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BIS GUIDED COMPARATIVE STUDY OF DEXMEDETOMIDINE AND MIDAZOLAM AS PREMEDICANT IN POSTERIOR FOSSA SURGERIES

Anesthesiology

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ABSTRACT

This prospective randomized controlled study aimed at comparing the intraoperative haemodynamics and propofol consumption and postoperative analgesic requirement, level of sedation, side-effects and recovery profiles of midazolam and dexmedetomidine when used before induction of general anaesthesia with propofol. 60 patients scheduled for posterior cranial fossa surgery in the age group of 18-60 years and in the ASA class I and II were included in the study. The patients were randomized into two groups: Group M patients received inj. midazolam 30µg/kg IV 3 minutes before induction, and group D patients received inj. dexmedetomidine 1µg/kg slow IV (over 10 min) started 15 minutes before induction. Maintenance with propofol infusion was titrated to achieve a BIS value between 40-60. A statistically significant reduction in heart rate, blood pressure and analgesic requirement was found in the dexmedetomidine group than in the midazolam group, but no significant difference was noticed in mean extubation time, postoperative side effects and sedation among the two groups.

KEYWORDS:

Dexmedetomidine, Midazolam, Neurosurgery, Propofol

Introduction

The goals of neuroanaesthesia are to provide good operating conditions and to ensure stable cerebral haemodynamics without sudden increases in intracranial pressure or acute brain swelling. Furthermore, rapid recovery from anaesthesia is often required to allow immediate postoperative neurological evaluation. During recovery, abrupt increases in arterial blood pressure can pose a risk for intracranial haematoma. Although analgesia provided by an opioid attenuates haemodynamic responses to awakening and extubation, it may cause respiratory depression due to high carbon dioxide tension with subsequent increase in the intracranial pressure.

The α_2 adrenergic agonists have been introduced in clinical anaesthesia for their sympatholytic, sedative, anaesthetic-sparing and favourable haemodynamic properties. Dexmedetomidine has also shown analgesic effects without significant respiratory depression.[1] Studies in animals suggest that it may have other beneficial effects in terms of neural protection.[2] As dexmedetomidine provides good perioperative haemodynamic stability with decreased intraoperative opioid requirements, it might be a suitable anaesthetic adjuvant to neurosurgical anaesthesia.

The aim of the study was to compare the perioperative hemodynamics, total propofol consumption, and recovery profiles such as sedation, postoperative analgesic requirement and undesirable side-effects, of midazolam and dexmedetomidine when used as premedicant before induction and maintenance of general anaesthesia (GA) undergoing elective posterior fossa craniotomy procedures.

Methods

With approval from the Institutional Research Ethics Committee, 60 ASA physical status I and II patients, aged 18-60 years of either gender, who were scheduled for elective posterior fossa surgery were enrolled for the study. Written and informed consent were taken from all patients. Exclusion criteria included patients with ASA III-IV, age less than 18 and more than 60 years, history of alcohol abuse, diabetes mellitus, hypertension, cardiovascular disease, history of allergy to the study drugs, Glasgow Coma Scale (GCS) less than 12 and patients requiring postoperative mechanical ventilation.

Before induction, routine standard monitoring devices viz. continuous electrocardiography (ECG), noninvasive blood pressure (NIBP) and pulse oximetry (SpO_2) were attached. The Bispectral Index (BIS) electrodes were placed on the forehead and were connected to an A-2000 BIS monitoring system (Aspect Medical Systems, BIS XP, Framingham, MA, USA). After recording baseline parameters, patients were allocated randomly into two groups using a computer-generated random numbers table (Group M: midazolam group; Group D: dexmedetomidine group). Each group compprised 30 patients. An anesthesiologist who was not participating in the analysis of the result was requested to prepare syringes containing either dexmedetomidine or midazolam. Dexmedetomidine 1µg/kg was prepared in a 10-mL isotonic solution. A 10-mL midazolam solution was also prepared for the midazolam group containing 30µg/kg of midazolam. Both syringes were labelled as "study drug" and coded to maintain the double-blinded nature of the study.

