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A Comparative Study of Intrathecal Levobupivacaine and Levobupivacaine with Midazolam in Lower Abdominal and Lower limb Surgeries

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Abstract

Context: Intrathecal midazolam as an adjuvant to levobupivacaine provides excellent intraoperative hemodynamic stability and also good postoperative analgesia. Present study was done to evaluate the efficacy, duration of pain relief, the incidence of adverse effects and complications when midazolam is given along with levobupivacaine intrathecally. *Aims:* To compare between intrathecal levobupivacaine (Group LB) and intrathecal levobupivacaine with adjuvant midazolam 1 mg (Group LBM) with respect to onset and duration of analgesia, motor blockade, intraoperative discomfort and postoperative analgesia requirement and complications like nausea, vomiting, respiratory depression etc. *Methodology:* In this prospective, randomized, double blind, placebo controlled study a total of 100 patients of American Society of Anaesthesiologists (ASA) grade I and II, undergoing elective lower abdominal and lower limb orthopaedic surgery under sub-arachnoid block were randomized into two groups. Group LB (n=50) received 3 ml of 0.5% isobaric levobupivacaine with 0.2 ml of normal saline and Group LBM (n=50) received 3 ml of 0.5% isobaric levobupivacaine with 0.2 ml midazolam (1 mg) (preservative free) as intrathecal anesthesia. Assessment of sensory blockade, motorblockade, duration of analgesia, intraoperative hemodynamics, discomfort and postoperative analgesia estimated. After surgery, patients were asked to score their pain at 2, 4, 6, 12, 18 and 24 hr by VAS score. The presence of postoperative nausea vomiting (PONV), pruritus and respiratory depression were recorded and compared between the two groups. *Statistical analysis:* For continuous variables the summary statistics of N, mean, standard deviation (SD) were used. For categorical data,the number and percentage were used in data summaries.Chi-square($\chi 2$)/ Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables was tested with unpaired *t*-test. *p*-value <0.05 was considered significant. Data were analysed using SPSS software v.23.0. *Results:* Group LBM had superior quality of analgesia,prolonged duration of analgesia, reduced postoperative analgesic requirement and minimal hemodynamic changes compared to Group LB. *Conclusions:* Intrathecal midazolam potentiates levobupivacaine effect leading to better quality and longer duration of analgesia, better sedation, better postoperative outcome with minimum side effects.

Keywords: Midazolam; PONV; Visual Analogue Pain Scale; Adjuvants, Anesthesia; Assessment, Pain.

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Introduction

Subarachnoid block is one of the most versatile regional anesthesia techniques available today. Subarachnoid block provides adequate anesthesia for patients undergoing lower abdominal and lower limb surgeries. In order to maximize quality of anesthesia and post operative analgesia, a number of adjuvants have been added to local anaesthetics. The benefits of intrathecal opioids and non-opioids as adjuvants in spinal anesthesia are well documented. The addition of intrathecal opioids is however associated with dose related adverse effect such as respiratory depression, nausea, vomiting, urinary retention, pruritus and sedation.[1] So, use of non-opioids such as ketamine, clonidine, neostigmine, magnesium sulphate, midazolam have become popular adjuncts for postoperative analgesia.[2]

Hyperbaric bupivacaine is one of the common local anaesthetic used for spinal anesthesia in patients undergoing lower abdominal and lower limb surgeries. However, it has considerable adverse effects on the cardiovascular and central nervous system. Enantiomers of bupivacaine may have the same desired pharmacological properties, but fewer side effects. Levobupivacaine, the S(-)-enantiomer of bupivacaine has been shown to provide a more selective neuraxial blockade than racemic bupivacaine.[3] Intrathecal midazolam abolishes pain of somatic origin, produces selective sensory block and depresses somatosympathetic reflexes without any neurotoxicity. It potentiates the blocking actions of local anaesthetics. It improves the quality of sensory and motor block, without prolonging the recovery and also provides good postoperative analgesia.

