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A Comparative Study of Dexmedetomidine and Midazolam For Intravenous Sedation in Dental Procedures

KEYWORDS

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ABSTRACT *AIMS AND OBJECTIVES: To compare the efficacy and safety of dexmedetomidine and midazolam as an intravenous sedative agent for dental procedures under local anaesthesia.*

MATERIAL AND METHODS: This randomized double blind study compared dexmedetomidine and midazolam for intravenous sedation during various dental procedures like wisdom tooth extraction, implant surgeries and minor soft tissue surgeries. Sixty patients received either dexmedetomidine up to 1 mcg/kg or midazolam up to 5 mg, which was infused until the Ramsay sedation score was four or the maximum dose limit was reached. Intra operative vitals, postoperative pain scores and analgesic consumption, amnesia and satisfaction scores for patients and surgeon were recorded.

RESULTS: Sedation was achieved by median doses of 47 mcg (39-52) or 0.88 mcg/kg (0.75-1.0) dexmedetomidine in Group D, or 3.6 mg (3.3-4.4) or 0.07mg/kg (0.055-0.08) midazolam in Group M. Heart rate and blood pressure during surgery were lower in dexmedetomidine group. There was no significant difference in satisfaction or pain scores. Midazolam was associated with greater amnesia.

CONCLUSION: Dexmedetomidine produces comparable sedation to midazolam.

INTRODUCTION: Now a days various dental procedures like wisdom tooth extraction, implant surgery etc. are routinely done. Previously it was done under local anaeshesia only which made the patient anxious and uncooperative during the procedure. Major consequences of such uncooperative behavior may include a delay or termination of treatment before completion, or a decrease in the quality of care provided. Simple addition of intravenous sedation along with local anaesthesia makes the patient calm and increases the level of comfort for both-the patient and the surgeon. Various drugs can be used for this purpose.

Midazolam is commonly used as an intravenous sedative agent for dental procedures (1). It has a quick onset and rapid recovery, but the drug and its metabolites have a long half life. After repeated administrations, there may be prolongation of sedation and hangover effects (2). It also depresses ventilatory response to carbon dioxide and results in respiratory depression (3).

Dexmedetomidine is a more selective alpha 2 agonist acting on the adrenoreceptor in many tissues including nervous, cardiovascular and respiratory systems (4,5). It acts in the central nervous system at the locus ceruleus (6) where it induces electroencephalographic activity similar to natural sleep. The drug also reduces catecholamine secretion thereby reducing stress and leading to modest (10-20%) decrease in heart rate and blood pressure which may be beneficial to the patients with cardiovascular diseases (7). Dexmedetomidine does not affect ventilator response to carbon dioxide (8,9). In addition to sedation, it also produces analgesia (10,11) which could potentially alleviate pain after tooth extraction.

AIM: To compare the sedative effect of dexmedetomidine and midazolam for dental procedures under local anaesthesia.

METHODS: After written, informed consent sixty patients aged between 18 and 50 years, with American Society of Anaesthesiologists (ASA) grade I or II were posed for different surgical procedures like removal of wisdom teeth, implant surgeries and oral soft tissue surgeries under local anaesthesia and intravenous sedation. Exclusion criteria included clinical history or electrocardiographic evidence of heart block, IHD, asthma, sleep apnoea syndrome, impaired liver, renal or mental function, chronic alcohol consumption, chronic sedative and analgesic user, and those who regularly used or known allergic to dexmedetomidine, midazolam or paracetamol.

After obtaining consent, demographic data were collected and a baseline Mini Mental State Examination (MMSE) was performed (12). Patients were then randomly allocated by a computer generated list to receive dexmedetomidine (Group D) or midazolam (Group M) for IV sedation. Either dexmedetomidine 1mcg/kg (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 drugs were clear solutions and patients, medical and nursing staff and data collectors were blind to the allocated drug.

On arrival to the operation theatre, a 20 gauge IV cannula was inserted. Heart rate, blood pressure, respiratory rate and oxygen saturation were recorded every 2 min during infusion of the study drug and thereafter every 5 min intervals from the time of commencing surgery to the end of the recovery. The 20 ml solution of study drug was infused over 10 min at a constant rate. During this period, the patients were assessed every minute using the Ramsay Sedation Score(RSS) (13). The infusion was stopped either when the RSS reached four , or the full 20 ml (dexmedetomidine 1mcg/kg or midazolam 5 mg) had been given, whichever was earlier. Following the infusion and prior to surgery, two

Volume : 5 | Issue : 10 | October 2015 | ISSN - 2249-555X

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 1:80000 adrenaline. Patients were asked to grade the pain resulting from the infiltration of local anaesthesia using a neumarical rating scale (NRS) where zero corresponds to no pain and 10 is the worst pain imaginable. Regular surgical procedures were performed without any further study interventions or intended sedative drug supplementation. Inadequate analgesia was treated with infiltration of local anaesthetic to surgical site. Upon completion of surgery, patients were transferred to recovery room and monitored for 30 mins. Then they were transferred to general ward if fully conscious and the vital signs were stable.

