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Sedation with 1 mg Intravenous Midazolam in Subarachnoid Block with Bupivacaine and Fentanyl for Lower Limb Surgeries Causes Clinical Sedation without Hemodynamic Compromise: A Randomized Controlled Trial

Ummul Fabeena Mangaladan[1], Jyotsna Punj[2], Ravindra Kumar Pandey[3], Vanlal Darlong[4], Bhavuk Garg[5]

[1,2,3,4,5]Professor, Department of Anesthesiology, Pain Medicine and Critical Care, AIIMS, New Delhi

Abstract

Background: In young healthy males intravenous (IV) sedation in subarachnoid block (SAB) is reported to cause cardiac arrest. Thus frequently IV sedation in SAB is frequently discouraged.

Hypothesis of the present study was that SAB with bupivacaine and fentanyl would correspond to a BIS < 90, level of clinical sedation and IV midazolam 1 mg in such patients may cause hemodynamic compromise.

Primary objective was to compare BIS post SAB with and without IV midazolam. Secondary objective was to compare hemodynamic parameters.

Methods: 60 patients of age 20-60 years, ASA 1 or 2, undergoing lower limb surgeries were given SAB with 0.5% hyperbaric bupivacaine 2 mL (10 mg) and fentanyl 0.5 mL (25mcg). Thereafter Group A (n=30) was given SAB with 1ml IV saline and Group B (n=30) was given SAB with IV 1mg midazolam.

Parameters were recorded at baseline, then every 15 minutes till 90 minutes.

Results: In Group B, BIS < 90 but not < 80 was noted from 30 minutes to at least 90 minutes. In Group A, BIS < 90 was noted from 45 minutes to 60 minutes and was > 90 at all other time frames. Mean BIS was significantly more in Group A compared to Group B (90.41 +/- 4.05 v/s 86.58 +/- 3.50 respectively) (P< 0.001). Hemodynamic parameters of heart rate, non-invasive blood pressure, oxygen saturation and respiratory rate were comparable between both groups (p value >0.05).

Conclusion: SAB does not result in adequate intra operative patient sedation. IV midazolam 1 mg causes BIS <90 from 30 minutes till at least 90 minutes without hemodynamic compromise.

Keywords: *Midazolam, sedation, subarachnoid block, bispectal index, fentanyl.*

Introduction

Patients operated under subarachnoid block (SAB), especially during orthopedic surgeries frequently feel intraoperative restlessness, anxiety and discomfort due to the sound of instruments and stress of surgery[(1)]. For comfort and sedation in these patients, various intravenous (IV) sedative drugs are given. However, Closed claim analysis by Caplan et al reported unanticipated cardiac arrest in healthy young patients under SAB implicating the use of IV sedatives[(2)]. The suggested cause was the hemodynamic compromise due to the additive effects of sedative agents and decreased afferent stimulation of the reticular activating system due to inherent sedative

Corresponding Author:
Dr. Prof Jyotsna Punj
AIIMS, New Delhi, India
e-mail: jyotsna_punj@yahoo.com

effects of SAB. Thus, it was suggested to inject lower or no IV sedative agents in these patients.

Bispectral Index (BIS) provides a numeric measure of the hypnotic effect of anesthetic or sedative drugs on brain activity. A value of 60-90 is the recommended range for sedation for patient comfort during SAB[10]. Previous reports for sedation in SAB with IV midazolam in dose ranging from 0.05mg/kg to 0.5mg/kg caused side effects like respiratory and cardiovascular depression resulting in higher chances of airway instrumentation and hypotension[3,4].

The hypothesis of the present study was that inherent sedation of SAB would correspond to a numerical measure of BIS less than 90 and that IV midazolam 1 mg, a common practice for intraoperative sedation during SAB, would not be essential for sedation in these patients and may also result in hemodynamic compromise.

Primary objective was to compare BIS post SAB with or without IV midazolam. Secondary objective was to determine hemodynamic parameters of heart rate, blood pressure, respiratory rate and oxygen saturation between both groups.