All patients were premedicated with inj. ondansetron 4mg i.v. and inj. butorphanol 30µg/kg i.v. 3-5 minutes before induction of anaesthesia. 15 minutes before the induction of anaesthesia, Group D patients received Dexmedetomidine slow IV (over 10 min), followed by 10 ml of normal saline injection. Similarly Group M patients received 10 ml of normal saline injection slowly (over 10 min), followed by 10 ml of prepared midazolam solution. Heart rate, peripheral oxygen saturation, non-invasive mean arterial pressure (MAP), end-tidal carbon dioxide, nasopharyngeal temperature and hourly urine output were monitored continuously in all patients. After recording bispectral index (BIS) values, the another anaesthesiologist induced anaesthesia with propofol until loss of verbal response. Inj. veccuronium 0.12mg/kg was used for neuromuscular relaxation and facilitation of endotracheal intubation. Anaesthesia was maintained with nitrous oxide and oxygen (50:50) and propofol infusion,. The dose of propofol was titrated to achieve a BIS value between 40 and 60. Controlled mechanical ventilation was adjusted to maintain the end-tidal carbon dioxide values between 30 and 35 mmHg. On completion of surgery, propofol infusion and nitrous oxide were turned off, and 100% oxygen was administered. Residual neuromuscular blockade was antagonized with neostigmine (0.04mg/kg) and glycopyrrolate (0.15mg/kg). Thereafter, the time for patients to "open eyes on verbal command" was recorded. The total dose of propofol used during the procedure (including induction dose) and duration of anaesthesia (induction to stoppage of propofol infusion) were noted.

Hemodynamic parameters were noted after the administration of study drugs (dexmedetomidine or midazolam), at induction, intubation, and at 15-minute intervals thereafter. Recovery from anaesthesia was assessed by Modified Aldrete recovery score. Once the patients were shifted to recovery room, hemodynamic parameters, Ramsay sedation score (RSS) and adverse events such as postoperative nausea vomiting (PONV) and shivering were recorded.

Unpaired Student's t-test and Chi-square tests were applied for quantitative and qualitative data respectively, whereas severity of adverse event, (none, mild, moderate and severe) was analysed by Fisher's exact test. SPSS 9.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. P<0.05 was considered as significant.

Results

The mean age in group D was 37.60±9.67 years and in group M was 41.97±10.70 years. The mean age of both groups was comparable. There were 18 male (60%) and 12 female (40%) patients in group D and in group M there were 16 male (53.3%) & 14 female (46.7%) patients. The mean time duration of anaesthesia was 208.03±28.03 minutes and 196.33±21.13 minutes in group D and group M respectively. The total dose of propofol used during induction and maintenance was 646.67±140.50 mg in group D, while it was 1138.83 ± 155.73 mg in group M (p<0.001). The mean extubation time following discontinuation of propofol infusion was 5.08±1.00 minutes in group D as compared to 5.56±0.93 minutes in group M (p=0.058) (Table 1).

Table 1: Demographic data

	Group D	Group M	p-value
Age (years)	37.60±9.67	41.97±10.70	p=0.103
Male:Female	18:12	16:14	p=0.602
Mean duration of anaesthesia (min)	208.03±28.03	196.33±21.13	p=0.067
Total propofol dose (mg)	646.67±140.50	1138.83±155.73	p<0.001
Mean extubation time (min)	5.08±1.00	5.56±0.93	p=0.058

The heart rates were observed at baseline, before the administration of study drug, 10 minutes after administration of study drug, after induction and every 15 minute thereafter. In group D, after drug administration the mean HR after premedication, induction and 15 minutes thereafter upto the end of surgery decreased significantly in comparison with group M. (p-value <0.001) (Table 2) (Figure 1)

