

## The effects of intrathecal midazolam on the duration of analgesia in patients undergoing knee arthroscopy

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### Abstract

**Background:** Spinal anaesthesia is a common anaesthetic technique for lower limb surgery. Many adjuvants have been tried to prolong the duration of analgesia provided by local anaesthetics when administered intrathecally. Midazolam has been shown to prolong the duration of analgesia when used as an adjuvant, providing the added advantages of mild sedation and amnesia, while being devoid of neurotoxicity, and the adverse effects of opioids. This study was designed to evaluate the effect of 2 mg preservative-free intrathecal midazolam added to spinal bupivacaine during postoperative analgesia, and the incidence of adverse effects, if any, in patients undergoing knee arthroscopies.

**Method:** Fifty consenting American Society of Anesthesiologists (ASA) physical status I or II patients of either gender (men = 19, women = 31), aged between 18-56 years, were randomly allocated to two groups (25 each). Group M received 0.5% hyperbaric bupivacaine with preservative-free midazolam 2 mg intrathecally, and Group S received 0.5% hyperbaric bupivacaine with saline intrathecally. Peak sensory level, total duration of analgesia, duration of motor blockade, pain score using the Visual Analogue Scale, and sedation score using the Observer Assessment Score of Sedation were assessed, along with vital parameters, namely heart rate and systolic, diastolic and mean blood pressure.

**Results:** The total duration of analgesia observed was significantly higher in Group M ( $399 \pm 88.11$  minutes) vs. Group S ( $301.60 \pm 110.14$  minutes), and the pain score was lower in Group M ( $33.6 \pm 4.68$  mm) vs. Group S ( $56.6 \pm 8.64$  mm).

**Conclusion:** The addition of preservative-free midazolam 2 mg to intrathecal 0.5% hyperbaric bupivacaine prolongs the duration of analgesia without any observed adverse effects in patients undergoing knee arthroscopies.

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### Introduction

Regional anaesthetic techniques provide an excellent means of managing postoperative pain following orthopaedic procedures. Spinal anaesthesia with bupivacaine is administered routinely for lower limb surgery, and provides effective analgesia in the early postoperative period.<sup>1</sup> Various adjuvants have been added to local spinal anaesthetics in an attempt to prolong postoperative analgesia, for example opioids,<sup>1</sup> ketamine,<sup>2</sup> clonidine,<sup>3</sup> neostigmine<sup>1</sup> and midazolam. Although the addition of opioids reduces the toxicity and cardiovascular effects of local anaesthetics, this combination may bring about additional side-effects such as itching, nausea, vomiting and respiratory depression.<sup>1</sup>

Midazolam, when administered intrathecally as an adjuvant to local anaesthetics, has been shown to prolong the

duration of analgesia, providing the added advantages of mild sedation and amnesia, while being devoid of neurotoxicity and the adverse effects of opioids.<sup>4</sup>

This study was designed to evaluate the effect of 2 mg preservative-free intrathecal midazolam added to spinal bupivacaine during postoperative analgesia, and the incidence of adverse effects, if any, in patients undergoing knee arthroscopies.

### Method

Patients belonging to American Society of Anesthesiologists (ASA) physical status I or II, aged between 18-65 years of either gender, and undergoing elective knee arthroscopies, were included in the study. Patients with contraindications to central neuraxial blockade, for example gross spinal

deformity, spinal tenderness, local pathological conditions in the spinal area, known sensitivity to the drugs used in the study, or the presence of peripheral neuropathy, were excluded from the study.

The study was a prospective, randomised, double-blind placebo-controlled study. A prior power analysis revealed that 25 patients were needed in each group to provide a power of 80% with a significance level (p-value) taken as 0.05. A total of 50 patients were enrolled in the study. Institutional ethics committee approval and written informed consent for participating in the study were obtained.

A detailed preanaesthetic evaluation of the patients enrolled in the study was conducted a day prior to the procedure. The age, weight and height of all the patients were recorded. Assessment of pain with the Visual Analogue Scale (VAS), consisting of a 100-mm line (with 0 indicating no pain, and 100 indicating intolerable pain), was explained to all the patients.

Prior to surgery, all patients were kept nil per os for six hours for solids and three hours for clear fluids. No sedative premedication was administered. This was done to avoid any residual sedation produced by the premedicative drugs and their potential interference with the sedation assessment produced by the administration of intrathecal midazolam.

All the patients enrolled in the study were randomly assigned to either of the two groups by drawing lots. The two groups were termed Group M and Group S. Patients in Group M each received a combination of 2 ml of 0.5% hyperbaric bupivacaine with 0.4 ml (2 mg) preservative-free midazolam. The preservative-free midazolam used in the study was Mezolam® (Neon Lab, India), available as 1-ml (5 mg/ml) snap-off ampoules. In Group S, each patient received a combination of 2 ml 0.5% hyperbaric bupivacaine with 0.4 ml 0.9% saline.