The subarachnoid midazolam was originally shown to have anti-nociceptive properties in studies performed in animals in early 1980's.[4] The subarachnoid midazolam has been used in humans since 1986 and doses up to 2 mg have been described.[5] There are many clinical studies in favour of intrathecal midazolam which has added advantages of sedation, amnesia and anti-nociceptive effects without any neurotoxicity or other side effects.

Hence, this study was designed to evaluate the efficacy, to know the duration of pain relief, to know the incidence of adverse effects and complications when midazolam (preservative free) is given along with levobupivacaine intrathecally.

Materials and Methods

This prospective, randomized, double-blind study was conducted at Department of Anaesthesiology, Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapur from December 2014 to June 2016. The study included 100 patients of ASA Grade I and II, age 20-45 years, body weight 50-80 kg who underwent elective lower abdominal and lower limb surgery. The study was approved by the institutional ethical committee.

Patients belonging to ASA grade III and IV, pregnant women, patients on long term analgesic therapy and chronic alcoholics, had any deformity or local pathology in lumbar spine region, history of convulsions, allergy to the drugs used, bleeding disorders, were uncooperative and with severe neurological deficit were excluded from the study. Patients with severe hypovolemia, anemia, receiving steroid medication and patients in whom spinal anesthesia failed and general anesthesia was required were also excluded from the study.

Preanaesthetic check-up was done on the day before surgery, and included a complete history and any known drug allergy, general and systemic examination and local examination of lumbar spine region. Pulse rate, blood pressure, respiratory rate, and weight and height of the patient were noted. Relevant investigations were done in all the patients.

The anaesthetic procedure was briefly explained to the patient. The patients were also introduced to Visual Analogue Scale (VAS) and taught how to use it. An informed written consent was obtained from the patient or his/her relatives.

The patients were randomized on the day of surgery into two groups of 50 each. Hundred pieces of paper, 50 with 'saline' written on them and 50 with 'midazolam' written were put in a box and the patients were asked to pick one piece of paper. This piece of paper was handed to an anaesthesiologist unconnected to the study who prepared the medications. Group LB patients received 3 ml of 0.5% isobaric levobupivacaine with 0.2 ml of normal saline and Group LBM patients received 3 ml of 0.5% isobaric levobupivacaine with 0.2 ml of midazolam (1 mg) (preservative free) intrathecally. [1 ml midazolam ampoule (preservative free) consisted 5 mg, of which 0.2 ml = 1 mg was given intrathecally].

On arrival in the operating room fasting status (at least for 8 hours), and written consent was checked,

the patient was connected to the routine monitors which included non invasive blood pessue, pulse oximeter and electrocardiogram. Base line pulse rate, blood pressure, respiratory rate, SpO_2 were recorded.

All resuscitation equipments like intubation trolley with airways, laryngoscopes, endotracheal tubes along with drugs like atropine, mephentermine were kept ready. The anesthesia machine was also checked along with the oxygen delivery system.

A18 or 20 gauge intravenous access was obtained and secured. All patients were preloaded with 15 ml/kg of Ringer's lactate prior to spinal anesthesia. The patients were then put in sitting position. Under strict aseptic precautions, lumbar puncture was performed by midline approach by using disposable Quincke spinal needle (25G) at L_3–L_4/ L_2-L_3 intervertebral space.

Patients were continuously monitored using sphygmomanometer, pulseoximeter and electrocardiogram. After spinal anesthesia, the patient's pulse rate and blood pressure were recorded at 0, 5, 10, 20, 30, 45, 60, 90 and 120 minutes.

Assessment of sensory blockade was tested by pin-prick method.

The time of onset: Time of injection of the drug into the subarachnoid space to loss of pin-prick sensation.

Maximum sensory block: Time of injection of drug to loss of pin-prick sensation at highest dermatomal level.

The time for two dermatomal segments regression of sensory level was noted.

Duration of sensory blockade: time of onset to time of return of pin prick sensation to L_2dermatomal area.

Assessment of motor blockade was done by Bromage scale.

Bromage Scale:

Grade-I (No block): Full-flexion of knees and ankle joint possible

Grade-II (Partial block): Just able to flex knees, but still full flexion of ankle joint possible

Grade-III (Almost complete block): Unable to flex knees. Flexion of ankle joint possible.

