Original Article

Comparative evaluation of two different loading doses of dexmedetomidine with midazolam-fentanyl for sedation in vitreoretinal surgery under peribulbar anaesthesia

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ABSTRACT

Background and Aims: Midazolam-fentanyl (MDZ:FEN) combination has been routinely used for intravenous sedation in ophthalmic surgeries. Dexmedetomidine (DEX), a recent α_2 adrenoreceptor agonist indicated for sedation for ophthalmic use at a loading dose of 0.5 μg/kg over 10 min, can cause deeper plane of sedation and surgeon dissatisfaction. Therefore, we proposed to evaluate the efficacy and safety of two different loading doses of DEX. **Methods:** In a prospective study, 60 patients aged 50-70 years, scheduled for retinal surgery under peribulbar block were divided equally to receive either MDZ:FEN or DEX 0.5 μg/kg (DEX full) or DEX 0.25 μg/kg (DEX half) loading dose over 10 min followed by titrated maintenance dose of DEX 0.25-0.4 μg/kg/h. Vital parameters, level of sedation (Ramsay Sedation Scale 1–6), effect on respiration and surgeon satisfaction were assessed at regular intervals. Surgeon satisfaction score (0–3) was noted. **Results:** 'DEX half' group patients had predominantly stable haemodynamics, level 3 sedation and surgeon satisfaction score of 2–3 (good to excellent operating conditions). This group had no vomiting and no respiratory depression. 'DEX full' group had a higher incidence of bradycardia, hypotension, level 4 sedation (Ramsay Sedation Scale) and lower surgeon satisfaction. Incidence of nausea and vomiting was higher in MDZ:FEN group compared to other two groups. **Conclusion:** DEX 0.25 μg/kg loading dose over 10 min followed by titrated maintenance dose is an effective alternative to MDZ:FEN and provides controlled (level 3) sedation and stable haemodynamics maximising surgeon satisfaction. Avoiding narcotic analgesics with its associated post-operative nausea and vomiting is an additional benefit.

Key words: Conscious sedation, dexmedetomidine, fentanyl, midazolam, vitreoretinal surgery

INTRODUCTION

Vitreoretinal surgery is commonly done under peribulbar anaesthesia supplemented with intravenous (IV) sedation. Current drugs include benzodiazepines (most commonly midazolam) with an opioid (often fentanyl), with or without propofol. Common adverse effects of midazolam include prolonged recovery after long term or high-dose use, hypoxaemia, hypotension and respiratory depression when paired with an opioid.[1] The adverse respiratory profile, unpredictable attenuation of stress response to surgery (tachycardia and hypertension) and associated post-operative nausea and vomiting (PONV) of benzodiazepines and opioids create the need for a sedative drug that can be used safely during monitored anaesthesia care (MAC).

The α_2 agonist dexmedetomidine (DEX), provides "conscious sedation" with adequate analgesia

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and minimal respiratory depression.[2] It is a sedative – hypnotic, anxiolytic and sympatholytic that can attenuate the stress response to surgery (mitigating tachycardia, hypertension) and also decrease intraocular pressure (IOP) during ophthalmic surgery under local anaesthesia.[3,4] It is the primary sedative drug for orthopaedic, ophthalmic (posterior segment surgery), dental, plastic surgeries, for sedation in intensive care and for various diagnostic procedures.[5-7] DEX is labelled for intensive care and procedural sedation in the USA and India. It has been recommended at a loading dose of 1μg/kg over 10 min, followed by maintenance infusion of 0.2–0.7 μg/kg/h.[2] Bradycardia and hypotension are noticed mainly with loading dose of DEX which can be avoided by omitting the loading dose or limiting the loading dose to 0.4 μg/kg in intensive care.[7]

The aim of this study was to compare the efficacy of two different loading doses of DEX with midazolam-fentanyl (MDZ: FEN) combination.

METHODS

After the approval of the Institutional Ethics Committee, a prospective study comprising 60 patients in the age range of 50–70 years (average 60 years) and American Society of Anesthesiologists physical Status 1-3 posted for vitreoretinal surgery under local anaesthesia and IV sedation was initiated. Informed written consent was taken from all the patients. Patients were randomly allocated into three groups of 20 each during the study period of 1 year from June 2012 to May 2013. All surgeries were performed by the same surgeon.

Patients with baseline heart rate (HR) <60/min, age more than 70 years, severe left ventricular dysfunction (EF <30%), hypovolaemia with systolic blood pressure (SBP) <90 mmHg, Mobitz type 2 or 3rd degree heart block, severe valvular disease (valve stenosis/regurgitation), chronic renal failure and hepatic impairment were excluded from the study.

