

## Original Research Article

# Comparison between intrathecal bupivacaine and combination of bupivacaine and midazolam for postoperative pain relief after infraumbilical elective surgeries

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### ABSTRACT

**Background:** Objective of the study was to identify the efficacy of midazolam as an adjuvant to intrathecal hyperbaric bupivacaine 0.5%, a prospective, randomized, double blind study was conducted to compare the onset, duration of sensory and motor block, postoperative analgesia, hemodynamic changes and complications.

**Methods:** Sixty patients, ASA I/II, Age 18-60 year, scheduled for infraumbilical surgeries, were randomly allocated to group BNS(n=30) to receive intrathecally 2.5 ml of 0.5% hyperbaric bupivacaine with 0.4 ml normal saline; and group BM (n=30) to receive 2.5 ml of 0.5% hyperbaric bupivacaine +2 mg preservative free midazolam 0.4 ml (5mg/ml). We observed onset, duration and regression of sensory and motor block, degree of sedation and pain scores, hemodynamic changes and adverse effects. (PS) version 3.0.0.34 was used for power and sample size calculation. Statistical analysis was performed using Microsoft (MS) office excel software with the student's t-test and chi-square test (P=0.05)

**Results:** Highest level of sensory blockade ( $p<.05$ ), motor block duration ( $179.67\pm14.94$  vs  $151.83\pm10.96$  min), sensory block duration ( $222\pm16.5$  vs  $174\pm12.53$  min) and time to first requirement of i.v. analgesia were significantly higher in group BM. Postoperative VAS score was significantly less in group BM. Both groups were comparable in demographic data and hemodynamic changes.

**Conclusions:** Intrathecal 2 mg midazolam found as an attractive adjuvant to 0.5% hyperbaric bupivacaine in spinal anesthesia in infraumbilical surgeries by producing significantly longer duration of motor and sensory block, good quality of intraoperative and postoperative analgesia with less incidence of nausea vomiting as compared to bupivacaine alone.

**Keywords:** Bupivacaine, Intrathecal injections, Midazolam

### INTRODUCTION

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" the International Association for the Study of Pain (IASP).<sup>1</sup> Post-operative pain is a major source of fear, anxiety and can result in neuro-endocrine stress response resulting in increased sympathetic tone, increased catecholamine levels and

catabolic hormone secretion. The effects include sodium and water retention, hypermetabolic state, hypercoagulability, hyperglycemia (leading to poor wound healing and depressed immunity) paralytic ileus, postoperative pulmonary complications, myocardial ischemia and infarction (in patients with underlying cardiac disease).<sup>2</sup> Regional anaesthesia (spinal and epidural anaesthesia) is a preferred technique for infraumbilical surgeries by providing good intra-

operative analgesia, excellent muscle relaxation, blunts stress response to surgery, less hemodynamic changes, no need for poly pharmacy, airway manipulation, hyper or hypo ventilation, postoperative pulmonary complications and metabolic complications. Local anesthetic agents have relatively shorter duration of action and early analgesic intervention is required in the postoperative period. So bupivacaine {1-Butyl-N-(2, 6-dimethylphenyl) Piperidine-2-carboxamide} amino-amide local anaesthetic with its longer duration of sensory (compare to lignocaine) and motor blockade, is the local anaesthetic of choice. But its duration of action is dose dependent. Increasing the dose of this hyperbaric bupivacaine leads to increased cephalic spread of drug which accounts for more incidence of hypotension, bradycardia, respiratory difficulty and cardio-respiratory arrest. To prolong the postoperative analgesia, many adjuvants tested and tried as they reduce the dose of local anaesthetic, provide long lasting postoperative analgesia with less incidence of central nervous system depression, motor effects or hypotension.<sup>2-3</sup>

Midazolam, a benzodiazepine used as an additive after the discovery of high density of benzodiazepine (GABA-A) receptors in Lamina II of the dorsal horn in the human spinal cord (in vitro autoradiography).<sup>4</sup>

The purpose of this study was to compare and evaluate the effect of intrathecal midazolam as an adjuvant to intrathecal bupivacaine on the onset and duration of sensory and motor block, duration of analgesia, incidence of side effects and prolongation of postoperative pain relief when 2 mg midazolam is added to hyperbaric bupivacaine 0.5% given intrathecally in patients undergoing elective infraumbilical surgeries.