Table 2: HR Intraoperative period

Time interval	Group D (n=30)	Group M (n=30)	t-value	p-value
Baseline_HR	81.83±8.828	84.90±9.897	1.266	0.210
Premed_HR	67.73±7.524	77.63±9.936	4.351	**<0.001***
Induction_HR	64.77±8.378	75.20±8.608	4.757	**<0.001***
HR_15min	64.67±9.452	74.70±8.142	4.405	**<0.001***
HR_30min	64.40±7.628	75.13±9.115	4.946	**<0.001***
HR_45min	64.97±7.237	75.67±8.568	5.226	**<0.001***
HR_60min	64.97±7.180	76.43±7.873	5.894	**<0.001***
HR_75min	64.30±7.840	76.07±8.056	5.734	**<0.001***
HR_90min	64.00±7.777	75.50±8.394	5.504	**<0.001***
HR_105min	64.10±7.554	75.93±7.763	5.984	**<0.001***
HR_120min	64.03±7.393	76.27±8.383	5.995	**<0.001***
HR_135min	64.30±7.023	75.80±6.099	6.772	**<0.001***
HR_150min	64.28±7.035	76.57±6.436	7.006	**<0.001***
HR_165min	64.62±6.710	76.27±6.142	6.958	**<0.001***
HR_180min	64.22±7.013	76.92±7.729	6.211	**<0.001***
HR_195min	63.74±6.903	78.81±5.845	7.129	**<0.001***
HR_210min	63.39±5.425	79.00±5.797	7.329	**<0.001***

[*p <0.05]

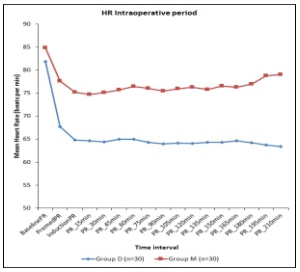

Figure 1: Mean intraoperative heart rate

After dexmedetomidine premedication, there were lower levels of MAP than those after midazolam. (Figure 2) The difference between the two groups was statistically significant with p value <0.001 at all intervals. (Table 3)

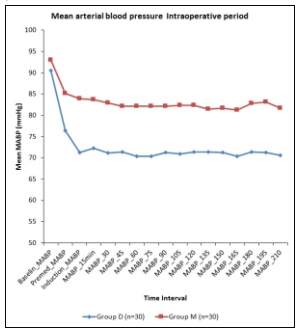

Figure 2: Mean intraoperative arterial blood pressure

Table 3: MAP Intraoperative period

Time interval	Group D (n=30)	Group M (n=30)	t-value	p-value
Baselin_MAP	90.48±7.642	93.00±10.024	1.082	0.284
Premed_MAP	76.43±9.591	85.10±10.384	3.358	**0.001***
Induction_MAP	71.27±6.438	83.97±7.559	7.006	**<0.001***
MAP_15min	72.30±7.130	83.67±7.068	6.201	**<0.001***
MAP_30	71.20±6.895	82.87±7.300	6.364	**<0.001***
MAP_45	71.37±6.985	82.07±7.896	5.559	**<0.001***
MAP_60	70.33±6.738	82.10±7.739	6.281	**<0.001***
MAP_75	70.37±7.005	82.13±8.788	5.735	**<0.001***
MAP_90	71.30±6.188	82.10±7.549	6.060	**<0.001***
MAP_105	70.90±5.944	82.40±7.262	6.712	**<0.001***
MAP_120	71.33±7.150	82.33±6.676	6.159	**<0.001***
MAP_135	71.33±6.488	81.47±6.543	6.024	**<0.001***
MAP_150	71.24±6.384	81.73±6.843	6.085	**<0.001***
MAP_165	70.34±6.212	81.23±7.454	6.084	**<0.001***
MAP_180	71.46±6.653	82.85±7.226	6.027	**<0.001***
MAP_195	71.25±6.395	83.11±7.760	5.494	**<0.001***
MAP_210	70.56±6.913	81.71±9.285	3.901	**<0.001***

[*p <0.05]

BIS values after premedication decreased significantly in group D (mean 76.23±7.157) when compared to group M (mean 93.47±5.309). (Table 4)

