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Original Research Article

A Comparative Study of Intrathecal Hyperbaric Bupivacaine 0.5 % and Hyperbaric Bupivacaine 0.5% with Midazolam in Lower Limb Surgery

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Abstract:

Background: Spinal anaesthesia is common for lower limb surgeries, addition of preservative free midazolam improves sensorimotor charisteristics.

Aim & Objectives: In this Retrospective, randomized, double- blind study, we investigated the postoperative analgesic efficacy of intrathecal midazolam 1mg as an adjunct to bupivacaine for spinal anesthesia in 60 patients undergoing lower limb orthopedic surgery. Patients were allocated randomly to 2 groups:

Group A: Received 3.5 ml bupivacaine plus 0.2 ml preservative free midazolam (5 mg/ml).

Group B: Received 3.5 ml hyperbaric bupivacaine 0.5% plus 0.5 ml saline intrathec

Results: Mean duration of postoperative analgesia was Group A :(370.16 ±15.91) min in group A compared with (512±74.71)min in group B ($p<0.001$). Supplemental analgesic dose requirement with diclofenac were significantly less in Group B (3±0.86) compared with Group A (1±0.49) ($p<0.001$). Time to onset of sensory analgesia, maximum level of sensory block, time to reach it, and time to two segment regression were comparable.

Conclusion: We conclude that intrathecal midazolam 1 mg provided moderate prolongation of postoperative analgesia when used as an adjunct to bupivacaine.

Keywords: Benzodiazepines, Intrathecal Midazolam, Postoperative Analgesia.

Introduction

Spinal subarachnoid block is one of the most versatile regional anesthesia techniques available today. Regional anesthesia offers several advantages over general anesthesia like, it blunts stress response to laryngoscopy and surgery, decreases intra operative blood loss, lowers the incidence of postoperative thrombo embolic events, and provides analgesia in early postoperative period. Spinal anesthesia is preferred as it is simple to perform, economical, produces rapid onset of anesthesia and complete muscle relaxation, among the local anesthetics, 0.5% hyperbaric bupivacaine is the most commonly used drug for spinal anesthesia.

The most important disadvantage of single injection SAB is limited duration, even when a long acting local anesthetic like bupivacaine is used. The duration of spinal anesthesia is short and higher doses of analgesics are required in the post-operative period. Intrathecal use of various drug additives with local anesthetic agent is simple and effective method to provide longer duration of anesthesia and analgesia for postoperative period. Any method of post-operative analgesia must be safe, effective and feasible. Effective post-operative analgesia reduces the incidence of respiratory and cardiac complications. Various adjuvant drugs used today include epinephrine, opioids like fentanyl, nalbuphine and morphine and non-opioids like midazolam, clonidine, neostigmine, ketamine etc.mThese adjuvants act at a site different from that of local anesthetic agents. Discovery of benzodiazepine receptors in spinal cord in 1977 triggered the use of intrathecal benzodiazepine for prolongation of spinal anesthesia.

Preservative free midazolam is potent short acting water soluble and most commonly used benzodiazepine as an adjuant in spinal anaesthesia. Midazolam is known to produce antinociception via spinal delta opioid receptor. It also potentiates effect of local anaesthetic through benzodiazepine GABA receptor complex within spinal cord

without having any significant side effect when given in neuroaxial block.The present study was under taken to evaluate and compare analgesic efficacy, hemodynamic stability and side effects of intrathecally administered bupivacaine heavy (0.5%) and midazolam as an adjuvant to bupivacaine heavy (0.5%) for lower limb surgeries.

Materials and Methods:

All patients were undergone a thorough pre-anaesthetic check-up which included history taking, general and systemic examination. Routine investigations like CBC, PT with INR, LFT, RFT, blood sugar, serum creatinine and X ray chest PA view, ECG and VAS was explained in detail to patient and were made well conversant with it.An informed, written and well explained consent regarding procedure, drug and its possible side effects. All patients were kept nil by mouth for at least 6 hours before surgery.

