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Dexmedetomidine *vs* midazolam for monitored anaesthesia care during cataract surgery

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Background. Cataract surgery is commonly performed under local anaesthesia with midazolam sedation. Dexmedetomidine, a sedative-analgesic, is devoid of respiratory depressant effects, and its use in cataract surgery has not been reported. This double-blind study compared the use of dexmedetomidine and midazolam in patients undergoing cataract surgery.

Methods. Forty-four patients undergoing cataract surgery under peribulbar anaesthesia randomly received either i.v. dexmedetomidine 1 μg kg^{-1} over 10 min; followed by 0.1–0.7 μg kg^{-1} h^{-1} i.v. infusion (Group D), or midazolam 20 μg kg^{-1} i.v.; followed by 0.5 mg i.v. boluses as required (Group M). Sedation was titrated to a Ramsay sedation score of 3. Mean arterial pressure (MAP), heart rate (HR), readiness for recovery room discharge (time to Aldrete score of 10), and patients' and surgeons' satisfaction (on a scale of 1–7) were determined.

Results. MAP and HR were lower in Group D compared with Group M [86 (SE 3) *vs* 102 (3) mm Hg and 65 (2) *vs* 72 (2) beats min^{-1}, respectively] ($P<0.05$). Group D patients had slightly higher satisfaction with sedation [median (IQR): 6 (6–7) *vs* 6 (5–7), $P<0.05$], but delayed readiness for discharge [45 (36–54) *vs* 21 (10–32) min, $P<0.01$] compared with patients in Group M. Surgeons' satisfaction was comparable in both groups [5 (4–6) *vs* 5 (4–6)].

Conclusion. Compared with midazolam, dexmedetomidine does not appear to be suitable for sedation in patients undergoing cataract surgery. While there was a slightly better subjective patient satisfaction, it was accompanied by relative cardiovascular depression and delayed recovery room discharge.

Cataract surgery is most frequently performed under local anaesthesia with monitored anaesthesia care and sedation.[1] Several drugs have been used for sedation during this procedure including propofol, benzodiazepines and opioids.[2–4] However, propofol may cause oversedation and disorientation,[2] benzodiazepines may result in confusion, particularly, when administered to elderly patients,[5] and opioids are associated with increased risk of respiratory depression and oxygen desaturation.[4] All of these untoward effects may hamper patients' cooperation during surgery,[6] and would make these agents less than ideal for the intraoperative management of sedation. In contrast, dexmedetomidine is a highly selective α_2-adrenoceptor agonist with both sedative and analgesic properties and is devoid of respiratory depressant effect.[7] It has been used to premedicate and sedate patients undergoing day care procedures without adverse effects,[8 9] and patients, typically, remain cooperative albeit being sedated. These properties along with its relatively short elimination half-life of 2 h (compared with 3–4 h for midazolam) make dexmedetomidine an attractive agent for sedation during monitored anaesthesia care for cataract surgery. Accordingly, this randomized, double-blind clinical study was undertaken to compare the effects of dexmedetomidine sedation with those of midazolam sedation in patients undergoing cataract surgery under peribulbar anaesthesia.

Methods

After institutional Ethics Committee approval, 44 ASA I–III patients signed a written informed consent to participate in

this randomized, double-blind clinical trial. Patients were included in the study if they were between 18 and 80 yr of age and were undergoing elective cataract surgery under local anaesthesia. They were excluded if they had serum creatinine >200 μmol litre^{-1}, advanced liver disease (liver enzymes twice the normal range or higher), history of chronic use of sedatives, narcotics, or both, history of alcohol or drug abuse, or allergy to any of the study medications. Using a computer-generated randomization schedule, patients were randomized to receive either dexmedetomidine (Group D) or midazolam (Group M) for sedation during surgery. The anaesthetist was blinded to the patient's group assignment, and the study data were recorded by a blinded observer. Drugs were prepared in pharmacy and were delivered to the anaesthetist in three maximally filled-up syringes. The largest syringe (size 50 ml) was labelled 'infusion drug', a 5 ml syringe was labelled 'repeat boluses' and a 3 ml syringe was labelled 'initial bolus'. Group D patients had dexmedetomidine 4 μg ml^{-1} in the 50 ml syringe and saline in the other two syringes; whereas Group M patients had saline in the 50 ml syringe, midazolam 1 mg ml^{-1} in the 5 ml syringe, and midazolam 20 μg kg^{-1} (based on patient's body weight) premixed with saline to a total volume of 3 ml in the 3 ml syringe.

