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MIDAZOLAM AND PROPOFOL FOR BIS-GUIDED SEDATION DURING REGIONAL ANAESTHESIA, A RANDOMIZED CONTROL STUDY

Anesthesiology

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ABSTRACT

Introduction: Regional anaesthesia has become an important anaesthetic technique. Effective sedation is an essential for regional techniques too.
Methodology: This study compares midazolam and propofol in terms of onset & recovery from sedation, dosage and side effects of both the drugs using Bispectral Index monitoring. 100 patients were randomly divided into two groups, one group received midazolam infusion while the other received propofol infusion until BIS reached 75. We observed Time to reach desired sedation, HR, MABP, time for recovery, dose to reach sedation and for maintenance of sedation and side effects if any.
Results: The time to reach required sedation was 11 min in Midazolam group(Group I) while it was 6 min in Propofol group(Group II) (p=0.0). Fall in MABP was greater with propofol. Recovery in with midazolam was slower than with propofol (18.6 vs 10.10min) (p=0.00).
Conclusion: We concluded that both midazolam and propofol are effective sedatives, but onset and offset was quicker with propofol, while midazolam was more cardio stable.

KEYWORDS

Midazolam, Propofol, Sedation, BIS

INTRODUCTION:

Supplementation of spinal anaesthesia with sedatives or anxiolytic has emerged as a standard protocol to alleviate the patients anxiety and to produce amnesia of the surgical procedure.[1] Common methods of monitoring the depth of sedation are patient based (e.g., visual analogue scale), observer based (e.g., observer's assessment of awareness/sedation {OAA/S} score and machine based (e.g., Bispectral index score {BIS}).[2-4] The OAA/S score has the disadvantage of frequent patient stimulation, which may alter the actual level of sedation. However, the BIS score gives a continuous objective assessment with minimal stimulation to patient. BIS monitor produces a single number to indicate the level of sedation. Midazolam, a benzodiazepine, has a property of rapid onset of action after intravenous (i.v.) injection. Propofol, a non-barbiturate anaesthetic agent, can produce rapid onset of sedation after i.v. administration in proper sub-hypnotic dose. There are studies comparing sedation with propofol and midazolam during regional anaesthesia.[5-8]

We performed a study comparing sedative effects of propofol and midazolam using BIS in regional anaesthesia. The aim of our study was to find out the time for onset and recovery from sedation with both drugs, using BIS as a standard measure of depth of sedation and to evaluate and compare the properties of propofol and midazolam in terms of haemodynamics, side effects and dosage requirement as adjuncts to spinal anaesthesia.

METHODS:

This study was conducted in Department of Anaesthesiology in KIMS Karad after taking approval of the ethical committee and duly signed informed consent. Patients of either sex (age 18-60 years, complying to ASA I/ASA II criteria) posted for elective infraumbilical operations (surgical, gynaecological, or orthopaedic) of approximate 90 min duration were included in this single blinded study. Patients refusing to participate in the study, accept spinal anaesthesia or receive sedation during the surgery were excluded. Other exclusion criteria included patients with contraindications for spinal anaesthesia, pregnant patients, and those with cardiorespiratory diseases, psychiatric illnesses or history of allergy to study drugs.
Patients were randomly allocated to one of the following two groups:

Group I- (n=50) Midazolam 0.1% infusion starting with 0.5 mg/kg/h[9] till BIS level reached 75 and then dose reduced and titrated to maintain a BIS of 65-85.

Group II- (n=50) Propofol 1% infusion starting with 6mg/kg/h[9] till BIS level reached 75 and then dose was reduced and titrated to maintain a BIS of 65-85.

A written informed consent was taken from all patients. They were fasted for a minimum of 6 hours before surgery. No preoperative opioids or prophylactic antiemetics were given. No other preoperative medication was allowed. Patients suffering from heart disease, hypertension, diabetes, spinal deformity, neurological problem or any bleeding disorder were excluded from the study. All patients were monitored with an electrocardiograph, noninvasive blood pressure,

pulse oximeter and BIS monitor. Baseline readings were recorded. Preloading was done with 15ml/kg of Ringer lactate prior to block. Combined spinal and epidural block was given. 1 % propofol or 0.1% midazolam infusion was started with the help of a manually controlled variable rate infusion pump. Propofol infusion was given at a rate of 6mg/kg/hr[9] and midazolam at 0.5 mg/kg/hr[9] and after reaching a BIS value of 75, the rate of infusion was reduced to half and then with subsequent observations, the anaesthetics were titrated to keep a BIS level between 65 and 85.