After taking patient in operation theatre 18G I.V. cannula inserted, I.V. fluid started and routine monitors like ECG, NIBP and SpO2 were attached and baseline vitals noted. Under all aseptic precautions with patient in sitting position Spinal anaesthesia was given in L2-L3 or L3-L4 intervertebral space with 23G spinal needle with study drug according to group allocation, Groups: Patients were randomly divided into two groups of 30 each. Group A: Inj hyperbaric 0.5% Bupivacaine 3 cc (15 mg) + Inj Normal Saline 0.2 ml .Group B: Inj hyperbaric 0.5% Bupivacaine 3 cc (15 mg) + Inj preservative free Midazolam 1 mg (0.2 ml).

Onset of sensory blockade: was defined as the time from injection of study drug to loss of pinprick sensation at the level of sensory dermatome T10 was noted. Highest level of sensory block and time to attain it were recorded. Duration of sensory block: was defined as time taken to achieve highest sensory block dermatome level to time of two segment regression of sensory block. Onset of Motor Blockade: was defined as the time from injection of study drug to the time to achieve modified Bromage grade 3.After adequate level of motor block (modified bromge grade 3/4) surgery was started and time noted.

Duration of motor block: was defined as time of onset of complete motor block to the restoration of normal musculature force (modified bromge garde 3/4 to grade 0)Ramsay Sedation score 9 noted at 30, 60 and 90 minutes after giving spinal anesthesia. VAS score noted post operatively every 4 hourly upto 24 hours. Depending on the weight of patient, IV fluids were administered and replaced according to loss during surgery.

Duration of Surgery: it is time duration between injections of study drug to the skin closure .After completion of surgery; patients were shifted to post-operative ward, where patients were monitored. Total duration of analgesia: Time of injection of study drug to first demand for rescue analgesia by patient when VAS ≥ 5.Intraoperative complications like bradycardia, hypotension, sedation, shivering, nausea, vomiting, dryness of mouth and respiratory depression was noted in patients. Hypotension was defined as systolic blood pressure > 20% decrease in baseline value. Hypotension was treated with inj. Mefentermin 6mg IV stat. Tachycardia was defined as heart rate >20% of baseline. Bradycardia was defined as heart rate < 60/mins or >20% decline than baseline value. Bradycardia was treated with Inj. Glycopyrolate 0.2mg i.v. Nausea and vomiting if occurred was treated with Inj. Ondansetron 4mg i.v. Warm fluids and covering of patient was used to treat shivering. After surgery, patients were monitored for 24 hours postoperatively. Postoperatively pain measurement was assessed by VAS scale and First rescue analgesic was given in the form of inj. Diclofenac 75mg when VAS ≥5.Total number of analgesic requests in 24 hours noted

Statistical Analysis

The data obtained, was tabulated in MS excel and statistically analyzed using suitable SPSS software by using unpaired student's t-test. Average percentage change in data over baseline values to detect trends.

"P" value > 0.05 statistically non-significant

"P" value < 0.05 statistically significant

"P" value < 0.001 statistically highly significant

Results

Table 1: Distribution of Demographic Data

	Group A	Group B	P Value	Interference
	Mean ± Sd	Mean ± Sd		
Age	44±10.89	44±8.37	1	NS
Sex	17:13	15:15		
Asa Grade 1&2	15:15	15:15		
Duration Of Surgery	126±17.97	126±17.15	1	NS

Table 1 shows demographic data between two groups which were normal and comparable in both groups. (p>0.05)

Table 2: Baseline Vitals Parameters

	Group A	Group B	P Value	Interference
	Mean ± SD	Mean ± SD		
HR(Per Min)	79±5.1238	77±5.3739	0.1455	NS
SBP(Mm Hg)	123±3.28721	124±6.3624	0.44	NS
DBP(Mm Hg)	80±4.374	78±4.887	0.1003	NS
RR(Per Min)	15±1.3796	15±1.033	1	NS
Spo2 (%)	98±0.8769	98±0.86037	1	NS

Table 2 shows Baseline Vital Parameters between groups A and B. There was no statistical significant difference with regard to Baseline Heart Rate, SBP, DBP, RR and SPO2 between the two groups (p>0.05).