Following arrival of the patients in the general ward, heart rate, blood pressure, oxygen saturation and NRS pain scores were assessed every 4 hourly. Patients were prescribed analgesic tablets, containing paracetamol 650 mg , on as required basis to a maximum of four times a day. Two hours after surgery, RSS was charted and a second MMSE was performed. After that, patients were asked whether they were relaxed during operation (yes or no) and to grade their overall satisfaction during procedure using NRS (zero being least satisfied and 10 being most satisfied). To test amnesia, they were asked if they were aware of certain events during procedure (infiltration of local anaesthetic, use of burrs, tooth extraction and suturing), and to identify the pictures shown immediately after the infusion of the sedation drug from a panel of 12 pictures. Unless anaesthetic comlications had occurred requiring intervention, patients were discharged from hospital at the discretion of the attending surgeon.

The chief dental surgeon was asked to grade the surgical conditions on a four point scale (good, fair, poor, very poor) and grade their satisfaction with sedation using NRS (zero being least satisfied and 10 being most satisfied).

The primary outcome measure of this study was the patient satisfaction scores using NRS from zero to 10. Perioperative vital signs were plotted into graphs and the mean area 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 the Mann-Whitney *U*- test. All categorical data were analysed using Chi-squared test.

RESULTS: Sixty patients were recruited. All of them underwent planned surgical procedures and received the allocated study drug. The patients' characteristics and operation data were similar between the two groups (table 1). Sedation was achieved with median dose of 47 mcg (39-52) or 0.88 mcg/kg (0.75-1.0) dexmedetomidine in Group D , or 3.6 mg (3.3-4.4) or 0.07mg/kg (0.055-0.085) midazolam in Group M. 23 (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 (93%) in Group M had a RSS of three or above at the end of the study drug infusion. One patient developed moderate aggressive behavior after receiving 4.8 mg midazolam (RSS =1). Another was fully awake but calm (RSS =2) despite maximum dose of midazolam.

All the baseline vital signs were similar between groups ($p > 0.05$; Figure 1,2). Heart rate decreased significantly after dexmedetomidine infusion and remained lower than Group M during the surgical and recovery periods ($p < 0.001$; Figure 1). Respiratory rates were similar between groups, but oxygen saturation was lower in Group M during drug infusion ($p = 0.003$) and lower in Group D during surgery ($p = 0.03$;figure 3). Oxygen desaturation (<90%) occurred in 6 patients (20%) receiving dexmedetomidine and 4 patients (13%) receiving midazolam ($p = 0.488$;figure 4). Oxygen saturation rapidly returned to normal upon treatment.

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

NRS pain scores during local anaesthetic infiltration and in the ward were similar ($p > 0.05$). median time to first oral analgesic use (187 min in Group D vs 185 min in Group M , $p = 0.903$) was similar between groups.

FIGURE 1: Comparison of heart rate between two groups.

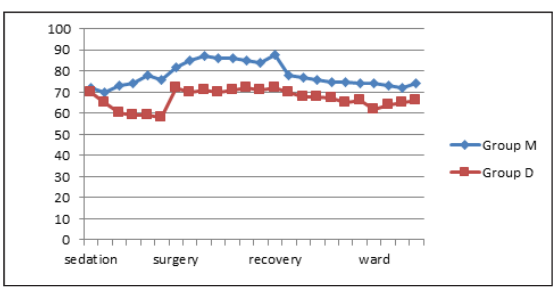


FIGURE 2: Comparison of mean arterial pressure between two groups.

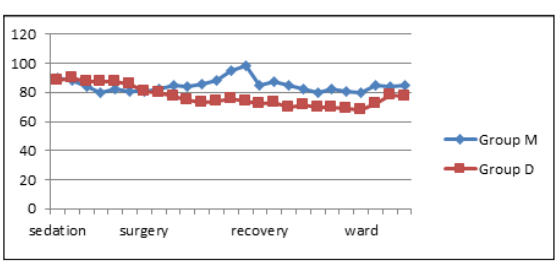
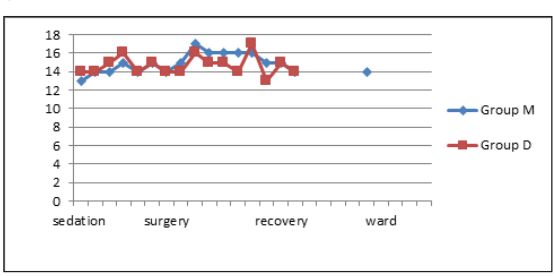


FIGURE 3: Comparison of respiratory rate between two groups.



Volume : 5 | Issue : 10 | October 2015 | ISSN - 2249-555X

FIGURE 4: Comparison of oxygen saturation between two groups.

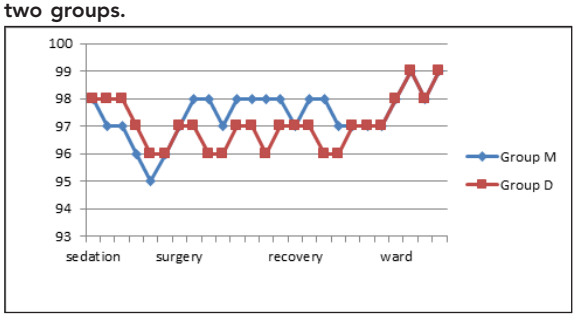


Table 1: The patient characteristics and operative data. Data shown are number (proportion) or means (SD) within the group.