Grade-IV(Complete block): Unable to flex knees or ankle joint

The time of onset: The time interval between injections of drug into subarachnoid space to the patient's inability to lift the straight extended leg.

Maximum motor blockade: time of injection of the drug to maximum degree of motor block.

Sedation score was assessed every 15 min both intra and postoperatively using a four point scale (1= awake, 2=drowsy but responding to verbal commands, 3=drowsy but responding to physical stimulus, 4=unresponsive to verbal/ physical stimulus).

Postoperative pain was measured and recorded using a 10 point Visual Analogue Scale (VAS). VAS consisted of a 10 cm line, one end labelled as No pain and other end as Worst possible pain. Patients marked on the scale as per severity. Patients were asked to score the pain both at rest and during movement at 2, 4, 6, 12, 18, and 24 hours after surgery.

The duration of effective analgesia :time of intrathecal drug administration to the time of first supplementation with rescue analgesic. Intavenous Diclofenac 75 mg was given as the rescue analgesic if VAS was found to be 4 or more.

The incidence of hypotension, bradycardia were noted during intraoperative period and also in the recovery room. Patients were monitored for any adverse event (e.g. nausea, vomiting, urinary retention etc.) during the following time periods 0–3, 3–6, 6–12, and 12–24 h.

Statistical analysis: For continuous variables the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in data summaries. Chi-square($\chi 2$)/Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables was tested with unpaired t-test. p-value <0.05 was considered significant. Data were analysed using SPSS software v.23.0.

Results

Our study consisted of 100 patients of ASA I and II divided into 2 groups. Group LB received 3ml of levobupivacaine and 0.2ml saline and group LBM received 3ml levobupivacaine and 0.2ml midazolam (preservative free 1mg).

Patient characteristics across the groups

The patients studied across the group did not vary much with respect to age, sex or height. The

type of surgeries performed were almost identical in both the groups. These parameters were kept identical in both the groups to avoid variations in the intraoperative and postoperative outcome of the patients (Table 1-3).

The mean age, sex, height, ASA grading and duration of surgery were similar in both the groups

Table 1: Percent Distribution of Age in two study groups

Age group	Group LB		Group LBM	
	N	%	N	%
21–25	12	24.0%	12	24.0%
26–30	10	20.0%	11	22%
31–35	12	24.0%	11	22.0%
36–40	6	12.0%	7	14.0%
41–45	10	20.0%	9	18.0%
Total	50	100.0%	50	100.0%

Table 2: Percent Distribution of Sex in two study groups

Sex	Group LB		Group LBM	
	N	%	N	%
Male	29	58.0%	25	50.0%
Female	21	42.0%	25	50.0%

Table 3: Percent Distribution of ASA grade in two study groups

ASA Grade	Group LB		Group LBM		*p* value
	N	%	N	%	
I	40	80.0%	32	64.0%	
II	10	20.0%	18	36.00%	0.075
Total	50	100.0%	50	100.0%	

Time of onset of sensory block was 153.2 ± 8.7 secs in group LB and 173.0 ± 5.8 secs in group LBM which was statistically significant (p<0.001). Time of onset of motor blockade between groups was statistically significant (p<0.001). The duration of analgesia was 139.6 ± 8.7 min in group LB and 263.80 ± 35.8 min in group LBM (P<0.001) and statistically significant. Two segment regression was 87.2 ± 3.4 min in group LB and 122.6 ± 3.6 min in group LBM (p<0.001) and statistically significant. The difference between the groups was statistically highly significant (Table 4).

VAS scores between groups LB and LBM at 3hrs was 0.43 ± 0.78 and 0.02 ± 0.43,at 6 hrs 4.22 ± 0.51 and 0.62 ± 0.65, at 12 hrs 5.41 ± 0.42 and 1.73 ± 0.76 respectively, which was statistically significant (p<0.001). The difference between the groups was statistically highly significant (Table 5).

The means of sedation score between the groups was comparable (Table 6).

There were 3 episodes of badycardia and hypotension in each of the 2 groups (p=0.999) (Table 7)

The difference in heart rate between the groups at different time intervals were statistically insignificant (*p*>0.05) (Fig. 1).