Pre-anaesthetic evaluation and fasting status of 4 h were ensured. Pre-operatively, baseline vital parameters such as HR, SBP, diastolic blood pressure (DBP), respiratory rate (RR), peripheral oxygen saturation (SpO_2) and rate pressure product (RPP) were noted and patients were premedicated with oral alprazolam 0.25–0.5 mg, ranitidine 150 mg and ondansetron 4 mg. Intraoperative monitoring included electrocardiogram, non-invasive blood pressure, SpO_2, respiration and Ramsay Sedation Scale. Oxygen 2–3 l/min was supplemented through a nasal cannula.

MDZ:FEN group patients received IV bolus midazolam 0.5–2 mg (0.02 mg/kg) with fentanyl 12.5 μg over 10 min. 'DEX full' group patients received DEX 0.5 μg/kg IV loading dose over 10 min through syringe infusion pump. 'DEX half' group patients received DEX 0.25 μg/kg loading dose over 10 min. All preparations were made to a volume of 20 ml with saline. Computer aided group randomization was followed. The drug combinations were prepared by an anaesthesiologist not involved in monitoring and follow up.

Peribulbar block with 8 ml of local anaesthetic comprising 3 ml of 0.5% bupivacaine, 5 ml of 2% lignocaine and hyaluronidase was given after 10 min of starting IV sedation (on completion of loading dose), and surgery was started after achieving adequate block. Vital parameters HR, SBP and DBP, RR, SpO_2 and level of sedation (RSS: 1–6) were noted every 5 min for the first 15 min (5, 10, 15), every 15 min until the end of surgery and every 30 min for 2 h in the post-operative ward. Level 3 sedation was targeted in the intraoperative period. In MDZ: FEN group aliquots of 0.5–1 mg of midazolam and 6.25–25 μg of fentanyl was given as determined by the level of sedation every 15–30 min. In DEX full and DEX half group, DEX was administered at a maintenance dose of 0.25 μg/kg/h via the infusion pump.[1]

Adverse effects (bradycardia, hypotension, respiratory depression and level 4 sedation) were noted and treated. After completion of surgery, surgeon satisfaction was assessed by rating the ease of performing surgery as - Excellent (score 3), Good (2), Fair (1), Poor (0). Poor operating conditions included deeper level of sedation (RSS 4), snoring, sudden involuntary movement of the head, respiratory depression causing raised IOP which made surgery difficult. In the postoperative period, nausea and vomiting was treated with IV ondansetron 4 mg. Post-operative pain was treated with diclofenac 75 mg IM/paracetamol 50-100ml IV infusion. Patients were discharged when the criteria for home readiness was satisfied.

The sample size of 20 in each group was determined based on the capacity of our centre to recruit patients undergoing vitreoretinal surgeries under IV sedation and peribulbar block in a reasonable period, i.e., 1 year. We estimated that this sample size was sufficient to highlight a significant effect on the main outcomes of the study.

Normality test, Kolmogorov–Smirnov and Shapiro–Wilks tests were applied to assess whether variables were normally distributed. Parametric tests were applied to analyse the data. Chi-square test, ANOVA between groups, Tukey's Honest Significant Difference *post-hoc* test for multiple pairwise comparisons and paired samples *t*-tests was done. One-way ANOVA was used to compare the mean values between groups. RM-ANOVA was used to compare within the groups at different time points taking into consideration the subject effect (If *P* value is <0.05 then it is considered as statistically significant).

RESULTS

The demographic data of the three groups were comparable, and no statistically significant difference was noticed.

HR values in 'DEX full' group were significantly lower than in MDZ:FEN and 'DEX half' group at 10 min ($P = 0.001$). MDZ: FEN group patients had lower HR than DEX full and DEX half group patients in the post-operative period (150, 180, 210 min) [Figure 1]. Two cases in the "Dex full" group required injection atropine for treatment of HR less than 50/min. 'DEX full' group patients had significantly lower SBP values at 10 min ($P = 0.018$), 90, 120, 150, 180 and 210 min ($P = 0.001$) as compared to patients in MDZ: FEN and 'DEX half' group. Lowest SBP in 'DEX full' group was noticed at 10 min [Figure 1]. 'DEX half' and 'DEX full' group patients persistently had lower DBP than MDZ:FEN group at various intervals 30, 45, 60, 75, 90, 120 and 150 min ($P = 0.001$) [Figure 1]. DEX full patients had significantly lower RPP as compared to MDZ:FEN and DEX half group in the intraoperative period at 5, 10, 90 and 120 min ($P = 0.001$). Lowest RPP in DEX full was seen at 10 min.