Blood pressure, heart rate, oxygen saturation, and BIS level were assessed every 2 min till maintenance dose was reached ie a BIS level of 65-85 and then every 10 min till 105 min or till the end of surgery whichever was earlier and every 15 min (if duration of surgery extended beyond that).

O2 inhalation by ventimask was given when SpO2 came down below 90% and vasopressor was given if MAP decreased beyond 20% of baseline.

Following observations were made:

1. Time to reach required level of sedation.
2. Duration of surgery
3. Duration of infusion
4. HR, Mean Arterial pressure, arterial saturation of oxygen were recorded every 2 minutes till required sedation level was reached and then every 10 min till 90 min or end of the surgery whichever was earlier and then every 15 minutes.
5. Time taken for recovery (for comparison, BIS>90 was taken as a recovery parameter)
6. Side effects
   a. Awareness

b. Nausea & Vomiting
c. Pain in arm
7. Dose to reach required level of sedation.
8. Dose to maintain required level of sedation

Statistical analysis was done with independent t test for age, weight, duration of surgery and end infusion, time for recovery, heart rate, mean arterial pressure, and SpO2 at various intervals. Chi square test was applied for sex distribution and for adverse effects as respiratory obstruction, apnea, laryngospasm, nausea & vomiting, awareness, hypotension, and oxygen supplementation. Paired t test was applied for intragroup variation in heart rate and mean arterial pressure. Fischer's exact test was used for incidence of complications.

RESULTS:

The mean age, sex and body weight in the two groups were statistically similar. The mean of various time intervals in the two groups is as shown in Table 1.

Table-1 Demography of the patients

	Group-I (n=50)	Group-II (n=50)	P value
Age in years	42.6	39.5	0.34
Sex (M/F)	16/34	18/32	0.54
Duration of surgery (min)	66.9	64.9	0.633
Initial dose of drug to reach target BIS (mg/kg/h)	0.5	6.0	-
Mean rate of infusion during maintenance	0.1	2.2	-
Time to reach required level sedation (min)	11.0	6.2	0.00
Time taken for recovery	18.6	10.1	0.00

The mean time to reach the required level of sedation in group I was (11.0) minutes which was about 5 minutes later than in group II (6.2 mins) (p=0.00), thus the difference in mean time to reach required sedation level was statistically highly significant. The difference in mean duration of infusion in the two groups was statistically insignificant (73.2 vs 71.1) (p=0.50). The time for recovery in group I (midazolam group) was more than in group II (propofol group) (18. vs 10.10) (p=0.00) and it was highly significant.

The mean ± SD of heart rates at various time intervals is shown in Table 2.

Table -2 Comparison of heart rate (bpm) in both groups at various time intervals

Time interval (min)	Group-I	Group-II	P value
0	86.8	85.3	0.557
4	84.7	79.0	0.051
8	79.9	77.4	0.404
12	77.8	77.9	0.945
16	78.8	80.9	0.482
25	78.6	75.6	0.199
45	79.4	77.0	0.362
65	85.4	80.2	0.085
85	86.3	85.5	0.880
90	88.0	101.5	0.014

In Group I, the initial mean heart rate was 86.0 per min which gradually decreased to 78.0 per min at 25 min while in Group II initial mean heart rate of 85.37 per min which gradually decreased to 75.6 per min at 25 min. In between group comparison of mean heart rate at various time intervals using independent t test in the two groups revealed the difference was not significant at almost all time intervals. However, the comparison of heart rate at various time interval with the baseline within the same group using t test showed significant difference at various time
Intervals

Mean arterial pressures: The mean ± SD of MAP values are shown in Table 3.

Table -3 Comparison of MABP(mmHg) in both groups at various time intervals

Time Interval	Group I	Group II	P value
0	81.7	83.1	0.363
4	77.6	77.4	0.848
8	76.8	75.7	0.443
12	76.7	74.8	0.214
16	75.9	74.4	0.314
25	76.0	73.7	0.183
45	78.7	71.3	0.000
65	75.3	68.9	0.084
85	84.6	68.3	0.000
90	82.1	68.2	0.032

The mean arterial pressure in Group I initially was 81.7 mmHg which gradually decreased to 76.8 mm Hg while, in Group II mean MAP at baseline was 83.1 mm Hg which gradually decreased to 68.25 mm Hg. Between-group comparison showed that the difference was not significant up to 25 min, but it become significant at 45,65 ,85 & 90 min.