## METHODS

After getting approved by our institutional ethical committee for the study protocol "Comparison between intrathecal bupivacaine and combination of bupivacaine and midazolam for Postoperative Pain Relief after infraumbilical elective Surgeries" and obtaining written informed consent from each patient, we conducted prospective, randomized and double blinded study in the Dept. of Anaesthesiology, Government Medical College and associated MBS hospital, Kota (Rajasthan).

A total of sixty patients of American society of anaesthesiologists (ASA) physical status Grade I and II, in the age group of 18-60 years, scheduled to undergo elective infraumbilical surgeries under subarachnoid block (SAB). Patients having weight >110 kg, height <140 cm, with any cardiac, psychological, hepatic or renal diseases and contraindications to spinal anaesthesia (bleeding disorder, known allergy to study drugs, infection at puncture site, preexisting neurological deficit in the lower limb, epilepsy etc.) were excluded from the study.

Complete medical history, physical examination including vital signs and airway assessment including mouth opening, mallampati grading, history of previous anaesthesia exposure, blood transfusion, drug allergy, Neurological disease, etc. general and systemic examination was done. All routine investigations including complete blood count, BT, CT, fasting blood sugar, renal function test, chest X-ray, ECG for all patients were done. Patients were kept fasting for 6-8 hrs pre-operatively.

All the selected patients were explained about the purpose, procedure and side effects of the study. They were also explained about assessment of pain with the help of Visual Analogue Scale. They were randomly divided into two groups of thirty each.

**GROUP BNS:** (n=30) Patient received 2.5ml of 0.5% hyperbaric bupivacaine with 0.4 ml normal saline intrathecally.

**GROUP BM:** (n=30) Patient received 2.5 ml of 0.5% hyperbaric bupivacaine +2 mg preservative free midazolam in 0.4 ml (5 mg/ml) intrathecally.

No premedication was given to patients. On the arrival of patients in operating theatre, all patients monitored and recorded for base line pulse rate, blood pressure, respiratory rate, oxygen saturation (SpO<sub>2</sub>). An Intravenous line with 18/20 G intravenous cannula secured, preloading was done with Ringer Lactate solution 10 ml/kg over a period of 20 minutes before giving spinal block.

Following preloading after checking basic necessities like anaesthesia trolley, resuscitation drugs and suction apparatus, spinal anaesthesia was administered under all aseptic conditions, at the L3-4 interspace via the midline approach using a 25-gauge Quincke needle in sitting position.

After confirmation of free flow of cerebrospinal fluid, drug prepared using tuberculin syringe to measure exact amount of Midazolam and normal saline, as per group of patients and injected slowly over 15 second with no barbotage. Immediately after block patients were asked to lie down. Time of drug injection was noted down. Surgery was started. Patients having no or inadequate surgical anaesthesia were excluded from the study.

All the observations including sensory block, motor block and hemodynamic measurements recorded before giving block and then after block every two minutes up to 10 minutes then in five minutes interval up to thirty minutes then ten minutes interval up to an hour then hourly basis up to ten hours. Post operatively patient was observed for 24hr for any complications. Vas Score, Ramsay Sedation Score and Rescue analgesia Requirement is checked at thirty minutes interval up to four hours and then hourly interval up to twenty four hours.

**Sensory block assessment:** assessed by pin prick method along the mid clavicular line using 26G hypodermic needle. Onset of sensory block taken as completion of intrathecal injection to the loss of sensation at the level of L1 dermatome.

Duration of sensory block taken as time interval from onset of block to when regain the sensation felt at L1 dermatome. Duration of pain free interval taken as time interval from onset of sensory block to when first rescue analgesic was given.

**Motor block assessment**

Assessed by modified Bromage scale.<sup>5</sup>

Grade 0: no motor block (no power impairment and able to raise straight leg)

Grade 1: unable to flex hip (unable to raise straight leg but can flex knee)

Grade 2: unable to flex knee

Grade 3: unable to flex ankle and foot-no movements

Onset of motor block defined as time to attain grade.<sup>3</sup>

Duration of motor block defined as time interval from onset of motor block to when grade became 0 again.