Methods

The prospective, randomized, double-blind study was conducted after obtaining approval by the Institute Ethics Committee (IECPG-496/23.09.2021, RT-19/28.10.2021, OT-13/23.12.2021), CTRI registration (REF/2021/06/044576) and written informed consent from the patient.

60 patients aged 20-60 years of either sex of American Society of Anesthesiologists (ASA) physical status I and II undergoing surgery of less than 2 hours under SAB were enrolled. In the operating room (OR), IV line was inserted, monitors of BIS, pulse rate, non-invasive blood pressure, oxygen saturation was attached according to standard guidelines and preloading with 250 ml of ringer's lactate solution was done. Under all aseptic precautions, patients were given SAB in the sitting position with a 27-gauge spinal needle at L2-L3 space with 0.5% hyperbaric bupivacaine 2 mL (10 mg) and fentanyl 0.5 mL (25mcg). Patients were then positioned supine for 5 min. Oxygen by face mask was given and simultaneously according to group allocation patient was given either IV midazolam 1ml of 1mg or 1 ml saline by an anesthetist blinded to the injectate. Group A (n=30): SAB with 1ml IV saline. Group B (n=30): SAB with IV 1mg midazolam.

To record baseline BIS, patients were placed in a quiet environment and left undisturbed for 5 min. Parameters of BIS, electrocardiography, heart rate, non-invasive automated blood pressure, pulse oximetry and respiratory rate were recorded every 15 min till 90 minutes post SAB during the study by a blinded anesthetist. Arousal of the patient was avoided during study duration.

Statistical analysis

For all statistical tests 'P' value less than 0.05 was taken to indicate a significant difference. For 90% power, 5% level of significance, pooled standard deviation of 12 from other similar studies & minimum clinically significant difference of 10, the minimum number required to conduct this study was 30 in each group. Data were recorded on a predesigned proforma and was managed on an excel spread sheet. IBM SPSS statistical software was used for statistical analysis. All entries were checked for any possible keyboard error. The quantitative variables were presented as mean ± SD. Categorical variables were expressed as frequencies and percentages. Chi-square test was used for categorical data and Students 't' test was used to compare mean of the two groups.

Results

The demographic profile including age, gender, ASA physical status, BMI of patients were comparable in both groups (P > 0.05). (Table 1)

Baseline BIS was comparable between both groups (p value >0.05). BIS decreased significantly in Group B from 30 minutes till at least 90 minutes compared to Group A (p value 0.042,0.001.0.00,0.00,0.009 respectively). From 30 minutes to 90 minutes, minimum BIS in Group B was at 60 minutes (83.33+-4.66) and maximum BIS was at 30 minutes (88.10 +- 4.11). In Group A, minimum BIS recorded was at 45 minutes (88.43±4.97) and maximum BIS at 75 minutes (90.73±5.16) (Table 2; Figure 1).

In Group A, mean BIS less than 90 was noted at 45 and 60 minutes (88.43±4.97, 89.37±6.00 respectively). In Group B, mean BIS was less than 90 at all time frames from 30 minutes to 90 minutes (88.10±4.11, 84.13±4.93, 84.13±4.93, 83.83±4.66, 84.57±4.61, 87.03±5.18 respectively) (Table 2; Figure 1). Mean BIS was significantly lesser in Group B (Mean +/- SD – 90.41 +/- 4.05 v/s 86.58 +/- 3.50 respectively, p < 0.001). (Table 3)

Heart rate was comparable between groups A and B at all time intervals. (Table 4,5) NIBP was comparable between groups A and B at all time intervals. (Table 6,7) SpO2 was comparable between groups A and B at all time intervals. (Table 8) Respiratory rate was comparable between groups A and B at all time intervals. (Table 9,10)

Discussion

The present study determines that SAB (0.5% hyperbaric bupivacaine 10 mg and fentanyl 25 ug in lower limb surgeries) does not produce numeric sedation of BIS less than 90 except from 45 minutes to 60 minutes whereas injection of IV midazolam 1mg results in BIS <90 from 30 minutes to at least 90 minutes. There is no hemodynamic compromise both with and without IV midazolam 1mg in these patients.