Systolic blood pressure comparison showed to be statistically insignificant (Fig. 2 and 3).

Means of sedation score were comparable in both the groups (Fig. 4).

Table 4: Variables in study (mean ± SD)

Variables	Group LB (n=50)	Group LBM (n=50)	*p* value	Significance
Duration of Analgesia (min)	139.6 ± 8.7	263.80 ± 35.8	<0.001	S
Onset of sensory block (sec)	153.2 ± 8.2	173.0 ± 5.8	<0.001	S
Onset of motor block (sec)	220.4 ± 7.3	240.4 ± 4.6	<0.001	S
Two segment regression (mins)	87.2 ± 3.4	122.6 ± 3.6	<0.001	S

Table 5: Comparison of Visual Analogue Scores at different time interval between two study groups

Time in hours	Group LB		Group LBM		Mean Difference	*p* value
	Mean	SD	Mean	SD		
3	0.43	0.78	0.02	0.43	0.5	<0.001*
6	4.22	0.51	0.62	0.65	-19.8	<0.001*
12	5.41	0.42	1.73	0.56	-20.0	<0.001 *

Table 6: Comparison of Means of Sedation Score in two study groups by different time (Min)

Time	Group LB		Group LBM		Mean Difference	*p* value	95% Confidence Interval	
	Mean	SD	Mean	SD			Lower	Upper
3''	0.0	0.0	0.0	0.0	-	-	-	-

6''	0.0	0.0	0.0	0.0	-	-	-	-
9''	0.0	0.0	0.0	0.0	-	-	-	-
12''	0.0	0.0	0.0	0.0	-	-	-	-
15''	0.0	0.0	0.0	0.0	-	-	-	-
20''	0.0	0.0	0.0	0.1	0.0	0.320	-0.1	0.0
25''	0.0	0.0	0.0	0.1	0.0	0.320	-0.1	0.0
30''	0.0	0.1	0.0	0.2	0.0	0.562	-0.1	0.0
40''	0.1	0.2	0.0	0.1	0.0	0.312	0.0	0.1
50''	0.0	0.0	0.1	0.2	-0.1	0.080	-0.1	0.0
60''	0.0	0.0	0.0	0.1	0.0	0.320	-0.1	0.0
90''	0.0	0.0	0.0	0.1	0.0	0.320	-0.1	0.0
120''	0.0	0.0	0.0	0.0	-	-	-	-
180''	0.0	0.0	0.0	0.0	-	-	-	-

Table 7: Percent Distribution of Complications in two study groups

Complications	Group LB		Group LBM		p value
	N	%	N	%	
Bradycardia	3	50.0%	3	50.0%	
Hypotension	3	50.0%	3	50.0%	0.999
Total	6	100.0%	6	100.0%	