Table 3: Characteristic of Motor Block

	Group A	Group B	P Value	Interference
	Mean ± SD	Mean ± SD		
Time of Onset of Motor Block(Sec)	114.5±7.35191	102.8±5.961948	<.0001	HS
Time of Peak Motor Block(Min)	2.6±0.2345	2.2±0.6805	0.0035	S
Duration of Motor Block(Min)	154.9±6.2308	186±6.34	<0.0001	HS

Table 3 shows Characteristics of Motor Blockade between groups A and B. The time of onset of Motor Blockade is prolonged in Group A (114.5 ± 7.35) sec as compared to Group B (102.8± 5.96)sec which is statistically highly significant (p<0.001) while Time for Modified Bromage grade 3 motor blockade was prolonged in Group A (2.6±0.23)min than group B(2.2±0.68)min which is statistically highly significant (p<0.001).

Duration of Motor block regression from Modified Bromage grade 3 to 0 was more in group B(186±6.34)min as compared to group A(154±6.23)min which is statistically highly significant (p<0.001).

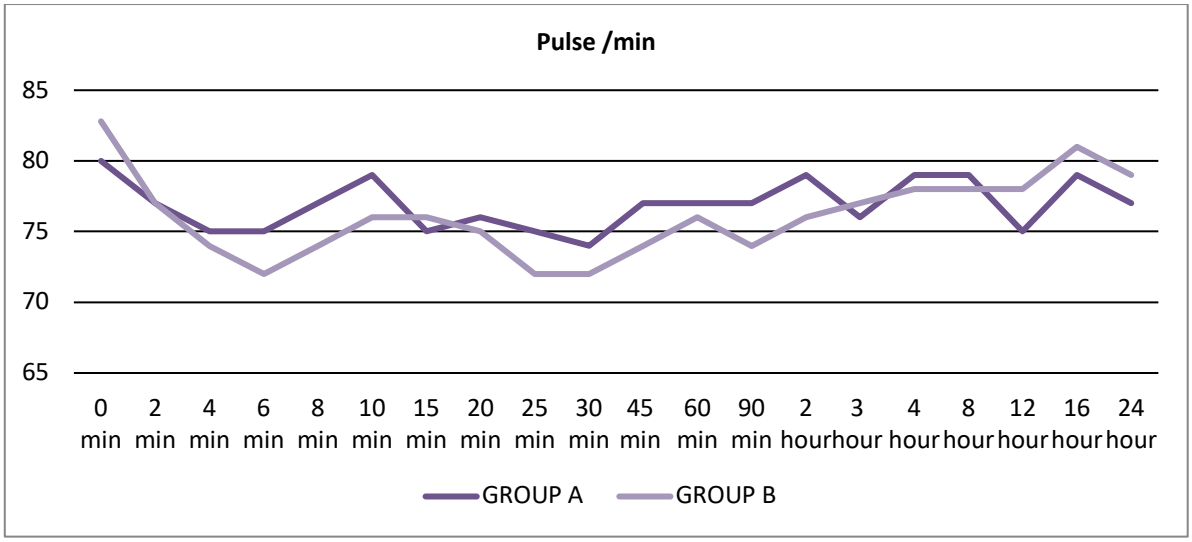
Table 4: Characteristic of Sensory Block

	Group A	Group B	P Value	Interference
	Mean ± SD	Mean ± SD		
Time of Onset Of Sensory Block(Sec)	126.2±6.915	115.3±7.169	<0.0001	HS
Time of Highest Sensory Block(Min)	8±0.8710	6.7±0.5784	<0.0001	HS
Time of Two Segment Regression (Min)	89.3±5.3905	96.4±9	0.0005	HS
Total Duration of Sensory Block(Min)	81.3±5.8263	89.7±9.2	0.0001	HS

Table 4 shows Characteristics of Sensory Blockade which shows time of onset of Sensory block is prolonged in group A(126.2±6.195) sec as compared to group B (115.3±7.16)sec (p<0.001) which is statistically highly significant.

