received dexmedetomidine recalled the infiltration of local anaesthetic but failed to remember the surgical procedure, most likely because the former is a greater stimulus. Similarly, the stimulation due to suturing is probably lower.

After surgery, most patients felt comfortable with the sedation with either drug. Both groups were highly satisfied with the surgery and expressed a preference for the same anaesthetic care (as opposed to general anaesthesia or local anaesthetic alone) in the future. Thus, both drugs appear to be equally acceptable to patients, although this could really only be truly evaluated with a crossover comparison. Fast recovery is desirable after sedation and short surgery, and the sedative effects of both drugs were also comparable in this regard. MMSE performance was completely normal within 2

hours which can suggest that they both may be suitable for day-stay surgery. Postoperatively, neither drug had an advantage in reducing side effects such as dizziness, nausea and vomiting.

In conclusion, dexmedetomidine provides comparable sedation to midazolam for unilateral wisdom tooth extraction under local anaesthesia. It is associated with a mild reduction in heart rate and blood pressure as opposed to a slight increase with midazolam. There is less amnesia but no improvement in analgesia. Dexmedetomidine may have an advantage in reducing patient movement. Oxygen desaturation can occur with both drugs as a result of loss of airway muscle tone rather than respiratory depression.

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Table 1

The patient characteristics and operative data.

	Dexmedetomidine (*n* = 30)	Midazolam (*n* = 30)
Male : Female	9 (30%) : 21 (70%)	9 (30%) : 21 (70%)
Age (years)	25.5 [20-36]	27.7 [18-47]
Body weight (kg)	54.3 [37-77]	56.5 [40-109]
ASA physical status		
I	29 (97%)	29 (97%)
II	1 (3%)	1 (3%)
Preoperative MMSE score	28.7 [25-30]	28.7 [24-30]
Duration of surgery (minutes)	21.4 [7-50]	21.1 [8-58]

Data shown are counts (percentage) or means [range] within the group.

Table 2

Comparison of patients' report on relaxation, preferences on anesthetic method for a similar procedure in future, patients' satisfaction scores and surgeons' satisfaction scores.

	Dexmedetomidine ($n = 30$)	Midazolam ($n = 30$)	P
Relaxed during surgery	24 (80%)	25 (83%)	0.739
Preferred the same intravenous sedation next time	27 (90%)	26 (87%)	0.688
Patients' satisfaction score	9 [8-9]	9 [8-10]	0.988
Surgeons' satisfaction score	9 [8-10]	8 [8-10]	0.531

Data shown are counts (percentage) or median [inter-quartile range].

Table 3

Amnesic effects of dexmedetomidine and midazolam.

Items or procedures recalled	Dexmedetomidine ($n = 30$)	Midazolam ($n = 30$)	P
Pictures shown when sedation was achieved	18 (60%)	2 (7%)	< 0.001
Infiltration of local anesthetics	25 (83%)	13 (43%)	0.001
Use of burs	22 (73%)	17 (57%)	0.176
Tooth extraction	22 (73%)	21 (70%)	0.774
Suturing	17 (57%)	17 (57%)	1.000

Data shown are counts (percentage).