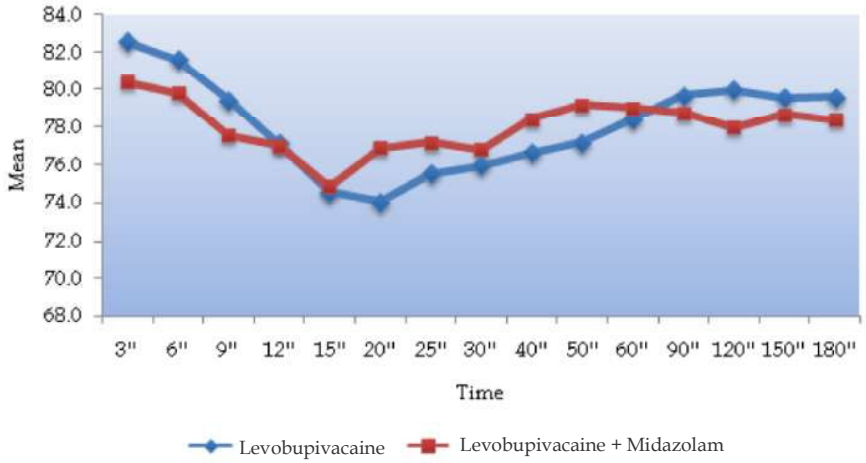

Fig 1: Comparison of means of heart rate in the two groups

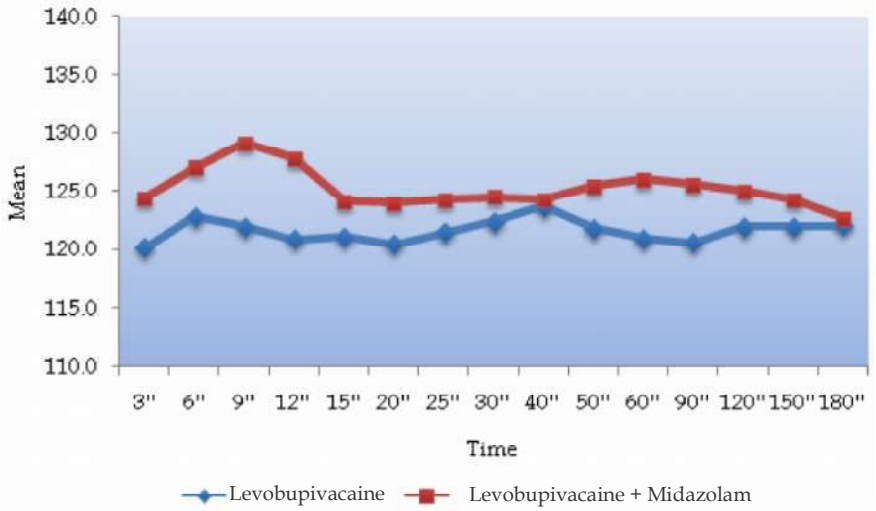

Fig 2: Comparison of Means of Systolic Blood Pressure in two study groups by different time (Min)

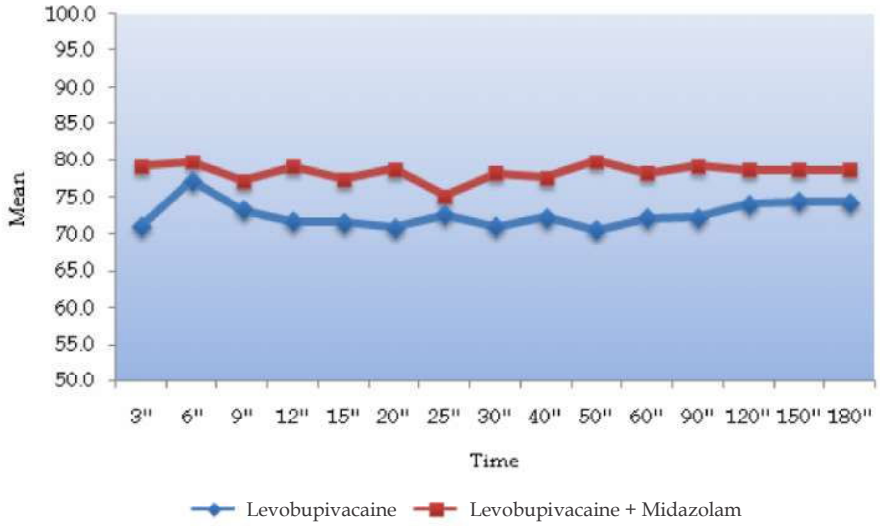

Fig. 3: Comparison of Means of Diastolic Blood Pressure in two study groups by different time (Min)