Table 4: BIS Intraoperative period

Time interval	Group D (n=30)	Group M (n=30)	t-value	p-value
Baseline_BIS	98.030.85	97.700.83	1.531	0.131
PremedBIS	76.23±7.157	93.47±5.309	10.592	<0.001*
InductionBIS	53.57±1.431	52.90±2.426	1.296	0.200
BIS_15	53.07±1.760	52.83±0.950	0.639	0.525
BIS_30	50.70±3.164	52.30±3.164	1.959	0.055
BIS_45	49.77±3.510	50.20±3.585	0.473	0.638
BIS_60	50.37±3.449	49.27±4.034	1.135	0.261
BIS_75	50.97±2.859	49.60±3.201	1.744	0.086
BIS_90	82.63±127.367	50.13±2.825	1.397	0.168
BIS_105	49.47±3.277	50.90±2.881	1.799	0.077
BIS_120	49.93±2.924	50.77±3.256	1.043	0.301
BIS_135	50.57±3.245	51.07±3.463	0.577	0.566
BIS_150	49.97±2.958	49.40±2.298	0.822	0.415
BIS_165	50.24±2.459	49.77±2.909	0.676	0.502
BIS_180	49.57±2.924	49.42±2.369	0.204	0.839
BIS_195	49.08±2.466	49.84±3.371	0.853	0.399
BIS_210	49.78±2.533	50.62±2.473	2.146	0.199

[*p <0.05]

MAP and HR in the postoperative period were significantly lower in the group D than those in group M (p<0.001). (Table 5, 6)

Table 5: Postoperative Mean Arterial Blood Pressure (MABP)

Time interval	Group D (n=30)	Group M (n=30)	p-value
Postop_MABP	80.43±7.964	90.33±6.440	<0.001*
Postop_30min_MABP	80.10±9.411	90.23±6.474	<0.001*
Postop_60min_MABP	80.67±9.845	89.70±7.498	<0.001*
Postop_90min_MABP	80.53±9.677	89.83±6.864	<0.001*
Postop_120min_MABP	80.07±10.038	91.03±7.531	<0.001*
Postop_150min_MABP	79.97±9.866	89.97±6.631	<0.001*

[*p <0.05]

Table 6: Post operative HR

Time interval	Group D (n=30)	Group M (n=30)	p-value
Postop_HR	69.97±10.387	82.27±8.586	<0.001*
Postop_30min_HR	69.60±9.658	81.97±6.672	<0.001*
Postop_60min_HR	69.20±9.575	83.43±8.076	<0.001*
Postop_90min_HR	69.93±9.752	83.67±6.860	<0.001*
Postop_120min_HR	70.33±10.223	82.80±7.208	<0.001*
Postop_150min_HR	70.77±9.598	82.00±6.427	<0.001*

[*p <0.05]

There was no episode of hypotension or bradycardia in the postoperative period in either group. The mean time of first analgesic requirement in group D was 4.965±1.714 hours and in group M was 1.666±0.479 (p<0.001). (Table 7, Figure 3)

Table 7: Postoperative_analgesia after extubation.

Group	Postop_analg_needed after extubation (h)	t-value	p-value
Group D (n=30)	4.965±1.714	10.139	**<0.001***
Group M (n=30)	1.666±0.479		

[*p <0.05]

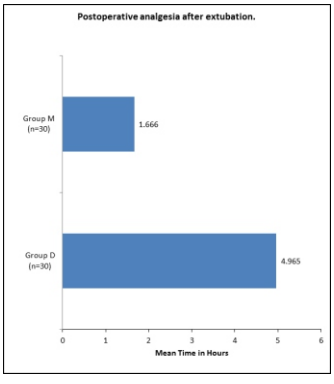

Figure 3: Duration of postoperative analgesia

In group D, 12% patients had sedation score of 0 and 88% had score of 1. In group M, 92.9% had sedation score of 0 and 7.1% had score of 1 (p<0.001). None of the patients experienced PONV or shivering.

Discussion

Perioperative hypertension in neurosurgical patients is associated with intracranial hemorrhage and prolonged hospital stay.[3] Hemodynamic instability may often be challenging, especially in hypertensive patients. An anesthetic technique that improves perioperative hemodynamics without increasing the incidence of undesirable events (such as increased intracranial pressure, prolonged recovery, etc.) is desirable.