	Dexmedetomidine (n = 30)	Midazolam (n = 30)
Sex; M:F	9 (30%): 21(70%)	9 (30%): 21(70%)
Age; years	25.5 (4.2)	27.7 (7.1)
Weight; kg	54.3 (10.2)	56.5 (13.9)
ASA Grade;		
1	29 (97%)	29 (97%)
2	1 (3%)	1 (3%)
Preoperative MMSE score	28.7 (1.5)	28.7 (1.5)
Duration of surgery; min	21.4 (10.8)	21.1 (12.2)

Table-2: Comparison of patients' report on relaxation, patients' satisfaction scores and surgeons' satisfaction scores. Data shown are number (proportion) or median (range). None of the differences between groups reached statistical significance.

	Dexmedetomidine (n = 30)	Midazolam (n = 30)
Relaxed during surgery	24(80%)	25(83%)
Patients' satisfaction score	8(5-9)	8(4-10)
Surgeons' satisfaction score	9(5-10)	8(1-10)

Table-3: Amnesic effects of dexmedetomidine and midazolam. Data shown are number (proportion).

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

NS- not significant

DISCUSSION: This study demonstrates that dexmedetomidine can provide comparable sedation when compared to midazolam for dental surgeries under local anaesthesia. A lower heart rate and blood pressure as well as less amnesia can be achieved by using dexmedetomidine.

There are significant pharmacogenetic differences in sedative drug response, which result in a large variation in dose requirements (14,15). Titration is important to reduce the risk of over sedation. The median dose required to achieve adequate sedation was 47 mcg (39-52) or 0.88 mcg/kg (0.75-1.0) dexmedetomidine or 3.6 mg (3.3-4.4) or 0.07mg/kg (0.055-0.085) midazolam. Extraction of third molar tooth and implant procedures are relatively short procedures, so supplementary intraoperative bolus or maintenance infusion of study drug was not given. All the patients receiving dexmedetomidine reached RSS of three or above immediately after the infusion, whereas two patients receiving midazolam did not, which means that the upper limit of 5 mg was not sufficient for some patients.

The onset time for IV midazolam is 3 min. Dexmedetomidine produces dose dependent sedation when it is infused over 2 min. Its peak effect is seen within 10 min of infusion. The upper dose limit of dexmedetomidine used in this study was 1 mcg/kg which is recommended loading dose. The study medications were titrated according to the clinical end point of a RSS greater or equal to four, as this was considered to be a clinically acceptable level of sedation.

Dexmedetomidine causes an increase in arterial blood pressure upon rapid bolus infusion (16). This is due to direct effects on vascular alpha receptors. This was minimized by infusing the drug slowly but this will take more time to reach sedation end point when compared to midazolam, which can be given as a bolus. Midazolam also has to be given reasonably slowly as it has a relatively slow time to peak effect (17). After infusion of dexmedetomidine, blood pressure, heart rate and cardiac output decreases slightly (16). The effects of alpha2 agonist in the cardiovascular system may be beneficial in high risk patients (18). Midazolam can cause respiratory depression (3) whereas dexmedetomidine does not (8,9). Respiratory rate did not differ significantly between two study groups but oxygen desaturation (S_aO_2 <90) did occur in both groups. All desaturated patients responded to verbal stimulus and low floe oxygen therapy.

Pain on local anaesthetic infiltration can be a stressful experience and pain after dental surgery may be considerable (19). The analgesic properties of dexmedetomidine have been demonstrated in healthy volunteer studies (11,20) ,but controversy still exists in clinical practice(21). When it is used preoperatively or intraoperatively the analgesic consumption was reduced without lowering the pain scores(22,23). In our study, dexmedetomidine did not exhibit additional analgesic benefit compared to midazolam, which has been reported to reduce pain after dental surgery when compared to placebo(24). The NRS pain scores recorded were similar. There was no difference in the time of taking the first analgesic tablet suggesting no pre-emptive analgesic effect.

It is known that midazolam has potent anterograde amnesic effect. On the other hand dexmedetomidine infusion also results in impairment of memory and psychomotor performance (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 two patients receiving midazolam did so. However amnesic effect of midazolam rapidly diminished with the 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.

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After surgery, most patients in both groups were satisfied with their sedation. Thus both drugs appear to be equally acceptable to patients. Rapid recovery is desirable after sedation and short surgery. The MMSE performance was completely restored two hours postoperatively, which confirms that both drugs are applicable to day surgery. Neither drug had an advantage in reducing side effects such as dizziness, nausea and vomiting.

CONCLUSION: Dexmedetomidine is a comparable alternative to midazolam for sedation in dental procedures under local anaesthesia. It is the preferred drug when a lower heart rate and blood pressure or less amnesia is desirable.

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