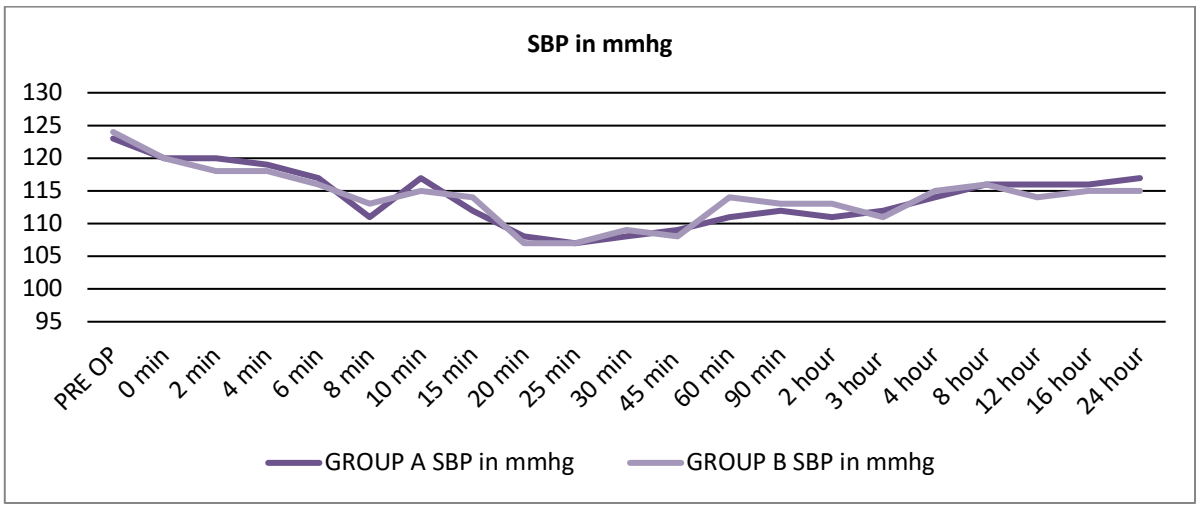
Time for highest Sensory Block is prolonged in group A (8.0 ± 0.87) min as compared to group B(6.7±0.57) min (p<0.001).Time for Two segment regression is more in group B (96.4±9.0) min as compared to group A (89.3±5.39) min which is statistically highly significant (p<0.001).Duration of sensory block was more in group B(89.7±9.2) than group A (81.3±5.83).which is statistically highly significant (p<0.001).

Graph 1 shows distribution of mean Pulse Rate between two groups which were normal and comparable in both groups and there is no statistical difference between two groups (p>0.05).