BIS gathers processed EEG parameters to provide a numeric measure of the hypnotic effect of anesthetic or sedative drugs on brain activity. It is derived from the EEG by a computer algorithm that produces a single numeric value, scaled from 0 to 100. According to the manufacturer, BIS more than 90 indicates an awake patient; values of 71–90 indicate mild to moderate sedation; values of 61–70 indicate deep sedation and values of 40–60 are recommended during general anesthesia[5]. BIS of 60-90 is the recommended range for sedation for patient comfort during SAB[10].

SAB is a neuraxial anesthesia technique in which local anesthetic is placed directly in the intrathecal space (subarachnoid space) to produce motor, sensory and sympathetic blockade. The pharmacodynamics of spinal injection of local anesthesia are wide ranging[6,7]. It is well recognized that SAB results in hypotension, however it is documented to also cause sedative effect[8]. There are several theories regarding this. Decreased stimulation of the reticular activating system due to blockade of afferent somatosensory pathway, reduced muscle spindle afferent impulse, blockade of ascending somatosensory drive onto reticulo-thalamocortical projection pathways, reducing their excitability and decreasing the arousal level of brain which lowers the level of consciousness and awakening and rostral spread of the local anesthetic with a direct action on the brain could cause innate sedation of SAB[8-10].

Innate sedation of SAB was explored by few authors. The onset time of sedation due to SAB was assessed by Guerrero et al using BIS and the entropy monitor during spinal anesthesia[11]. Their study population was patients aged above 60 years and the intrathecal drug used was heavy bupivacaine 0.5% -12mg to achieve a block height of T8+/- 2. They observed that neuraxial blockade decreased the cortical activity after 30 min, as measured by OAA/S (Observer's Assessment of Alertness and Sedation Score) and depth anesthetics monitors. However, the present study did not show a significant decrease in BIS score post neuraxial anaesthesia. The difference in results among both the studies could be because of the study population which was patients aged above 60years in Guerro's study and 20-60years in the present study. Also, the dose of the intrathecal drug was different between the studies (12mg in Guerro's study and 10mg in the present study). H I Toprak et al in their study found that spinal anaesthesia with hyperbaric bupivacaine with a maximum spread in the middle thoracic dermatomes may be associated with sedative effects and thus a reduced need for further sedation with midazolam[4]. Sixty unpremedicated patients were allocated to three equal groups. Patients in Groups I and II received hyperbaric bupivacaine 0.5% 10 and 17.5 mg respectively for spinal anaesthesia and Group III was a control group without spinal anaesthesia. In Groups I and II, after the evaluation of sensory block, patients received intravenous midazolam 1 mg per 30 s until the Ramsay sedation score reached 3 (drowsy but responsive to command). In Group III, general anaesthesia was induced after sedation score had reached 3 using midazolam. The total dose of midazolam (mg kg(- 1)) given to each patient, the level of sensory block and complications were recorded. The doses of midazolam were comparable in groups 1 and 2 and were significantly different from that of group 3. The results also showed that different doses of hyperbaric bupivacaine for spinal anaesthesia do not affect the midazolam requirements for sedation. However, the present study did not correlate with their finding as there was no significant sedation with spinal anaesthesia alone. The difference could be because of the different tools used to assess the level of sedation (Ramsay Sedation Score in Toprak's study and BIS in the present study). J E Pollock et al in a study where twelve volunteers underwent BIS monitoring and observer sedation scoring (Observer's Assessment of Alertness/Sedation Scale [OAA/S]) before and after spinal anesthesia with 50 mg hyperbaric lidocaine, 5% found that spinal anesthesia was accompanied by significant sedation progressively when compared with controls as measured by OAA/S and self-sedation scores[12]. There was a statistically significant change from baseline in the BIS score over time (P = 0.003). The largest deviations in BIS from baseline occurred at 30 and 70 min after the initiation of spinal anesthesia. This effect was not related to block height. He also found that BIS was not a sensitive measure of the sedation associated with spinal anesthesia in the randomized, blinded portion of this study. However, in the present study BIS monitor alone was used to assess the sedation following spinal anesthesia and could be one of the reasons for the difference in conclusion between Pollock's study and the present study. Also the drug