Midazolam acts synergistically with general anaesthetics. Studies have shown a synergistic interaction of midazolam with propofol to loss of response to verbal commands as the clinical end point.[4,5] However, it has been reported that administration of midazolam 5 minutes before induction of GA produced a statistically significant fall in HR and MABP when propofol was used as an inducing agent.[6]
Dexmedetomidine, an α_2 agonist with sedative, sympatholytic, and analgesic properties, could be a potentially useful anesthetic adjuvant for neurosurgical cases.[7] Some investigations have examined its use in patients undergoing intracranial surgery[8]. These studies indicate that the addition of dexmedetomidine improves perioperative hemodynamic control. Dexmedetomidine augments anesthesia produced by most other anaesthetic drugs and may reduce blood pressure by stimulating central $\alpha_2$and imidazoline receptors.[8,9]

The final common pathway leading to perioperative hypertension appears to be activation of the sympathetic nervous system, as evidenced by increased plasma catecholamine concentrations in patients after craniotomy.[10] Dexmedetomidine has been shown to decrease plasma epinephrine and norepinephrine level perioperatively.[11] It is reasonable to assume that dexmedetomidine would attenuate hypertensive responses associated with surgical stimulation. In our study, the comparison of the effects IV dexmedetomidine and IV midazolam premedication in two groups indicated that dexmedetomidine stabilizes BP and HR at low levels.

Dexmedetomidine produces major hemodynamic effects, such as hypertension, hypotension, and bradycardia. Patients undergoing supratentorial craniotomy sedated with dexmedetomidine and maitntained with volatile anaesthetics have shown that none of the patient required administration vasodilator or vasopressor.[12] In our study significant reduction in heart rate was seen in Group D patients similar to other studies. Relative hypotension observed in the dexmedetomidine group could be due to the greater depth of anesthesia either because the doses of the drugs chosen were not precisely equipotent, or because they differ in their degree of potentiation of propofol.

BIS values were significantly lower in dexmedetomidine group after premedication and just before induction. BIS values were comparable among both groups at all study points intra operatively. BIS is now considered to have a reliable predictive power of adequate anaesthetic depth, thus could guard against the occurrence of major haemodynamic events during the induction period.[13] There is wide consensus among anesthesiologists that BIS values between 40 and 60 are indicative of adequate depth of general anesthesia for surgery and help improve recovery.[14] In the current study, BIS readings of adequate anaesthetic depth were achieved among both groups at all time points of data collection with the readings between 40 and 60. Propofol infusion and administration of the test drugs (dexmedetomidinein group D and midazolam in group M) were standardized among both groups and the target BIS value was solely achieved by manipulations of propofol infusion rates. Thus the adjuvant anaesthetic effect of dexmedetomidine can be considered superior to that of midazolam, as BIS values achieved with dexmedetomidine were comparable to those of midazolam but at lower propofol infusion rates. The BIS scores may decrease by 31% after a 60-min dexmedetomidine infusion at 0.2mg/kg/hr in healthy volunteers.[15] We observed a significant decrease in BIS values after premedication with dexmedetomidine when compared with midazolam (Table 4).

Clinical investigations have reported that midazolam in a dose of (0.13 mg/kg) reduced the propofol dose required to prevent movement in response to a tetanic stimulus.[16] However, the large doses of midazolam used in this study were inconsistent with those used in routine clinical practice. Other clinical studies have failed to demonstrate that midazolam, administered before the induction of anesthesia, reduced the doses of propofol required to maintain anesthesia.[17] Dexmedetomidine premedication has been reported to reduce the sevoflurane requirement in supratentorial tumor surgery.[18,19] It has been reported that dexmedetomidine has sedative, anesthetic and analgesic effects at an IV dose of 0.5-2µg/ kg.[20]

Our study showed that when dexmedetomidine was used perioperatively maintaining BIS value in a range of 40-60, the doses of propofol for induction and maintenance were significantly reduced (Table 1). This finding is supported by other reports in which the use of dexmedetomidine has been shown to decrease isoflurane requirements to maintain haemodynamic parameters within predetermined limits.[20] Seagel et al. have found that it reduces halothane requirements by up to 90% in rats .[21] The adjuvant anaesthetic effect of dexmedetomidine is well appreciated, and had been investigated in diversity of patient populations and most studies rendered consistent results that dexmedetomidine decreased the anaesthetic dose requirements.[22]

Various anaesthetic agents have been used in neuroanaesthetic clinical practice.[23] High concentrations of volatile anaesthetics can blunt the carbon dioxide response and render CBF pressure passively.[24] In this respect the simultaneous use of dexmedetomidine appears to be

advantageous as it reduces the overall dose of the inhalational anaesthetic used for maintenance of anaesthesia.