**Sedation score assessment**

Assessed by Ramsey sedation score.<sup>6</sup>

Ramsay 1: Anxious, agitated, restless

Ramsay 2: Cooperative, oriented, tranquil

Ramsay 3: Responsive to commands only

Ramsay 4: Brisk response to light glabellar tap or loud auditory stimulus

Ramsay 5: Sluggish response to light glabellar tap or loud auditory stimulus

Ramsay 6: No response to light glabellar tap or loud auditory stimulus.

**Pain assessment**

Assessed by Visual Analogue Scale score (VAS score).<sup>7</sup>

It is a 10 cm scale graded from 0-10, 0 denotes no pain and 10 denote most excruciating pain. Patients were asked to mark the point on the scale that corresponded to their level of pain intensity at the time of observation.

The duration of effective analgesia or pain free interval was counted from onset of sensory block to when VAS score of 4 or more. Then patients were given rescue analgesic Inj Diclofenac Sodium 1.5mg/kg IM. Number and time of rescue analgesic required in 24 hr postoperative period was noted down. Interpretation.

No pain (0-4 mm)

Mild pain (5-44 mm)

Moderate pain (45-74 mm)

Severe pain (75-100mm)

**Intra and postoperative complications**

Patients were monitored for various intra and post operative complications like bradycardia, hypotension, respiratory depression, nausea, vomiting, shivering, rigors, hallucination, emergence phenomenon, post dural puncture headache, backache, urinary retention, neurological and behavioral side effects.

Bradycardia defined as pulse rate <20% of preoperative value. It was treated with Inj Atropine 0.6mg IV bolus.

Hypotension defined as systolic blood pressure <20% of pre-procedure value. Inj Mephentermine 6mg IV bolus was given when hypotension occurs.

Respiratory depression defined as respiratory rate less than 10/min or oxygen saturation less than 90%. It was treated with oxygen if required.

**Analysis of result**

A master chart was prepared to arrange the observed parameters of each and every case. Mean and standard values was taken out. power and sample size (PS) version 3.0.0.34 was used for power and sample size calculation.

Stastical analysis was performed using Microsoft (MS) office excel software with the student's t-test and chi-square test (level of significance P=0.05).

Student's paired t-test for intra group comparison and unpaired t-test for intergroup comparison. For VAS and Sedation score analysis chi-square test was applied.

**RESULTS**

**Table 1: Demographic data.**

Variables	Control group (n=30)	BNS	Midazolam group (n=30)	BM
Age (yrs)	39.3±10.99		41.3±11.47	
Weight (kg)	56.73±4.52		56.66±4.52	
Height (cm)	153.87±6.39		153.67±5.48	
Gender (M/F)	20/10		19/11	
ASA status (I/II)	18/12		16/14	
Duration of surgery (min)	110.167±19.97		116.0±26.98	
Type of surgery (ortho/surg/gynae)	15/6/9		17/6/7	
P value	>0.05			
Significance	NS			

In this study, distribution of patients with respect to age, sex, weight, ASA grading, type and duration of surgery,

and i.v. fluid administered as preloading are comparable in both groups. ( $p>0.05$ ) (Table 1). Group BNS consisted 2.5 ml of 0.5% hyperbaric bupivacaine with 0.4 ml normal saline and Group BM was 2.5 ml of 0.5% hyperbaric bupivacaine +2 mg preservative free midazolam in 0.4 ml (5 mg/ml). M denoted Male and F denoted Female.

Values are in mean±SD or number of patients. Spinal anaesthesia was successful in all the patients included in study in both the groups and no patient in either group required rescue analgesia or general anaesthesia. Characteristics of motor and sensory block summarized (Table 2). Median peak sensory block level achieved in group BNS was T6, with the range of T5-T7 and T5 in group BM, with the range of T4-T6 which was comparable and statistically nonsignificant ( $P>0.05$ ).

No statistically significant difference was found in group BNS and group BM with respect to time to reach peak sensory block level ( $p>0.05$ ) as the onset of sensory block, group BNS (3.70±0.67 min) and group BM (3.13±1.33 min) and complete motor block, group BNS (5.23±0.87 min) and group BM (4.57±1.34 min) was

found to be comparable between both the study groups ( $p>0.05$ ).