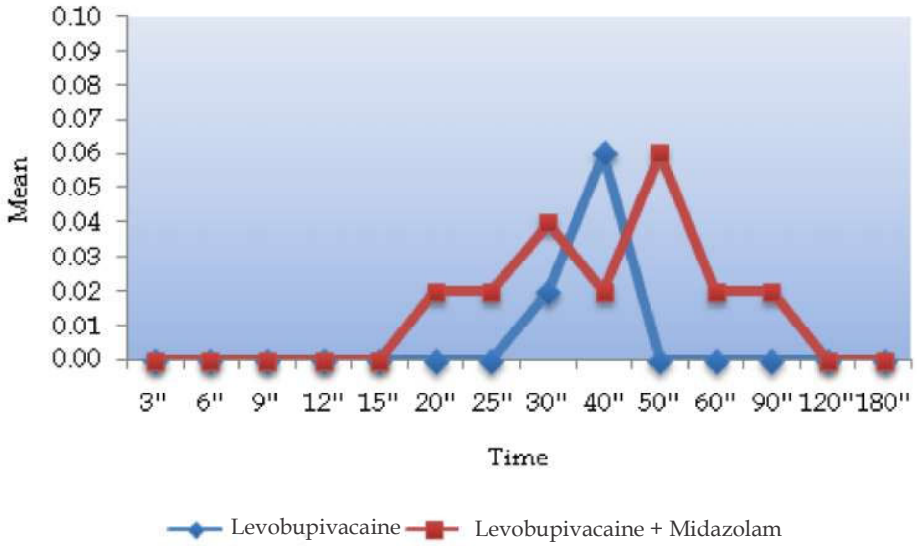

Fig. 4: Comparison of Means of Sedation Score in two study groups by different time (Min)

Discussion

The subarachnoid blockade is the common form of centrineuraxial blockade performed for lower abdomen and lower limb surgeries.Intrathecal midazolam has been used as an adjuvant to local anaesthetics since 1980s. It has been tried widely and antinociceptive effect with neurological safety has been well established in animals and humans.

The intrathecal benzodiazepine induced analgesia is spinally mediated. The binding sites of midazolam are GABA receptors which are abundant in dorsal root nerve cells of spinal cord. The maximum concentration of GABA receptors are found within lamina II of dorsal nerve cells, a region which plays prominent role in processing nociceptive and thermoceptive stimulation. Acting over the GABA receptors benzodiazepines induce changes in chloride conductance and enhance GABA induced presynaptic inhibition of primary afferent terminals.

Changes in the perioperative cardiovascular parameters

In the present study, the incidence of hypotension was equal, with 3 patients in each group had a fall in blood pressure. Hypotension was corrected by administration of injection mephentermine 6 mg

IV in incremental doses and giving IV fluids. Heart rate, systolic and diastolic blood pressure in both the groups did not vary significantly. Goodchild CS, Noble J in 1987[5], Bahar M, Cohen ML *et al.* in 1997[6], Batra YK and *et al.* in 1999[7] and Bharti N and *et al.* in 2003[8] found no difference in the hemodynamic responses to the drugs used. Our study correlated with. Rosa Herrera and *et al.*[9] study of stable hemodynamics with isobaric levobupivacaine.

Changes in respiratory parameters

None of the patients in the present study had respiratory depression. Bahar M and *et al.* in 1997[6] found no changes in the arterial blood gases or respiratory rate when given intrathecal midazolam in animal model. Sen A and *et al.* in 2001[10] found that intrathecal midazolam produces better tranquility of patients of caesarian section delivery without much sedation and respiratory depression. Apgar score of baby in 1st and 5th minute of delivery was found to be normal.In our study we did not include caesarian section deliveries. Bharti N and *et al.* in 2003[8] studied the effect of intrathecal 1 mg of midazolam with hyperbaric bupivacaine in patients undergoing lower abdominal surgery and found no change in oxygen saturation.

The above observations were similar to our study results. We conclude that intrathecal midazolam 1 mg is safe to use without causing respiratory depression.

Changes in the onset of sensory and motor blockade

In our study the onset of sensory blockade in group-B was 153.2 ± 8.2 seconds compared to 173.0 ± 5.8 seconds in group-II which was statistically highly significant ($p < 0.001$). It shows that addition of midazolam to local anaesthetic delays the onset of analgesia. Similarly the onset of motor blockade in group-B was 220.4 ± 7.3 compared to 240.4 ± 4.6 seconds in group-BM which was also statistically highly significant ($p < 0.001$) i.e., the addition of midazolam to local anaesthetic delays the onset of motor blockade. Yegin A and *et al.* 2004[11] did not find anydelay in onset of sensory and motor blockade with addition of 2 mg of midazolam to hyperbaric bupivacaine in spinal anesthesia in patients undergoing perianal surgery. But in our study we used isobaric levobupivacaine instead of bupivacaine.