Fig. 1

Vital signs of patients receiving dexmedetomidine (Group D, denoted by square data points ■) and midazolam (Group M, denoted by round data points ●) during study drug infusion, surgical procedures, recovery period and in the ward. Data shown are mean values with error bars representing one standard deviation. Data points were slightly shifted horizontally to avoid overlapping. LA = local anesthetic. (a) Heart rate in Group D was significantly lower than Group M at all 4 periods ($P < 0.001$). Compared to Group M, blood pressure in Group D tended to be higher during study drug infusion ($P = 0.183$), but significantly lower during surgery, recovery and in the ward ($P < 0.001$). (b) Respiratory rates were similar between groups (all $P > 0.05$). Oxygen saturation was lower in Group M during study drug infusion ($P = 0.003$), lower in Group D during surgery ($P = 0.03$), and similar during recovery period and in the ward ($P > 0.05$).
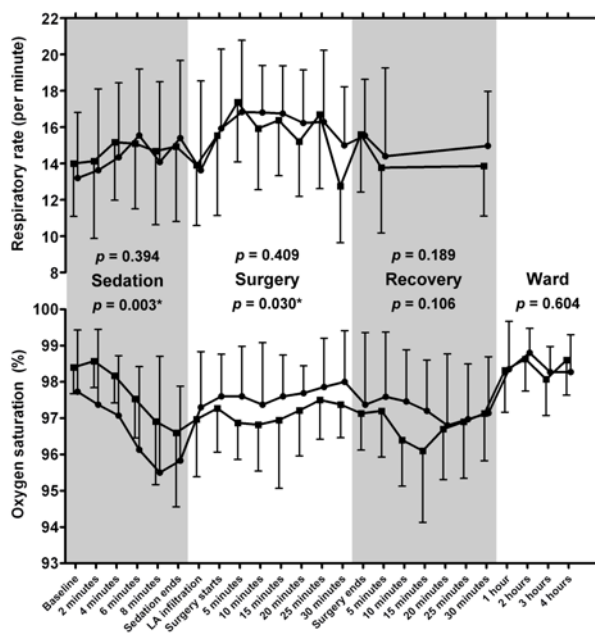
(a)
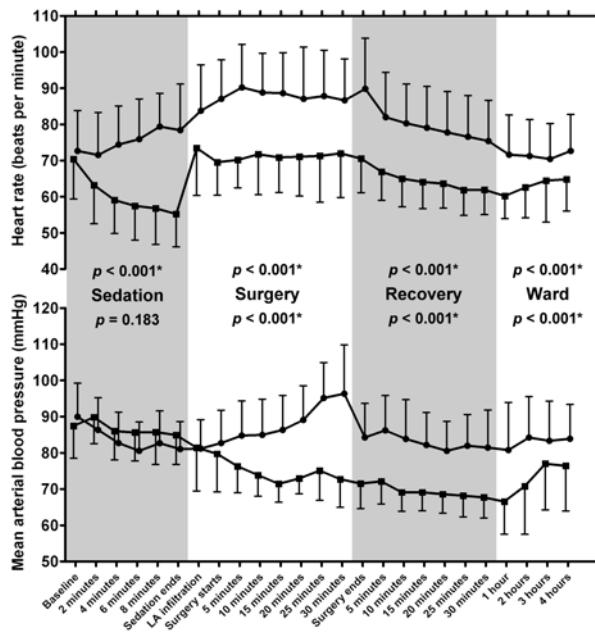
(b)

Fig. 2

There was no significant difference between median postoperative (postop) numerical rating scale (NRS) pain scores of patients receiving dexmedetomidine and midazolam (all $P > 0.05$).
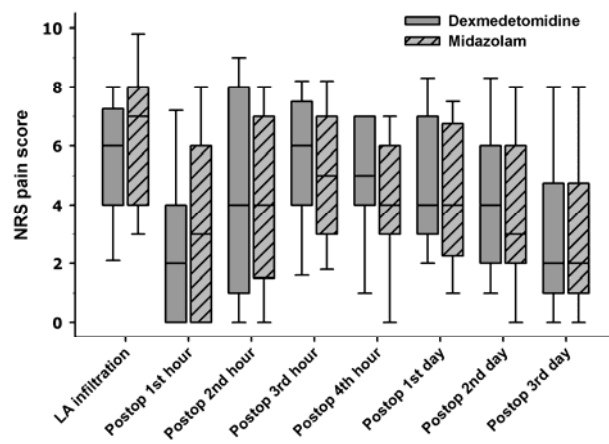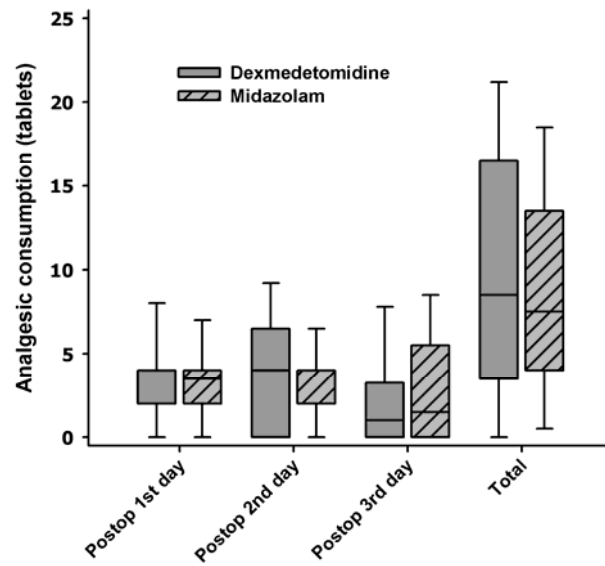
Fig. 3

Median postoperative (postop) analgesic consumption of patients receiving

dexmedetomidine and midazolam were not significantly different (all $P > 0.05$).

Appendix 1

The Ramsay Sedation Score:

1. Patient is anxious and agitated or restless, or both

2. Patient is co-operative, oriented, and tranquil

3. Patient responds to commands only

4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus

5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus

6. Patient exhibits no response