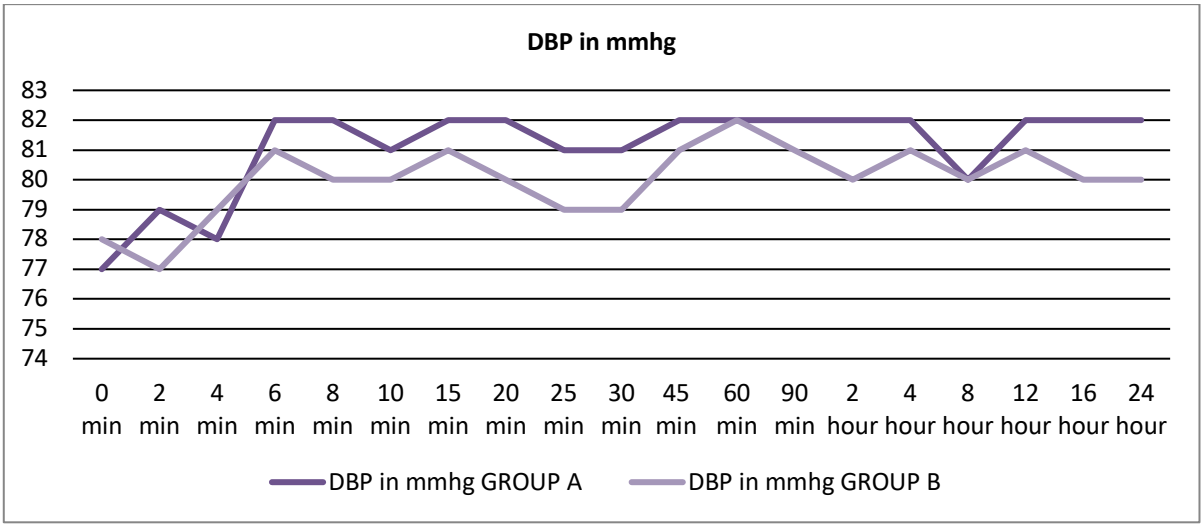
Graph 1

Graph 2 shows changes in Perioperative SBP between two groups which were normal and comparable in both groups and there is no statistical difference between two groups (p>0.05).



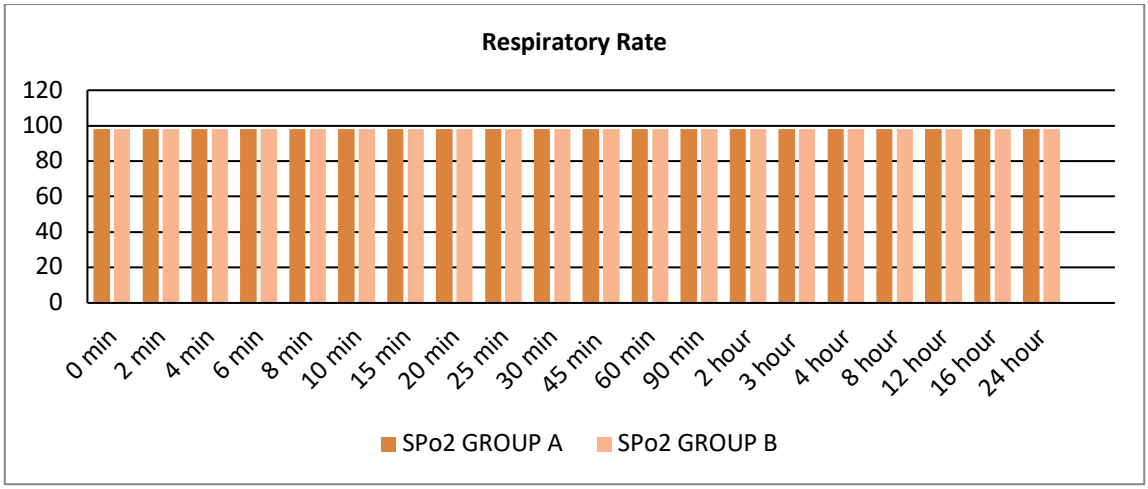
Graph 2:

Graph3 shows distribution of DBP in both groups

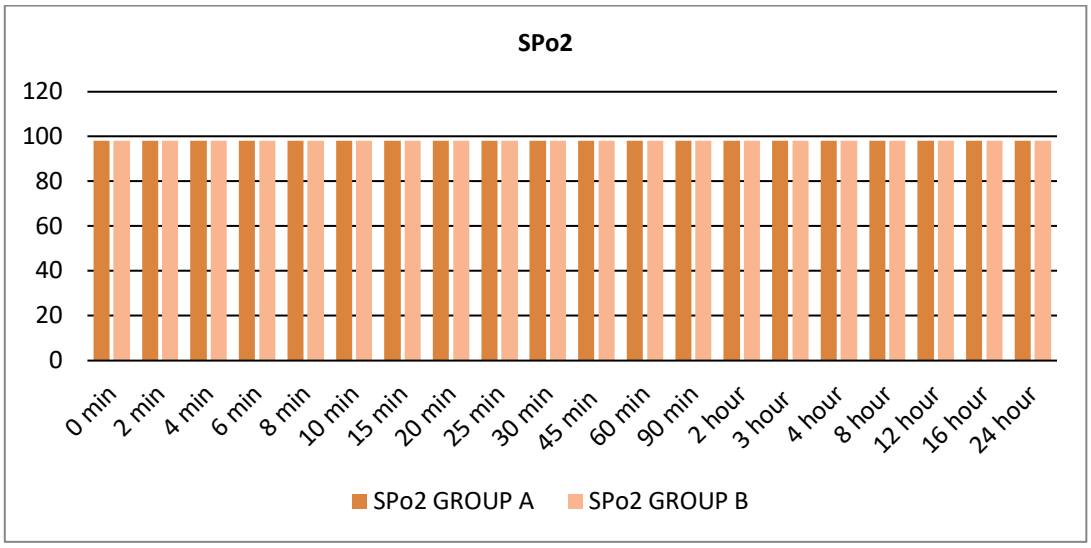


Graph 3:

Graph 4 & 5 show perioperative change in Respiratory Rate and SpO2 between two groups which were normal and comparable in both groups and there is no statistical difference between two groups (p>0.05).