given for subarachnoid block was different in both the studies (heavy lignocaine 5% in Pollock's study and heavy bupivacaine 0.5%in the present study).

Few studies have concluded that a decrease in the dose of IV hypnotic agents like midazolam, thiopental and propofol agents should be made in SAB especially in high SAB[13-16]. A study concluded that SAB causes sedation per se, but the level of sedation is not clinically significant, and is not enough to avoid sedative agents for allaying anxiety in patients intraoperatively[17] Varma et al compared the effect of subarachnoid block with bupivacaine and bupivacaine with fentanyl on entropy and sedation. Patients were randomly allocated into two groups: Group C: SAB was administered with 2.5 mL (12.5 mg) of 0.5% hyperbaric bupivacaine; Group D: SAB was administered with 2.5 mL of 2 mL (10 mg) of 0.5% hyperbaric bupivacaine and 0.5 mL (25 µg) fentanyl. Propofol infusion was started if the state entropy (SE) value was ≥75, at the rate of 100 µg/kg/min till the SE value reaches in the range of 60-75 (recorded as onset time). Thereafter the infusion rate was titrated to maintain SE value between 60 and 75. The level of sedation was measured with SE and Ramsay sedation (RS) scale. After placement of SAB, decrease in SE and RE was noted in both the groups. The mean fall in SE value from a baseline of 88.7 ± 1.6-87.9 ± 3.1 in Group C (P = 0.103) whereas 88.4 ± 3.7-85.8 ± 6.2 (P = 0.007) in Group D within 20 min of SAB when the block height was fixed. The fall of RE values in Group C was from a mean value of 97.7 ± 1.21- 95.43 ± 5.77 (P < 0.0001) and that in Group D was from a mean value of 97.43 ± 2.69-94.83 ± 5.81 (P < 0.0001) within 20 min of SAB. The fall in RE was statistically significant in both groups but the fall did not reach clinically significant levels. It was concluded that subarachnoid block causes sedation per se, but the level of sedation is not clinically significant and the sedation caused is not enough to avoid sedative agents for allaying anxiety in patients intraoperatively. This statement is supported by the present study as the distribution of mean BIS Score was significantly different in groups A (spinal bupivacaine 10mg and fentanyl 25mcg) and B (spinal bupivacaine 10mg and fentanyl 25mcg with intravenous midazolam 1mg) with group B showing a lesser BIS value (Mean +/- SD – 90.41 +/- 4.05 v/s 36 86.58 +/- 3.50 respectively) with p value less than 0.001.

In the present study, it was hypothesized that innate sedation of SAB would result in BIS < 90 and thus IV midazolam 1 mg would not be required for patient comfort during surgery. However, the study results were contradictory. It was revealed that BIS<90 was not achieved without IV midazolam 1mg for majority of the study period. On the other hand, IV midazolam resulted in favorable BIS < 90 from 30 minutes to at least 90 minutes, the end point of study, without hemodynamic compromise. Further studies to explore the effect of IV midazolam 1 mg beyond 90 minutes should be sought. The effect of IV midazolam 1 mg causing BIS < 90 started from 30 minutes, which probably corresponds to peak effect of 0.5% bupivacaine. For patient comfort till 30 minutes when BIS < 90 is reached, additional sedation maybe given though this remains to be explored in future studies. In the present study, BIS < 90 in the study period was not correlated to sedation scores, which remains a limitation.