Patients arrived in the operating room un-premedicated. A 20 gauge cannula was inserted into one of the two nasal prongs of an oxygen nasal cannula, and was connected proximally to the CO_2 sampling tubing of the end-tidal CO_2 module of the patient monitor (Cardiocap^{TM}/5, Datex-Ohmeda Division, Helsinki, Finland) to measure patients' expired CO_2. Other standard monitors including ECG, non-invasive arterial pressure and pulse oximeter were also applied, and oxygen was administered at 2 litre min^{-1}. Group D patients received dexmedetomidine 1 μg kg^{-1} i.v. over 10 min (from the 50 ml syringe labelled 'infusion drug') using an infusion pump (AS50^{TM}, Baxter Health Care Co., Singapore), and normal saline 3 ml i.v. bolus (from the 'initial bolus' syringe). This was followed by a continuous infusion of dexmedetomidine 0.1–0.7 μg kg^{-1} h^{-1}, starting at 0.4 μg kg^{-1} h^{-1} and titrated every 10 min, in steps of 0.1 μg kg^{-1} h^{-1}, to a Ramsay sedation scale[10] of 3. Furthermore, with each increment in the infusion rate of dexmedetomidine, normal saline 0.5 ml i.v. bolus was administered concomitantly (from the 'repeat boluses' syringe) to maintain blinding. In contrast, Group M patients received normal saline 0.25 ml kg^{-1} i.v. over 10 min using the AS50^{TM} infusion pump and the 50 ml syringe labelled 'infusion drug', along with midazolam 20 μg kg^{-1} i.v. bolus (from the 'initial bolus' syringe). This was followed by normal saline infusion starting at 0.1 ml kg^{-1} h^{-1} and

titrated every 10 min, in steps of 0.025 ml kg^{-1} h^{-1}, to a Ramsay sedation scale of 3. In addition, with each increment in the infusion rate, midazolam 0.5 mg i.v. (from the 'repeat boluses' syringe) was administered. The infusion pump was stopped at the end of the procedure in both groups. Rescue sedation with propofol 300 μg kg^{-1} i.v. was available to patients in both groups, and was administered if the patient was still anxious 10 min after, both, a two-step increase in the infusion pump rate and the administration of two bolus doses from the 'repeat boluses' syringe.

After completing the loading dose of the study drug, the blinded ophthalmologist performed peribulbar block using 7 ml of a mixture of bupivacaine 0.25% and lidocaine 1%. Heart rate (HR), mean arterial pressure (MAP), ventilatory frequency, oxygen saturation (Sp_{O_2}) and expired CO_2 were recorded every 5 min throughout the surgery. In the recovery room, Aldrete score[11] was determined every 5 min until discharge and the requirement for postoperative analgesia was documented. Patients were deemed ready for discharge when they had achieved an Aldrete score of 10. Patients were asked to answer the question 'How would you rate your experience with the sedation (or analgesia) you have received during surgery?' using a 7-point Likert-like verbal rating scale[9 12] (Fig. 1). This assessment of patients' satisfaction with sedation and analgesia was performed just before recovery room discharge to minimize the effects of sedation on patients' judgement. Moreover, the surgeons were asked to rate their satisfaction with patient sedation using the same method and scale at the end of surgery. All adverse events including, but not limited to, bradycardia (HR <60 beats min^{-1}), hypotension (MAP <60 mm Hg sustained for >10 min), respiratory depression (ventilatory frequency ≤10 bpm), oxygen desaturation (Sp_{O_2}<92%) or unplanned hospital admission were recorded.

Statistical analysis

Sample size was calculated based on a difference of 2 in patients' satisfaction scores with sedation between groups, a population variance of $(2)^2$, a two-sided α of 0.05, and a power of 90%. Haemodynamic and respiratory data were analysed using repeated measures ANOVA, satisfaction scores were compared using Mann–Whitney test, and Aldrete scores data were analysed using the log-rank test after constructing Kaplan–Meier survival curves for times to achieving an Aldrete score of 10. All statistical procedures were performed using PS Power and Sample Size Calculations Program®, version 2.1.31 (Copyright © 1997 by WD Dupont and WD Plummer[13]) and SPSS® statistical software (SPSS Inc., Chicago, IL, USA), version 13.0 for Windows®.