DEX full group had increased incidence of level 4 sedation predominantly in the first 30 min of IV sedation [Figure 2]. Clinically, MDZ:FEN and DEX full group patients had lower RR in the 1st 10 min of sedation as compared to DEX half; however, the difference is not statistically significant and did not warrant any intervention. Clinically, SpO_2 was lower in DEX full group patients at 5 and 10 min intervals as compared to MDZ:FEN and DEX half group; however, patients did not need any intervention and SpO_2 increased once loading dose was completed and maintenance infusion started.

Operating conditions were excellent in two patients in DEX full group as compared to 7 in MDZ: FEN group and 9 in DEX half group. Poor operating conditions reported in two patients in DEX full group and none in MDZ: FEN and DEX half group.

DEX full group patients had statistically significant bradycardia ($P < 0.001$), hypotension ($P = 0.008$) and level 4 sedation ($P = -0.001$). MDZ:FEN group patients had significantly higher incidence of nausea ($P = 0.001$) and vomiting ($P = 0.002$). Respiratory depression (with RR <8/min or SpO_2 <90%) was not seen in any of the groups.

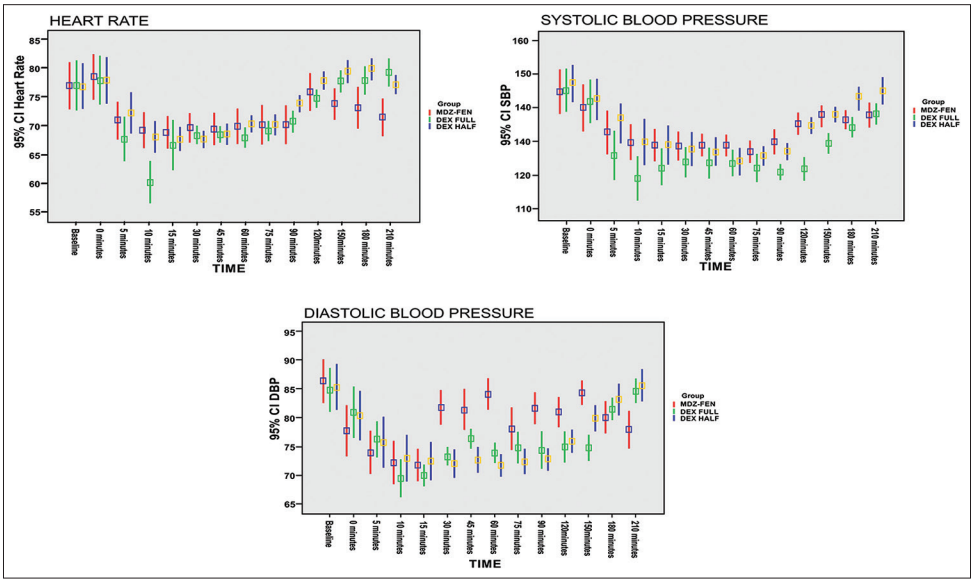

Figure 1: Heart rate, systolic blood pressure and diastolic blood pressure

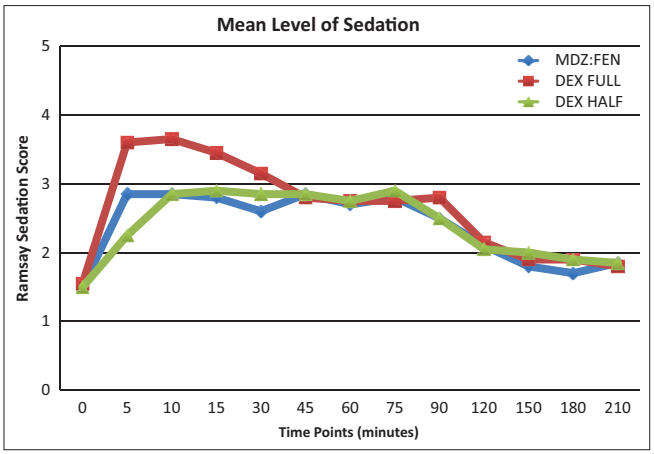

Figure 2: Mean level of sedation

DISCUSSION

In vitreoretinal surgeries moderate sedation is a very useful adjunct to the local anaesthetic (peribulbar) block as it enhances patient comfort, ameliorates anxiety and facilitates stabilisation of haemodynamics during surgery.