Graph 4:



Graph 5:

Table 5: Distribution of mean sedation score at different time interval

	Group A	Group B	P value	Interference
	Sedation score (Mean ± SD)	Sedation score (Mean ± SD)		
30 min	2±0.25	2±0.18	1	NS
60 min	2±0.25	2±0.30	1	NS
90 min	2±0.18	2±0.18	1	NS

Table 5 shows Sedation Score in both groups, which were normal and comparable in both groups and there is no statistical difference between two groups (p>0.05).

Table 6: Distribution of mean Total duration of analgesia (min) and Total analgesia require in 24 hours

	Group A	Group B	P value	Interference
	Mean ± SD	Mean ± SD		
Total duration of analgesia (min)	370.167±15.91	512±74.71	<0.0001	HS
Total rescue analgesia required in 24 hours	3±0.86	1±0.49	<0.0001	HS

Table 10 shows Duration of Post-Operative Analgesia which is more in group B (512±74.71)min as compared to group A (370±15.91)min and Total Analgesic Requirements which is more in group A (3 ± 0.86) as compared to group B (1.± 0.49) which is statistically highly significant (p<0.001).

Table 7: Association between Peri operative complications

	Group A	Group B	P value	Interference
	Mean ± SD	Mean ± SD		
Bradycardia	1(3.33%)	1(3.33%)	1	NS
Hypotention	2(6.66%)	2(6.66%)	1	NS
Shivering	-	-	-	-
Nausea	-	-	-	-
Vomiting	-	-	-	-
Sedation	-	-	-	-
Urinary retention	-	-	-	-
Respiratory depression	-	-	-	-

Table 7 shows Perioperative Adverse Effects between both groups, with incidence of Hypotension and Bradycardia

Discussion:

The most commonly used regional anaesthesia technique is "Spinal anesthesia."One of the main stay of balanced anaesthesia is relief of pain during operation and postoperative period. Postoperative pain relief is a growing concern for an anesthesiologist. Uneventful postoperative period make all surgeries, comfortable proposition for surgical patients.Spinal anaesthesia using local anaesthetics alone has shorter duration of action with early requirement of analgesia for postoperative pain relief.

So many adjuvants have been used along with local anaesthetics "to hasten the onset of sensory & motor block and to improve quality and duration of postoperative analgesia, reducing postoperative analgesic requirements, without significant side effects, facilitating early ambulation & reducing the hospital stay of the patient."The aim of this study was to compare the effect of intrathecal bupivacaine plus normal saline and intrathecal bupivacaine plus midazolam for post-operative analgesia in patients undergoing elective lower limb surgeries. Our study consisted of 60 patients aged between 18 and 60 years, ASA grade I or II scheduled for lower limb surgeries under spinal anesthesia. They were divided into two groups with 30 patients in each group and informed written consent was taken.

The drugs used in study are FDA approved and having no major side effects.

- Group A: received 0.5% Hyperbaric bupivacaine heavy 3 cc(15mg)+ 0.2 ml normal saline
- Group B: 0.5% Hyperbaric bupivacaine 3 cc(15mg) + 1 mg (0.2ml) preservative-free midazolam.

Demographic Parameters

In Our study, we had observed that the difference in demographic data (Age, Gender distribution, American Society of Anaesthesiologists status) was statistically not-significant among both groups. ($p>0.05$)The aim of combining different analgesic drugs is to obtain synergistic or additive action which allows the use of a smaller dose of each agent, hence improving the safety profile and reducing related side effects.Similarly, Agrawal Nidhi et al [26] (2005) observed no significant difference between the two groups with respect to age, gender of the patient and ASA status.