Midazolam is seen to cause transient baroreflex depression and a sustained decrease of sympathetic tone in humans[1]. BIS was compared using IV midazolam or dexmedetomidine on hemodynamics and recovery profiles in patients who underwent SAB with 0.5% hyperbaric bupivacaine. Hypotension occurred more frequently in the midazolam group and bradycardia occurred more frequently in the dexmedetomidine group. The dose of IV midazolam in this study was higher than the present study (approximately 3mg for a 50 kg patient) and thus above side effects were not seen in the present study. Studies have concluded that IV midazolam depresses resting ventilation however, the present study does not show any respiratory depression. This could be because of use of much lower dose of IV midazolam in the present study[3].

The closed claim analysis done by Caplan et al implicated the use of IV sedatives as one of the patterns which led to unanticipated cardiac arrest in healthy patients (ASA 1 and 2 with age group 36+/-15) under SAB (2). The most common local anaesthetic used for SAB was tetracaine (6-14mg). Others were lignocaine, procaine and mepivacaine. Highest level of block documented before cardiac arrest averaged T4+/-1. The authors suggested the possible importance of respiratory changes produced by sedation in combination with the physiologic changes of spinal anesthesia. The sedatives used in the above analysis were fentanyl (25-200mcg), diazepam (2-10mg), droperidol (1.25-7.5mg) and thiopentone (50-200mg). In the present study, IV midazolam 1mg was used with SAB (0.5% bupivacaine and fentanyl 25 mcg) in adult ASA 1 and 2 patients with no compromise of hemodynamic parameters with numeric BIS < 90 and thus appears to be safe for sedation and patient comfort. In the present study, decreased reticular activating system activity after subarachnoid block did not produce numerical sedation of Bispectral index < 90 during surgery whereas intravenous

1 mg midazolam resulted in above without hemodynamic compromise.

Limitations of the present study are that intraoperative anxiety scores were not compared in both groups. Sedation with IV 1 mg midazolam with SAB was not studied beyond 90 minutes and the relation between level of spinal block with sedation was not studied. This was a single centre study with a small sample size including only ASA1 and 2 patients thus not allowing us to generalize the study results to general population. Future studies targeting BIS less than 90 from execution of SAB till 30 minutes post SAB with higher doses of IV midazolam is to be explored. Patient comfort and sedation was not formally studied corresponding to BIS levels.

To conclude, inherent sedation of SAB (0.5% bupivacaine 10 mg and 25 ug fentanyl in lower limb surgeries) does not produce numeric BIS <90 and thus may not result in patient sedation and comfort and thus IV midazolam 1 mg should be injected which produces numeric BIS < 90 from 30 minutes to at least 90 minutes without any hemodynamic compromise. Duration of effect of sedation of IV midazolam 1 mg beyond 90 minutes should be studied.

Table 1: Demographic data of two groups

Demographic Variable	Group A	Group B	P-value
Age (in years)	35.10 ±13.26	38.43± 12.96	0.329
ASA I()	26(87)	28(93)	0.389
ASA II()	4(13)	2(07)	
Gender (male & female)()	Male:23(77) Female:07(23)	Male:20(67) Female:10(33)	0.390
BMI	23.18 ± 2.12	23.98 ± 2.27	0.163

Table 2: Comparison of BIS between Groups

Group Time Interval	Group A (n=30)	Group B (n=30)	P-value
0 Min	95.87±0.68	96.10±0.66	0.184
15 Min	93.57±2.01	92.37±2.82	0.063
30Min	90.27±3.96	88.10±4.11	0.042**
45 Min	88.43±4.97	84.13±4.93	0.001**
60 Min	89.37±6.00	83.83±4.66	0.000**
75 Min	90.73±5.16	84.57±4.61	0.000**
90 Min	90.63±5.06	87.03±5.18	0.009**

*Significant at 5% level, ** Significant at 1% level

Table 3: Comparison of Mean BIS between Groups

Group	Mean ± SD	't' Statistics	P-value
Group A	90.41± 4.05	3.915	<0.001**
Group B	86.58± 3.50		