In our study, there was significantly increased incidence of bradycardia and hypotension with DEX loading dose of 0.5 μg/kg. However, such adverse effects were not significant when DEX loading dose was reduced to 0.25 μg/kg. DEX at an initial loading dose of 1 μg/kg over 10 min followed by maintenance dose of 0.7 μg/kg/h resulted in adverse haemodynamic effects of either hypotension or bradycardia significantly during loading dose infusion.[8] The potential adverse haemodynamic effects of DEX such as bradycardia and hypotension occur with the initial loading dose. Use of low-dose DEX intravenously can be a preferred mode of sedation for better control of intraoperative hypertension and avoid last minute cancellation of surgery. Elderly patients who are over sedated may stop obeying verbal commands, thus resulting in a communication breakdown. This can also be associated with hypoventilation, hypercapnia and airway obstruction, together with restlessness, and unexpected or unwanted movements during the surgery.[9] The perioperative period is characterised by increased sympathetic activity, leading to stress-induced tachycardia and hypertension. By attenuating sympathetically mediated hyperdynamic responses, α_2 adrenoceptor agonists ameliorate the haemodynamic profile during the perioperative period.[10] The magnitude of decrease in HR and blood pressure was proportional to the dose of DEX and at lower doses, the decrease was of modest clinical interest and did not warrant corrective action.[11]

In our study, MDZ: FEN group patients needed repeated incremental doses to maintain target level of sedation and DEX full group patients had a higher incidence of level 4 sedation requiring frequent titration of maintenance infusion dose. DEX half group achieved and maintained target level of sedation easily. One study of MAC with DEX indicated significantly increased ease of achieving and maintaining targeted sedation in DEX group when compared to midazolam.[12] Comparison of DEX (1 μg/kg loading dose, 0.2 μg/kg/h infusion) with midazolam (0.06 mg/kg) plus fentanyl (1 μg/kg) for tympanoplasty showed that DEX is comparable to MDZ: FEN sedation.[13]

In our study, though the RR was lower in MDZ: FEN group, it was not statistically significant and hypoxaemia requiring intervention was not noticed probably because of the lower dose of midazolam and fentanyl used. There was no significant respiratory depression in both DEX groups. The incidence of respiratory depression was lower in DEX treated patients as compared to patients treated with MDZ: FEN.[12]

In this study, MDZ: FEN group patients had a higher incidence of PONV (may cause increased IOP), which can be detrimental in ophthalmic surgery. DEX shows superiority to placebo, in the prevention of nausea and vomiting. This beneficial antiemetic effect may be explained by direct antiemetic properties of α_2 agonists. In addition, since nausea and vomiting may be induced by high catecholamine concentrations, a decrease of sympathetic tone could explain the antiemetic effect of DEX. Finally, consumption of intraoperative opioids, which increases the risk of PONV, may be reduced through the use of DEX.[14]

In this study, surgeon satisfaction was better with lower loading dose of DEX 0.25 μg/kg (DEX half) when compared to 0.5 μg/kg (DEX full) loading dose. Better surgeon satisfaction was observed with DEX than MDZ: FEN combination for sedation in tympanoplasty.[13]

In this study, the RPP was lowest in DEX full group; lower RPP may compromise the coronary perfusion pressure and precipitate coronary ischaemia in elderly group of patients in deeper planes of sedation.

The need for decreased loading dose of DEX, especially in vitreoretinal surgery may be explained by the age group involved (mostly elderly >60 years), mostly diabetic patients (with impaired autonomic nervous

system), procedure being done under peribulbar block (analgesia present) and level 4 sedation being associated with sudden head movement that can result in ocular injury during surgery.

This study is an open study that could have resulted in some internal bias due to non-randomisation. The study did not include the assessment of variation in response to DEX by beta-blocked patients as compared to non-beta blocked patients. Pre-operative HR of <60 beats/min was an exclusion criterion whether the patient was beta blocked or not. Hence, this is an area for future research.

CONCLUSION

DEX (DEX half) is a comparable, safe and effective primary sedative alternative to traditional MDZ: FEN combination for vitreoretinal surgery under peribulbar anaesthesia. DEX at loading dose of 0.25 μg/kg over 10 min followed by maintenance dose of 0.25-0.4 μg/kg/h provides an adequate level of sedation, stable haemodynamics and better surgeon satisfaction.

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Conflicts of interest

There are no conflicts of interest.

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