**Table 2: Comparison of level and quality of sensory and motor blockade.**

Variables	Control group Group BNS (n=30)	Midazolam group Group BM (n=30)
<b>Sensory level at 15 min median range (pin prick)</b>	T6 (T5-T7)	T5(T4-T6)
<b>Motor block at 15 min median range (modified bromage)</b>	2 (1-2)	3(2-3)
<b>Quality of block-no. (%)of pt</b>	2 (6.67)	19(63.33)
<b>Excellent</b>		
<b>Satisfactory</b>	13 (43.33)	4(13.33)
<b>Poor</b>	13 (43.33)	5(16.67)
<b>Inadequate</b>	2 (6.67)	2(6.67)

**Table 3: Duration of sensory and motor analgesia.**

Variables	Control group Group BNS (n=30)	Midazolam group Group BM (n=30)
<b>Onset of sensory block (min)</b>	3.70±0.67	3.13±1.33
<b>Onset of motor block (min)</b>	5.23±0.87	4.57±1.34
<b>Time to 2-segment regression of sensory block</b>	73(50-100)	135(100-175)
<b>Time to regression of sensory block to s<sub>2</sub> segment</b>	188.40±13.63	236.60±17.60
<b>Duration of motor block</b>	151.83±10.96	179.67±14.94
<b>Duration of effective analgesia</b>	174±12.53	222±16.5

**Table 4: Comparison of degree of sedation (Ramsay sedation score)**

Degree of sedation	Group B		Group BM		P value	Significance
	Number	%	Number	%		
<b>Grade 1</b>	22	73.3	8	26.6	0.005 ( $<0.05$ )	S
<b>Grade 2</b>	8	26.6	16	53.3		
<b>Grade 3</b>	0	0	6	20		
<b>Grade 4</b>	0	0	0	0		
<b>Grade 5</b>	0	0	0	0		
<b>Grade 6</b>	0	0	0	0		

The regression of sensory and motor blockade in midazolam group was significantly longer when compared with control group as shown by 2 segment regression time group BNS 73min (50-100 min) and group BM 135 min (100-175 min), ( $p<0.05$ ) regression time to S<sub>2</sub> level group BNS (188.40±13.63 min) and group BM (236.60±17.60 min) ( $p<0.05$ ) and duration of motor block group BNS (151.83±10.96 min) and group

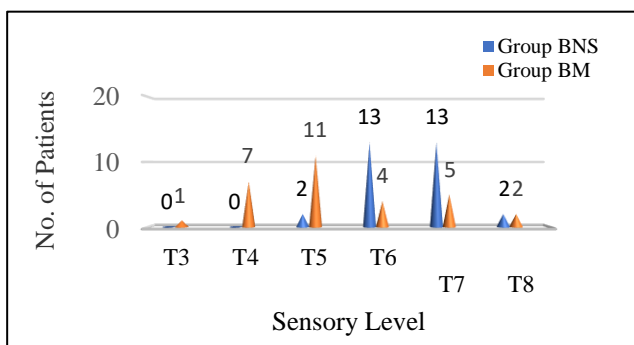
BM (179.67±14.94 min) ( $p<0.05$ ) (Table 3). Time to first postoperative analgesia was significantly longer in group BM (222.0±16.5 min) when compared to group BNS (174.0±12.53 min) ( $p<0.05$ ) (Table 4). Degree of sedation score (ramsay sedation score) was found increased and statistically significant ( $P<0.05$ ). On statistical analysis maximum pain score on VAS, number of diclofenac injections required in first 24 hours were

significantly less in group BM ( $p < 0.05$ ) (Table 5). Although incidence of bradycardia was more in group BM, rest hemodynamic parameters were found to be comparable and nonsignificant in both the study groups.