**Significant at 1% level of significance. (highly Significant)

Table 4: Comparison of HR between Groups

Group Time Interval	Group A	Group B	P-value
0 Min	82.90±9.18	84.40±11.16	0.298
15 Min	76.73±10.37	82.10±12.98	0.232
30Min	75.13±9.25	78.70±11.95	0.174

Group Time Interval	Group A	Group B	P-value
45 Min	76.23±9.62	78.13±11.39	0.367
60 Min	77.57±8.85	79.23±10.30	0.416
75 Min	78.33±9.70	81.27±11.38	0.397
90 Min	81.37±9.79	83.63±11.39	0.421

Table 5: Comparison of Mean Heart Rate between Groups

Group	Mean ± SD	't' Statistics	P-value
Group A	77.69 ± 9.09	-1.104	0.274
Group B	80.58 ± 11.13		

Table 6: Comparison of MAP between groups

Group Time Interval	Group A	Group B	P-value
0 Min	87.23±6.26	85.93±6.05	0.858
15 Min	82.73±6.80	80.93±6.30	0.687
30Min	79.70±6.65	78.20±6.86	0.874
45 Min	79.00±5.88	79.67±6.87	0.406
60 Min	79.20±6.90	80.40±8.08	0.397
75 Min	80.40±7.06	80.83±7.31	0.854
90 Min	82.97±5.65	83.03±7.67	0.105

Table 7: Comparison of NIBP between groups

Group	Mean ±SD	't' Statistics	P-value
Group A	80.72 ± 5.56	0.124	0.902
Group B	80.53 ± 6.26		

Table 8: Comparison of SPO2 between Groups

Group Time Interval	Group A	Group B	P-value
0 Min	99.83±0.65	99.73±0.87	0.620
15 Min	100±0.00	100±0.00	
30Min	100±0.00	100±0.00	
45 Min	100±0.00	100±0.00	
60 Min	100±0.00	100±0.00	
75 Min	100±0.00	100±0.00	
90 Min	100±0.00	100±0.00	

Table 9: Comparison of RR between both groups

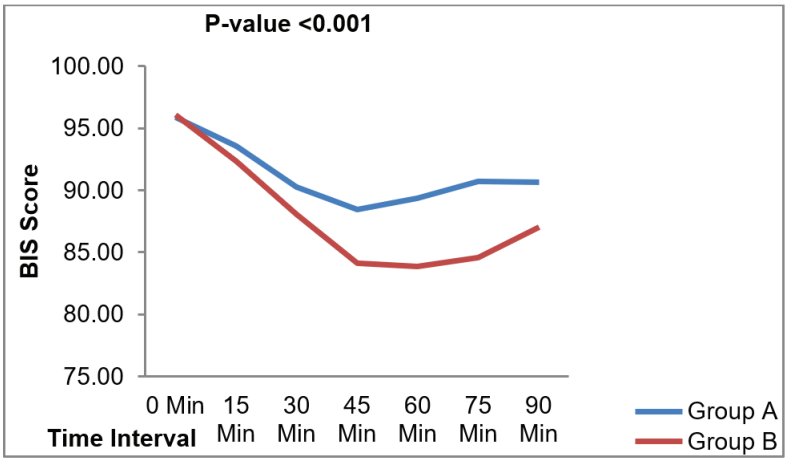
Group Time Interval	Group A	Group B	P-value
0 Min	12.10±0.40	12.20±0.61	0.457
15 Min	12.10±0.40	12.20±0.61	0.457
30Min	12.10±0.40	12.20±0.61	0.457

Group Time Interval	Group A	Group B	P-value
45 Min	12.10±0.40	12.20±0.61	0.457
60 Min	12.10±0.40	12.20±0.61	0.457
75 Min	12.10±0.40	12.20±0.61	0.457
90 Min	12.10±0.40	12.20±0.61	0.457