In our study there was no significant difference in mean extubation time among two groups. (Table 1) Single-dose dexmedetomidine(0.5g/kg body weight) just before the end of surgery has been associated with attenuation of hypertensive response during extubation as well as decreased agitation and cough scores.[25,26] Talke and colleagues continuously used dexmedetomidine infusion from the preinduction to the postoperative period, and showed a decrease in HR and noradrenaline level during the emergence in their study populations.[27] Dexmedetomidine produces conscious sedation with minimal respiratory depression.[12] In a study on dexmedetomidineuse in ICU, it has been shown that the mean time required from cessation of dexmedetomidine infusion to extubation was 28 min (range 20–50 min).[14]

The studies using dexmedetomidine have commonly reported side effects of sinus pause or bradycardia and recommended glycopyrrolate or atropine for the treatment.[28] Peden *et al*. have suggested anticholinergic prophylaxis before dexmedetomidine administration in the patients less than 40 years of age.[29] In our study, though the heart rate was relatively lower in dexmedetomidine group, none of them required therapeutic anticholinergic drug.

Some studies comparing dexmedetomidine with placebo have reported shorter recovery time.[30] In our study, postoperative sedation levels of both groups evaluated through RSS were similar and also the post operative recovery parameters were similar.

Shivering is one of the common side effects of anaesthesia during the recovery period; it has been reported to be as high as 70% depending upon the anesthetic or analgesic agents used.[31] In our study, none of the patients in either group showed post operative shivering. Use of propofol as an agent for the maintenance of anaesthesia could be one factor responsible for relatively lower incidence of shivering in our study. The effects of benzodiazepines on nociception have been investigated in humans and animals. These studies have shown contradictory results.[32] Some investigators reported that benzodiazepines cause spinally mediated analgesia and enhance opioid-induced antinociception.[33] However, other studies in humans indicate that benzodiazepines do not augment the analgesic effects of morphine.[34] Moreover, in another study, it was reported that incidence of patients requiring analgesics in the PACU was greater in the group that received midazolam in comparison with placebo.[35]

One of the advantages of dexmedetomidine used as a premedicant is relatively lower amount of analgesic agents requirement.[18] There are very few studies on postoperative analgesic requirement after premedication with dexmedetomidine. In our study it was observed that mean time of first analgesic requirement using VAS scales was significantly longer in dexmedetomidine group. (Table 7) Feld JM et al. studied various alternative methods for analgesia in bariatric surgery.[36] In their study, they reported that dexmedetomidine, when compared to fentanyl, provided both stable perioperative hemodynamics and postoperative analgesia, thereby reducing the use of supplementary morphine. Similarly, Tanskenen PE et al. reported that dexmedetomidine provided good perioperative hemodynamic stability compared to fentanyl in patients undergoing brain tumor surgery and that it also reduced intraoperative opioid requirements.[37] Hence dexmedetomidine could be conveniently used as an adjuvant anesthetic in neurosurgical anesthesia.

Conclusions

Our study indicates that dexmedetomidine stabilizes BP and HR at lower levels, and reduces the overall propofol dose requirements. There is stastically significant lowering heart rate, BP and lesser analgesic requirement in dexmedetomidine treated patients postoperatively. No significant difference exists in mean extubation time, incidence of post-operative nausea and vomiting and postoperative shivering among the two groups.

Thus, to conclude, dexmedetomidine and midazolam are useful adjuncts to anaesthesia for patients undergoing cranial neurosurgical procedures. The main drawback of midazolam is intraoperative transient hemodynamic instability and probable intracranial haemodynamic alterations. Dexmedetomidine provides sustained hemodynamic stability and reduces the anaesthetic requirement.

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