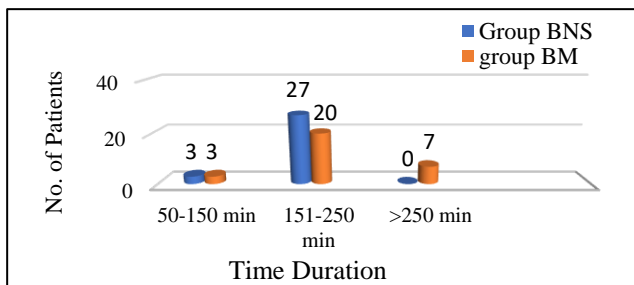
Respiratory parameters like decrease in respiratory rate were more in group BM but it was not statistically significant and  $SPO_2$  changes were comparable and statistically nonsignificant ( $p > 0.05$ ).

**Table 5: Intra-operative and postoperative changes in vas score.**

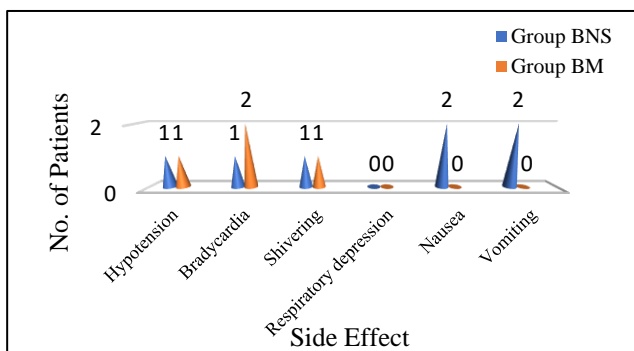
Time	Group BNS		Group BM		P value	Significance
Preop	5.5	0.94	5.37	0.86	>.05	NS
After spinal 30min	0	0	0	0	0	NS
60 min	0	0	0	0	0	NS
90 min	1.22	0.67	0	0	<.05	S
120 min	2.67	1.05	0.67	0.42	<.05	NS
150 min	2.79	1.53	0.77	0.7	<.05	S
180 min	1.98	1.1	1.53	1	>.05	NS



**Figure 1: Comparison of highest level of sensory block achieved.**



**Figure 2: Duration of sensory blockade (mean ±SD).**



**Figure 3: Side-effects (intraoperative and early postoperative period)**

**DISCUSSION**

Midazolam, despite of being the commonest benzodiazepine used in anaesthesia and perioperative care, is a relatively newer addition to the list of adjuvants used in subarachnoid block.

In this comparative, prospective, randomized, double blind study we found that intrathecal midazolam as an additive to hyperbaric bupivacaine significantly improves the duration and quality of spinal anaesthesia and provides prolonged perioperative analgesia without any significant side effects.

**Demographic parameters**

The demographic data in terms of age, weight, height, sex distribution, ASA status grade are quite comparable and statistically nonsignificant. ( $p > 0.05$ )

**Onset of sensory block and motor block**

Our study showed onset was earlier in group BM but no statistically significant difference in the mean onset of sensory and motor block between both the groups ( $p > .05$ ). Our results coincide with Kim and Lee, Prakash et al and Shukla et al.<sup>8-10</sup>

A study by Sanwal et al showed that it's the dose of bupivacaine and not the dose of adjuvant that determine the time to onset of sensory and motor block.<sup>11</sup> In our study we used an equal amount of bupivacaine and both groups were comparable regarding the time of onset of sensory and motor block.

**Time duration of analgesia**

Our study has shown that the addition of 2mg midazolam to 0.5% hyperbaric bupivacaine significantly prolongs the duration of analgesia as compared to control group ( $p < 0.0001$ ).

In study by Shukla et al time to first postoperative analgesia was significantly longer in bupivacaine dexmedetomidine group (380.0±18.0 min) and bupivacaine midazolam group (220.1±14.8 min) compared to control Group (bupivacaine alone) ( $p < 0.05$ ).<sup>10</sup>

Our study showed consistent results with Shukla et al and Valentine et al studies regarding less analgesia requirement times in midazolam group.<sup>10-12</sup>

### **Highest level of sensory block achieved**

In group BNS no patient achieved highest sensory level up to T3 and T4, 2(6.67%) patients up to T5, (43.33%) patients up to T6 level, 13(43.33%) patients up to T7 level and 2(6.67%) patients up to T8.<sup>13</sup>

In group BM 1(3.33%) patient achieved highest sensory level up to T3, 7(23.33%) patients up to T4, 11 (36.66%) patients up to T5, 4(7.5%) patients up to T6 level, 5(16.66%) patients up to T7 level and 2(6.67%) patients up to T8.