1	2	3	4	5	6	7
Extremely dissatisfied	Dissatisfied	Somewhat dissatisfied	Undecided	Somewhat satisfied	Satisfied	Extremely satisfied

Fig 1 A 7-point Likert-like verbal rating scale for assessment of patients' satisfaction with intraoperative sedation/analgesia.

Results throughout the text, tables and figures are presented as mean (SD) unless otherwise indicated, and statistical significance was defined as $P<0.05$.

Results

Baseline characteristics and anaesthesia time were similar in both study groups (Table 1). Group D patients received a total of 79.5 (21.7) µg of dexmedetomidine, whereas those in Group M received 1.5 (0.6) mg of midazolam;

Table 1 Patient characteristics. Group D, dexmedetomidine; Group M, midazolam. Data presented as mean (range or SD) or absolute numbers

	Group D (*n*=22)	Group M (*n*=22)
Age (yr)	61 (34–79)	61 (40–75)
Weight (kg)	68.9 (10.7)	70.6 (12.0)
Gender (male/female)	11/11	7/15
ASA class I/II/III (*n*)	4/15/3	3/16/3
Preexisting disease		
Hypertension (*n*)	8	10
Ischaemic heart disease (*n*)	3	2
Diabetes mellitus (*n*)	10	13
Anaesthesia time (min)	63 (24)	64 (15)

however, none of the patients in either group required rescue sedation with propofol. Although there were no differences in baseline measurements of HR and MAP between groups, patients in Group D had lower HR and MAP over time compared with those in Group M ($P<0.05$) (Fig. 2). In contrast, there was a trend towards higher ventilatory frequency and lower Sp_{O_2} over time among patients who received midazolam compared with those who did not ($P=0.06$) (Fig. 2). Nevertheless, there were no episodes of bradycardia, hypotension or desaturation in either group. Furthermore, there were no changes in expired CO_2 over time within and between study groups. Group M patients achieved an Aldrete score of 10 faster and were, thus, ready for discharge sooner than those in Group D ($P<0.01$) (Fig. 3). Median (IQR) times to readiness for discharge were 21 (10–32) *vs* 45 (36–54) min for Groups M and D, respectively ($P<0.01$). On the other hand, median (IQR) satisfaction with sedation in Group D was 6 (6–7) compared with 6 (5–7) in Group M ($P<0.05$). In contrast, patients in both groups were similarly satisfied with their analgesia [median (IQR) 7 (5–7) *vs* 7 (5–7)]. Furthermore, surgeons' satisfaction with patients' sedation was similar for both groups [median (IQR) 5 (4–6) *vs* 5 (4–6)].
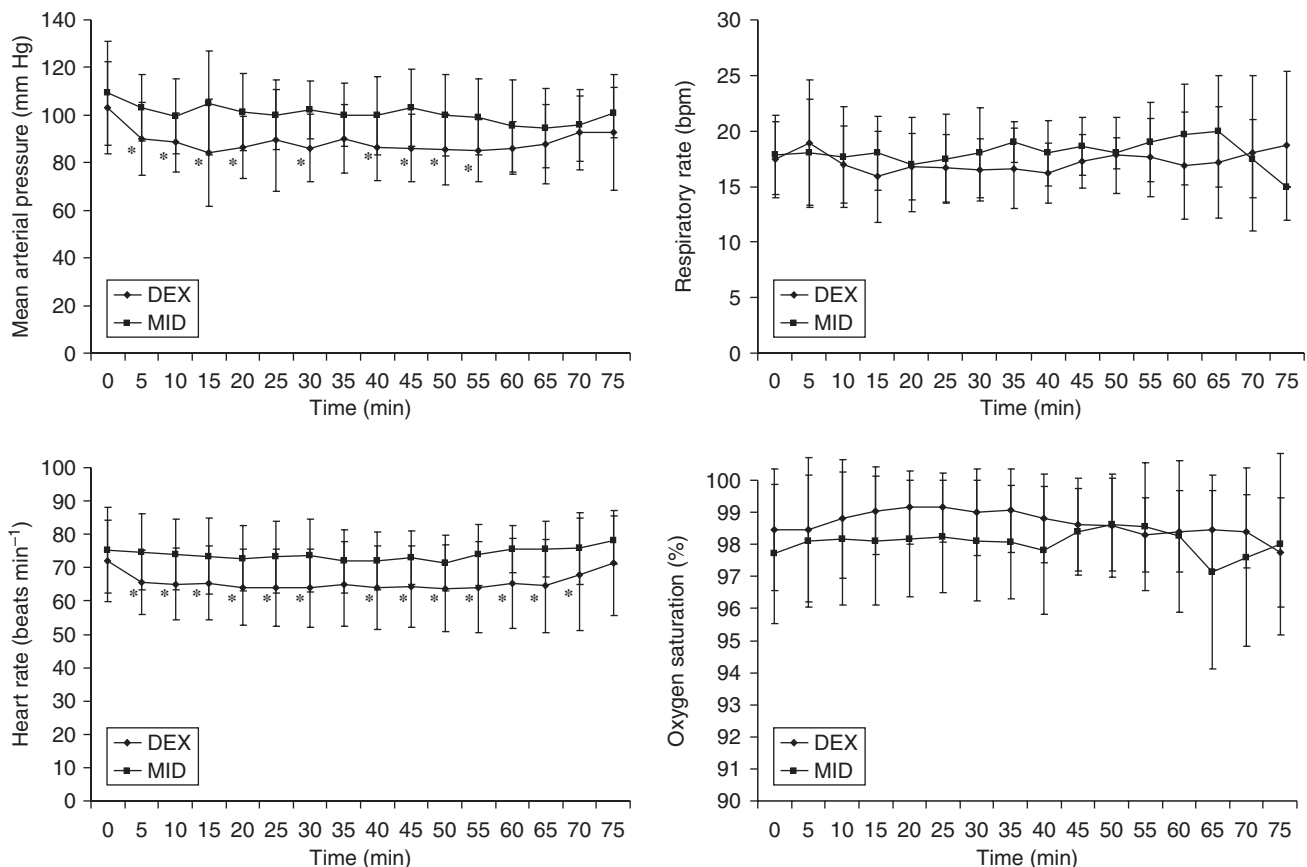