Drug and Dosage

In our study, we had added 1mg of preservative free midazolam to hyperbaric bupivacaine. Anirban chattopadhyay [7] (2013) administered 2mg of preservative free midazolam along with hyperbaric bupivacaine. N Bharti, R. Madan et al [18] (2003) administered 1mg of midazolam along with 0.5 % hyperbaric bupivacaine. Kim MH, Lee YM [13] (2001) administered 1mg of midazolam in group BM1 , 2 mg of midazolam in group BM2 along with 0.5% hyperbaric bupivacaine. TUKER at al [2] (2004) suggested that intrathecal midazolam safe dose in human is < 0.03 mg /kg

Characteristics of Sensory Blockade

In our study , we observed the onset of Sensory block is prolonged in group A (126.2±6.195) sec as compared to group B (115.3±7.16) sec ($p<0.001$). which was statistically highly significant and Time for Two segment regression and is more in group B (96.4±9.0) min as compared to group A (89.3±5.39) min which is statistically highly significant ($p<0.001$). Duration of sensory block was more in group B(89.7±9.2) min than group A (81.3±5.83)min. which is statistically highly significant ($p<0.001$) Shadangi B.K [5] (2011) observed the onset of sensory blockade was 4.8 minutes in control group and 4.6 minutes in midazolam (2mg) group. The duration of sensory blockade was prolonged in the midazolam (2mg) group 115.8 min compare to 90.8 min in the control group. Malvika kulkarni [15] (2012) observed the duration of sensory block was significantly longer in midazolam(1mg) group (266.36 ± 22.56 min) than control group (187.8 ± 22.92 min). Konkyana Suresh Kumar [14] (2018) observed the mean duration of sensory blockade in group B (control

group) is 89.1±2.95 minutes were as in group M (midazolam 1mg) group it is 118.94±10.83 minutes.

Characteristics of Motor Blockade

In our study, time of onset of Motor Blockade is prolonged in Group A (114.5 ± 7.35) sec as compared to Group B (102.8± 5.96) sec which is statistically highly significant (p<0.001) Duration of Motor block regression from Modified Bromage grade 3 to 0 was more in group B(186±6.34)min as compared to group A(154±6.23) min which is statistically highly significant (p<0.001). Shadangi B.K [5](2011) observed the duration of motor block 151.8 min in midazolam (2mg) group as compared to control group 151.3 min.

Anirban Chattopadhyay [7] (2013) found that use of midazolam (2mg) as adjuvant with the local anesthetic in spinal anaesthesia significantly increases the duration of motor block 255 min in midazolam (1mg) group and 195 min in control group. Konkyana Suresh Kumar [14] (2018) The mean duration of maximum motor blockade in control group is 163.3±16.6 with a range being 135 to 210 minutes. In midazolam group(1mg) the mean duration of maximum motor blockade is 180.24±27.40 minutes with a range being 152 to 245 minutes.

Post-Operative Analgesia

In our study ; the mean duration of analgesia was prolonged in Group B (512±74.71mins) as compared to group A (370.16±15.91 mins) which was statistically highly significant (p < 0.01) .Time for first resque analgesic(VAS ≥5) in Group B(512±74.71) as compared to GroupA(370.16 ±15.91) was prolonged which was statistically highly significant. Total postoperative analgesic consumption in 24 hrs was less in group B (1±0.49) than in group A (3±0.86) (p<0.01)which was statistacally highly significant.These results show that midazolam when used as adjuvant to intrathecal bupivacaine it prolonged post-operative analgesia and decreses total requirement of post-operative analgesics in 24 hours.