From the above study we conclude that there is variation in the onset of sensory and motor blockade in different studies. Though it is statistically significant in our study it does not have any clinical implications.

Time for two dermatomal segments regression of sensory level

In our study, the two segment regression of sensory level in group LB was 87.50 ± 4.4 minutes compared to 122.00 ± 3.6 minutes in group LBM which was statistically highly significant ($p < 0.001$). This shows that addition of midazolam increases the duration of sensory blockade.

Bharti N and *et al.* in 2003 found that duration of sensory block (ie., time to regression to S_2 segment) was significantly longer in the midazolam group than the control group (218 min vs 165 min, $p < 0.001$). Venkatesh Selvaraj, Tapan Ray in 2015[12] had similar finding with midazolam as an adjuvant to intrathecal lignocaine. So we can conclude that intrathecal midazolam increases the duration of sensory blockade.

Time of first request of analgesics

In our study, the time of first request of analgesics in group LB was 139.00 ± 8.77 minutes compared to 263.8 ± 35.8 minutes in group LBM which was statistically highly significant ($p < 0.001$). This shows that there was significantly longer period of analgesia with intrathecal midazolam. Kim MH and *et al.* in 2001[13] found significantly greater time to first analgesia in the midazolam group in patients undergoing haemorrhoidectomy. Amr M and *et al.* in 2003[14] had similar finding in patients undergoing knee arthroscopy. Valentine J.M. J and *et al.* in 1996[15], Shah FR *et al.* in 2003[16] found prolonged duration of postoperative pain relief with midazolam as adjuvant. These studies validate our findings of prolonged first request of supplemental analgesics in the postoperative period.

Visual Analogue Score

In our study, there was significant reduction in the visual analogue score of the patients in group LBM in comparison with higher VAS in group LB recorded at 3 hours, 6 hours and 12 hours of spinal anesthesia. Shah FR and *et al.* in 2003 showed that patients treated with intrathecal midazolam had better pain relief judged by visual analogue scroe on coughing ($p = 0.0013$) and a nursing mobility score ($p < 0.0001$). Yegin A and *et al.* in 2004 found significantly lower visual analogue pain scores in midazolam group at the first 4 hours.

Above studies support that intrathecal midazolam potentiates the sensory blockade of levobupivacaine, there by reduce the visual analogue scores in the early post operative period bringing about better post operative outcome.

Sedation Score

The sedation score was assessed by scoring system of Chernic *et al*.[17]

In our study the sedation score ranged from 0 to 1 in both the groups. Most of the patients in group LBM were calm and sleeping comfortably were as most of the patients in the group LB were awake and alert. Nishiyama T 1995[18] studies used midazolam for pre and post operative sedation which showed the sedation scores were higher in the patients receiving midazolam by the epidural or intrathecal route. Vaswani *et al*.[19] found sedation scores were less but more sustained when the midazolam is administered intrathecally. Anjana Sen *et al*. also reported the higher sedation scores with intrathecal midazolam.

The results of present study are consistent with both the authors though the duration of the sedation is less. This may be because of different doses of the drug.

Adverse Effects

In the present study, 3 patients had hypotension and bradycardia, 1 patient had shivering and nausea vomiting in group LBM compared to 3 patients of hypotension, 2 patients of shivering and 1 patient of nausea & vomiting in group LB. This signifies that adverse effects are minimal with intrathecal midazolam.

Studies in humans by Valentine JMJ *et al*. in 1999, Sen A and *et al*. in 2001, Bharti N and *et al*. in 2003, Shah FR and *et al*. in 2003, Amr M and *et al*. in 2003, Tucker AP and *et al*. in 2004, found no adverse neurological symptoms in those received intrathecal midazolam. They also found that intrathecal midazolam has mild sedative and antiemetic effect.

Conclusion

With all the above observations we conclude that addition of midazolam to levobupivacaine provides prolonged analgesia, superior pain relief and better sedation with minimal side effects compared to levobupivacaine alone in spinal anesthesia**.**

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