Fig 2 Changes in MAP, HR, ventilatory frequency and oxygen saturation (Sp_{O_2}) over time. DEX, dexmedetomidine; MID, midazolam. Time '0', start of study drug administration. Data presented as mean (SD). *$P<0.05$, different from the corresponding data point in Group M.

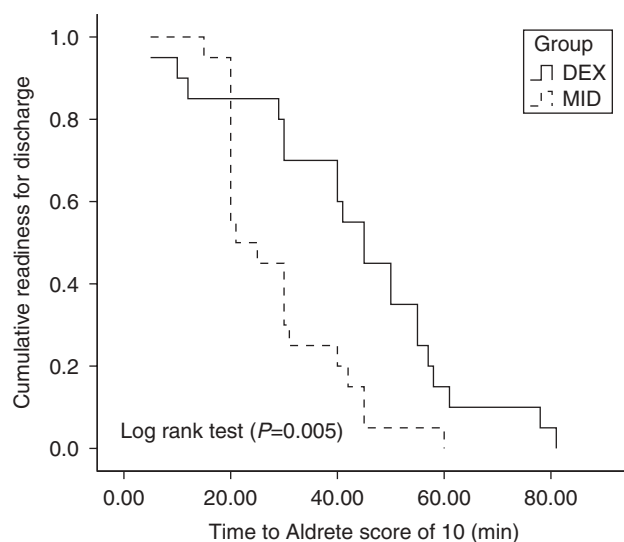**Fig 3** Kaplan–Meier curves for time to achieving an Aldrete score of 10. DEX, dexmedetomidine; MID, midazolam.

No major adverse effects were observed in this study including unplanned hospital admission or conversion to general anaesthesia. Only two patients in Group M requested analgesia in the recovery room and both had received a single dose of fentanyl 25 μg i.v.

Discussion

Dexmedetomidine has been used mainly in the intensive care unit as a sedative agent with some analgesic properties; however, its efficacy outside the critical care environment has also been documented.[9] This randomized, double-blind study demonstrated that sedation with dexmedetomidine was equally effective to that with midazolam in patients undergoing cataract surgery under local anaesthesia. This was evident from the facts that none of the patients in either group required rescue sedation with propofol, and that surgeons were equally satisfied with both sedative regimens. These results are in keeping with those reported by Virkkila and colleagues,[14] who have demonstrated that a single dose of i.m. dexmedetomidine administered 45 min before operation provides sedation comparable with that produced by i.m. midazolam.