Application of Chi Square test showed that this difference was statistically significant ( $p < 0.05$ ). It shows that adding midazolam affect the cephalad spread of local anaesthetic and achieves greater dermatome level of sensory block. Synergism with local anaesthetics may also enhance this effect. The findings were similar to Shukla et al who found that midazolam increase the highest level of sensory block as compared to placebo.<sup>10</sup>

### **Duration of motor block**

In our study, the mean duration of motor block was in Group BNS was 151.83±10.96 minutes and in Group BM was 179.67±14.94 minutes so the difference in mean duration of motor block between Group BNS and Group BM, was statistically significant ( $p < 0.05$ ). The difference between Group BNS and Group BM in mean duration of motor block was statistically highly significant ( $p < 0.0001$ ).

This result is consistent Kim and Lee, Prakash et al.<sup>8,9</sup> They observed analgesic effects of intrathecal midazolam 1mg or 2mg along with bupivacaine and concluded that duration of postoperative analgesia was significantly prolonged with the addition of intrathecal midazolam in a dose dependent manner. Our study also reports prolonged duration of sensory and motor blockade in midazolam group as compared to control group.

### **Haemodynamics and side effects**

Our study demonstrated no clinically significant difference in the hemodynamic parameters and incidence of adverse effects between the two groups. In our study hypotension and bradycardia were more in the in the

midazolam and control group, but it was not statistically significant.

Nausea and vomiting were observed 6.66% in group BNS. No incidence of nausea and vomiting seen with midazolam group so. This suggested that the incidence of nausea and vomiting was changed significantly with midazolam. Our study results are in accordance to the finding of Valentine et al<sup>12</sup>

No patient had residual neurological deficit, postdural puncture headache or transient neurological symptom. In study by Shukla et al the overall incidence of adverse/side effects was found to be similar among study groups ( $p = 0.595$ ).<sup>10</sup>

Hypotension and bradycardia was mild to moderate in both the study groups except in dexmedetomidine group, in which only 1 patient had blood pressure of  $< 80$  mm of Hg, and required 12 mg ephedrine to maintain her blood pressure. All patients in both study groups had complete recovery of sensory and motor functions.

No patient in either group had any neurological impairment like pain or numbness in leg, back or buttock, incontinence or retention of urine, headache. Joshi et al, compared 2mg midazolam to 30 mcg of clonidine added to 15mg of 0.5% hyperbaric bupivacaine and found a higher incidence of hypotension/bradycardia in the clonidine group compared to the midazolam group (44%/36% versus 16%/0%).<sup>13</sup>

One study demonstrated that the higher dose of bupivacaine is responsible for perioperative hypotension rather than the use of midazolam. Our study results are in accordance to the finding of Kim and Lee, Prakash et al.<sup>8,9</sup> Although both groups were comparable regarding the occurrence of hypotension and bradycardia, the higher incidence of hypotension and bradycardia could be due to avoidance of preloading and a higher dose of hyperbaric bupivacaine.

### **Sedation**

In our study group BNS, 22 patients belonged to Grade 1 of Ramsay sedation score and 8 patients were in Grade 2 and in group BM, 8 patients belonged to Grade 1, 14 patients were in Grade 2 and 6 patients were in Grade 3. Hence there was statistically significant difference found regarding sedation ( $p < 0.05$ ). Midazolam have intra-operative sedative effects so our results are quite similar to Bharti et al. No patients in either group were heavily sedated as is evident by overall sedation level between 0 and 3.<sup>14</sup>

### **Respiratory rate and saturation**

Although the respiratory rate and saturation decreases more in midazolam group but no statistically significant changes were found in mean of saturation and respiratory

rate changes in both the groups at different time intervals (p value >0.05).

## CONCLUSION

Intrathecal 2 mg midazolam seems to be an attractive adjuvant to 0.5% hyperbaric bupivacaine in spinal anesthesia in infra umbilical surgeries. It is associated with prolonged motor and sensory block, provides good quality of intraoperative analgesia and excellent quality of postoperative analgesia, allay anxiety with less incidence of nausea vomiting as compared to bupivacaine alone.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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