Table 10: Comparison of Mean Respiratory Rate between both groups

Group	Mean ±SD	't' Statistics	P-value
Group A	12.10 ± 0.40	-0.749	0.457
Group B	12.20 ± 0.61		

Figure 1: BIS at different time intervals



References

1. Jo YY, Lee D, Jung WS, Cho NR, Kwak HJ. Comparison of IV Dexmedetomidine and Midazolam for Bispectral Index-Guided Sedation During Spinal Anesthesia. Med Sci Monit Int Med J Exp Clin Res. 2016; 22:3544–51.
2. Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. Anesthesiology. 1988;68(1):5–11
3. Gauthier RA, Dyck B, Chung F, Romanelli J, Chapman KR. Respiratory interaction after spinal anesthesia and sedation with midazolam. Anesthesiology. 1992;77(5):909–14
4. Toprak HI, Ozpolat Z, Ozturk E, Ulger MH, Sagir O, Ersoy MO. Hyperbaric bupivacaine affects the doses of midazolam required for sedation after spinal anaesthesia. Eur J Anaesthesiol. 2005 ;22(12):904–6
5. Bispectral Index Monitoring of Sedation Depth in Pediatric Dental Patients - PMC [Internet]. [cited 2023 Apr 27]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3198129/
6. Olawin AM, M Das J. Spinal Anesthesia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Apr 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK537299/
7. Spinal Anesthesia - NYSORA | NYSORA [Internet]. [cited 2023 Apr 28]. Available from: https://www.nysora.com/techniques/neuraxial-and-perineuraxial-techniques/spinal-anesthesia/#toc_PHARMACODYNAMICS-OF-SPINAL-ANESTHESIA
8. Iida R, Iwasaki K, Kato J, Ogawa S. Bispectral index is related to the spread of spinal sensory block in patients with combined spinal and general anaesthesia. Br J Anaesth. 2011 ;106(2):202–7
9. Tverskoy M, Fleyshman G, Bachrak L, Ben-Shlomo I. Effect of bupivacaine-induced spinal block on the hypnotic requirement of propofol. Anaesthesia. 1996 ;51(7):652–3
10. Relationship between Bispectral Index, Sedation Score and Plasma Concentration, during Midazolam Sedation [Internet]. [cited 2023 Apr 28]. Available from: https://www.jdapm.org/search.

php?where=aview&id=10.17245/jkdsa.2001.1.1.21&code=1223JKDSA&vmode=PUBREADER

11. Guerrero JL, Matute E, Alsina E, Tapia B, Blanco B, Roses R. Monitorization of induced neuroaxial blockade sedation: A-138. Eur J Anaesthesiol EJA. 2006 ;23:36

12. Pollock JE, Neal JM, Liu SS, Burkhead D, Polissar N. Sedation during Spinal Anesthesia. Anesthesiology. 2000 ;93(3):728–34

13. Gentili M, Huu PC, Enel D, Hollande J, Bonnet F. Sedation depends on the level of sensory block induced by spinal anaesthesia. Br J Anaesth. 1998 ;81(6):970–

14. Ozkan-Seyhan T, Sungur MO, Senturk E, Karadeniz M, Basel A, Senturk M, et al. BIS guided sedation with propofol during spinal anaesthesia: influence of anaesthetic level on sedation requirement. Br J Anaesth. 2006 ;96(5):645–9

15. Tverskoy M, Shagal M, Finger J, Kissin I. Subarachnoid bupivacaine blockade decreases midazolam and thiopental hypnotic requirements. J Clin Anesth. 1994;6(6):487–90

16. Ben-David B, Vaida S, Gaitini L. The influence of high spinal anesthesia on sensitivity to midazolam sedation. Anesth Analg. 1995 ;81(3):525–8

17. Varma P, Darlong V, Pandey R, Garg R, Chandralekha, Punj J. Comparison of subarachnoid block with bupivacaine and bupivacaine with fentanyl on entropy and sedation: A prospective randomized double-blind study. J Anaesthesiol Clin Pharmacol. 2014;30(4):543