The lower HR and MAP observed in Group D could be explained by the decreased sympathetic outflow and circulating levels of catecholamines that are caused by dexmedetomidine.[15] Similar haemodynamic changes have been reported by Arain and Ebert,[16] who compared dexmedetomidine with propofol for sedation during surgery under regional anaesthesia. An interesting observation, in this study, was the trend towards higher ventilatory frequency in Group M ($P=0.06$). This could not have been caused by patients' discomfort during surgery as none

of them required supplemental analgesia intraoperatively, and satisfaction scores with analgesia were nearly identical in both study groups. It is possible, however, that midazolam had resulted in decreased patients' tidal volume, and the observed increase in ventilatory frequency was, thus, a compensatory response to maintain minute ventilation. In support of this hypothesis is the observed trend towards lower Sp_{O_2} in Group M, which would suggest that breathing was likely shallow with consequent atelectasis and ventilation–perfusion mismatch. In contrast, it is unlikely that the lower Sp_{O_2} in Group M was responsible for the increase in ventilatory frequency in this group as none of the patients had an $Sp_{O_2} \leqslant 92\%$. Other investigators have also observed low Sp_{O_2} readings among patients, who received midazolam sedation, and this has been attributed to hypoventilation or lack of supplemental oxygen administration.[17–19] In this study, all patients received supplemental oxygen; however, hypoventilation could have existed despite the apparent lack of measurable changes in expired CO_2 over time in both groups. This could be attributed to the limitation of the method of CO_2 measurement used in this study (see study limitations below). The observed directional changes in HR, MAP, ventilatory frequency, Sp_{O_2} and expired CO_2 at 55 min, and thereafter (Fig. 2) were likely because of the smaller number of patients remaining at these time intervals and were, therefore, difficult to interpret.

Although both drugs were effective in providing adequate intraoperative sedation, group DEX patients were more satisfied with their sedation than those in group MID. This could be explained, at least in part, by the additional analgesic property of dexmedetomidine that could have contributed to improved patients' perception of this form of sedation, and in part, by potential differences in the quality of sedation of the two drugs. Nevertheless, the difference in satisfaction with sedation between groups is small and its clinical importance is probably minor. An important finding, in this study, was the delayed readiness for recovery room discharge among patients in group DEX. It is unlikely that this was a result of an overdose of dexmedetomidine as the drug infusion was titrated to a predefined endpoint (Ramsay score of 3) and the dosage used was in keeping with standard practice. This finding, however, could be attributed to sustained therapeutic plasma concentration of dexmedetomidine which was likely present on arrival at recovery room as dexmedetomidine has an elimination half-life of about 2 h,[7] and the drug infusion was continued up to the end of surgery. This was done because surgeons were unpredictable as far as operation finish time was concerned. Similar findings have been reported when dexmedetomidine was administered for sedation in patients undergoing extracorporeal shockwave lithotripsy for urinary calculi.[9] The importance of this observation is the cost implications of longer stay in recovery room in the current environment of cost containment. This investigation, however, was not designed to address this issue.

This study was underpowered to detect the differences in ventilatory frequency and Sp_{O_2} between groups, as these were not the primary outcome measures of the study. Another limitation is the method used for determining expired CO_2 and the inherent limitation of examining end-tidal CO_2 without establishing the gradient that normally exists between end-tidal and arterial CO_2.[20] However, obtaining arterial blood gases to establish the end-tidal-arterial CO_2 gradient could not be justified given that expired CO_2 was not the primary outcome variable in this study. In addition, the obtained CO_2 measurements lacked precision because of the inflow of oxygen through the nasal cannula,[21] and the potential for rebreathing given that patients' faces were covered with surgical drapes.[22] Other investigators, however, have used a similar method to measure expired CO_2 in sedated patients,[21] and this limitation affected both study groups similarly. Another potential point of criticism is the use of Ramsay sedation scale, in this study, as an endpoint for administering study drugs as opposed to the bispectral index. This was done because bispectral index is not a standard monitor during monitored anaesthesia care and is not readily available in all institutions. One could also argue that the doses of study drugs were not comparable; however, as both drugs were titrated to a predefined endpoint (Ramsay score of 3), it is unlikely that this was an issue as far as study outcomes were concerned. Furthermore, there are no published studies that compare the dose–response relationships of dexmedetomidine and midazolam.

In conclusion, this study showed that dexmedetomidine does not appear to be a suitable agent for sedation in patients undergoing cataract surgery. Compared with midazolam, while there was a slightly better subjective patient satisfaction, it was accompanied by cardiovascular depression and delayed recovery room discharge.

Acknowledgements

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