Anirban chattopadhyay [7](2013) observed The duration of analgesia was significantly higher in patients receiving bupivacaine and midazolam (2mg) in comparison to bupivacaine alone (median 320 min versus 220 min). Kim MH et al [13] (2001): observed the time to first analgesia in control group was 3.99 hours, 6.03 hours in the group given 1 mg midazolam (BM1), 8.37 hours in the group given 2 mg midazolam (BM2) intrathecally. Thus, the time to first analgesia was significantly longer in midazolam (1mg or 2mg)group than the control group (p < 0.01) Time to first analgesia in group BM1(midazolam 1mg) was significantly less than that in Group BM2 (midazolam 2mg) (p < 0.05). This suggests dose dependent effect of intrathecal midazolam. Bharti N et al [18] (2003) found that the duration of effective analgesia was 199 minutes in the midazolam group(1mg) and 103 minutes in the control group (p<0.001).

Agrawal Nidhi et al [19] (2005) observed that the time to first rescue analgesia was 17.56 + 8.8 hours in midazolam(1mg) group and 4+3.5 hours in control group (p<0.0001). B K Shadangi [5] (2011): observed the duration of effective analgesia was significantly longer in the midazolam (2mg) group compared to the control group (121.3 versus 221.1 min, p-value is 0.001) Yegin [29] (2004) : observed in midazolam(2mg)group the postoperative visual analogue pain scores were significantly lower at the first 4 h (P < 0.05) the average time until the first dose of additional analgesic requirement was significantly longer as campared to control group (P < 0.05) Konkyana Suresh Kumar [14] (2018) observed in control group the mean duration of analgesia is 125.46±7.18 minutes with a range of 110 to 142 minutes. In midazolam (1mg) group the mean duration of analgesia is 243.26±24.41 minutes with a range of 173 to 273 minutes.

Y K BATRA [28] (1999) All patients received rescue analgesia in control group at a mean duration of (258 +/-46.8 minutes) whereas only one patient in midazolam group required supplemental analgesia within this period. Yegin [29] (2004) : observed in midazolam (1mg) group , the postoperative visual analogue pain scores were significantly lower at the first 4 h (P < 0.05) the average time until the first dose of additional analgesic requirement was significantly longer as campared to control group (P < 0.05) Smita Prakash [27] (2006): observed that Supplemental analgesic requirements with diclofenac were significantly less in group BM2 (midazolam 2mg) (93 +/- 29 mg) compared with control group (145 +/- 12 mg) and group BM1 (midazolam 1mg) (148 +/- 16 mg, P < .001) A Gupta [1] (2007): observed that Supplemental analgesic dose requirement with diclofenac were significantly less in midazolam (2.5mg) group (2.17 ± 0.50) compared with control group. (3.00 ± 0.39) (P< 0.001).

Perioperative Haemodynamics

In our study, hypotention and bradycardia occur and managed by fluid administration no need of any vasopressors. there was no statistically significant change in mean pulse rate, systolic blood pressure, diastolic blood pressure and Spo2, in both group intraoperatively and post operatively.(p>0.05) Batra YK et al [28] (1999) found no significant changes in heart rate, arterial blood pressure and oxygen saturation intraoperatively and postoperatively. Bharti N et al

[18] (2003) observed that blood pressure, oxygen saturation, heart rate were comparable in both groups.

Perioperative Adverse Effects

In our study,hypotention and bradycardia occur and managed by fluid administration no need of any vasopressors and complications like nausea, vomiting, rigors, neurological deficits were not detected in either group. In our study, Most of the patients showed Ramsay sedation score 2 after giving spinal anaesthesia. This shows intrathecal midazolam has no sedative effect; patients did not require any supplemental oxygen and did not have any respiratory depression. Kim MH et al [13](2001) found that there no episodes of bradycardia, hypotension, sedation or dizziness In any patients who were given intrathecal midazolam(1mg or 2mg) 3 of 15 patients from each group developed urinary retention. No neurological deficits were detected on discharge. Agrawal Nidhi et al [19] (2005) observed no episodes of bradycardia, hypotension, sedation and dizziness, vomiting and neurological deficit in both group .

Conclusion

Intrathecal preservative free midazolam used as adjuvant to hyperbaric bupivacaine 0.5% ; provides early sensory and motor onset, provides stable heamodynemics, increases duration of anaesthesia and post-operative analgesia without any significant complications. We recommend midazolam as good adjuvant to intrathecal bupivacaine in lower limb surgeries.

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