The incidence of complications is as shown in Table 4.

Table-4 Incidence of complications

	Restlessness	Pain in arm	Nausea & Vomiting	Awareness
Group I (n=50)	4(8%)	0(0%)	8(16%)	10(20%)
Group II (n=50)	7(14%)	3(6%)	4(8%)	8(16%)
P value	0.24	0.11	0.40	0.86

Hypotension defined a decrease of MAP > 20% from baseline was seen in 8 (16%) cases in Group I while in group II, it was seen in 13 cases (26%); the difference was not significant.

To maintain the desired sedation i.e BIS 65-75, maintenance dose of 2.2 ±0.5 mg/kg/h propofol and 0.12±0.38 mg/kg/h for midazolam had to be given in the two groups respectively.

Oxygen supplementation: It was provided when SpO2 level was below 90. The incidence of oxygen supplementation was 14 (28%) in group I as compared to 10 (20%) in group II ($p < 0.05$). Awareness: 10 (20%) patient in Group I and 8 (16%) patient in Group II complained of awareness 2 hrs after surgery. Awareness was defined as recall of intraoperative events. This difference was statistically not significant.
Pain in Arm: Pain in arm due to infusion of sedative agent was found in 3 patients in Group II as against none in Group I. Nausea and vomiting was seen in 8 (16%) patients in Group I and against 4 (8%) patients in Group II which was statistically not significant.

Restlessness was seen in 4 (8%) patients in Group I as compared to 7 (14%) in Group II, which was statistically not significant.

DISCUSSION:

When using sedative medication during regional anaesthetic technique, the anaesthesiologist attempts to titrate the drug to optimize patient comfort while maintaining cardiorespiratory stability and intact protective reflexes. The assessment of depth of sedation has been traditionally performed by observing clinical parameters such as appearance, response to voice, and pain on surgical stimulation. These parameters are qualitative and assessment of response to voice requires patient stimulation, which may itself alter depth of sedation.

BIS has advantage of not requiring patient stimulation and provide a quantitative measure. During recovery the MAP reached almost baseline in midazolam group; in propofol group, MAP remained below baseline, throughout the study period. Similar findings were reported by Hidaka *et al*[10] in a comparison of the effects of propofol and midazolam on the cardiovascular autonomic nervous system during combined spinal epidural anaesthesia.

Arterial oxygen saturation in both the groups decreased significantly after the start of sedation. The number of patients requiring supplemental oxygen was also similar in both the groups. Almost similar results were found in Win's study.[11]

The mean recovery time (as defined by BIS >90) was significantly lower in the propofol group than the midazolam group (10.1±3.6 vs 18.6±6.5 min) (p=0.00). Similarly recovery times were observed by

Wilson *et al*[12] (9.2±1.5 vs 2.1±0.3 min).

As the desired sedation level was reached, the dose of anaesthetic agents was reduced and a maintenance dose of 2.2 ±0.5 mg/kg/h propofol and 0.12±0.38 mg/kg/h for midazolam had to be given. The dose for midazolam was found to be similar to Nishiyama *et al*[13] who found that during combined spinal epidural block, midazolam 0.6 mg/kg/h was given until closing of eyes followed by midazolam 0.15 mg/ kg/h with a Ramsay sedation score of 4 along with stable haemodynamics and respiration. The incidence of side effects related to airway maintenance were similar in both the groups. However, the incidence of restlessness and pain in arm was more in propofol group but the difference was insignificant.

This study showed that though both Midazolam and propofol are effective sedative agents, the time to reach effective sedation was less with propofol than midazolam and similarly the time to recovery time from sedation was lesser with propofol. Though complications were insignificant with both the drugs, propofol caused a greater fall in MABP, thus providing lesser haemodynamic stability than midazolam.

CONCLUSION:

A divergence exists between the time to reach BIS score 70 using midazolam, compared to propofol, during onset of sedation. Monitoring sedation with BIS score demonstrates poor correlation during onset of sedation using midazolam. Better correlation was found while using the propofol. Clinical sedation is our area of interest. Hence, relying solely on an EEG based monitor to attain a number on the screen may not be wise enough as this might end in an inappropriate level of sedation with loss of airway control.

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