On the day of surgery, patients were transferred to the operating room. Standard monitors, which included an electrocardiograph (monitoring lead II and V5), a non-invasive blood pressure monitor and a pulse oximeter, were connected, and baseline vitals were recorded before the induction of spinal anaesthesia. All patients received 15 ml/kg intravenous Ringer's lactate before induction of the spinal anaesthesia.

The spinal anaesthesia drug solutions were prepared by Observer 1, a consultant anaesthesiologist, or anaesthesiology resident, with more than one year's experience in the field of anaesthesiology, and who did not partake in subsequent study observations. Spinal blockade was performed in all patients at the L3-4 interspace by Observer

2 (a primary investigator), adhering to the standard technique in the right lateral position, utilising a 25G Quincke spinal needle.

After confirmation of the free flow of clear cerebrospinal fluid (CSF), each patient received either a combination of 2 ml of 0.5% hyperbaric bupivacaine with preservative-free midazolam 2 mg (0.4 ml) (Group M), or 2 ml 0.5% hyperbaric bupivacaine with 0.4 ml 0.9% saline (Group S). The time of intrathecal injection was noted, and all the patients were turned supine immediately. Supplemental oxygen (2 l/minute by nasal prongs) was administered to all the patients. The level of spinal anaesthesia was confirmed by loss of sensation of cold. Vital parameters including heart rate, blood pressure, respiratory rate and oxygen saturation were recorded every two minutes for the first 20 minutes, and subsequently, every 10 minutes until the end of the procedure. The time taken for sensory spinal level regression by the two segments was noted.

Pain scores using the VAS were recorded in the postoperative period by Observer 2 every 30 minutes after the end of the procedure for the first six hours, and subsequently, every two hours for the next six hours, or until the patient received rescue analgesia, thereby ending the study. Rescue analgesia was provided with the injection of tramadol 1 mg/kg with an antiemetic (ondansetron 4 mg) on patient request, or when the VAS score was 40 mm or more, and the time was noted. The duration of analgesia (pain-free period) was recorded as the time from completion of the spinal blockade to the time when rescue analgesia was administered in the postoperative period.

Sedation was assessed in the perioperative period using the Observer Assessment Score of Sedation (OASS):

- 0 - Awake.
- 1 - Sleeping comfortably, but easily arousable.
- 2 - Deep sleep, but arousable.
- 3 - Deep sleep, and not arousable.

Motor blockade was assessed by the Bromage Scale, as shown below:

- 1 - Able to lift and extend leg.
- 2 - Decreased knee flexion, but full extension of feet and ankles.
- 3 - Flexion of ankle and feet only.
- 4 - Cannot move knee, leg, ankle or toes.

After administration of the spinal anaesthesia, hypotension (defined as a decrease in systolic blood pressure more than 20% below baseline) was treated by an increase in the rate of intravenous fluid administration and/or the intravenous injection of mephentermine 3 mg boluses. Bradycardia

(defined as a heart rate of less than 60 beats per minute) was treated with an intravenous injection of atropine sulphate 0.6 mg. The incidence of nausea, vomiting, shivering, urinary incontinence, respiratory depression, and any other neurological sequelae during the observation period, was recorded.

## Results

The data were analysed using the SPSS version 10.0 for Windows®. No patients experienced complications during the study or observation period, and no patients were excluded from the study.

Demographic data were compared using the chi-square test for gender and age, and Student's t-test for weight and height. Haemodynamic data were compared using Student's t-test. Patients with a 20% or more baseline change in haemodynamic parameters, sedation score and peak level of sensory blockade, were compared using the chi-square test. Sedation score  $\geq 1$ , two-segment regression time, total duration of analgesia, total duration of motor blockade, and rate of complications between the two study groups, were compared using Student's t-test. P-values  $< 0.05$  were considered as significant,  $< 0.01$  as highly significant, and  $< 0.001$  as very highly significant.

There was no statistical difference in the patient characteristics relating to age, weight, height and gender distribution between the two groups (see Table I).

**Table I:** Demographic data

Variables	Group M	Group S	P-value
	(n = 25)	(n = 25)	
	Mean $\pm$ <sup>a</sup> SD	Mean $\pm$ SD	
Age (years)	32.48 $\pm$ 11.13	35.24 $\pm$ 10.91	0.380
Weight (kg)	63.36 $\pm$ 11.79	60.08 $\pm$ 8.45	0.264
Height (cm)	164.34 $\pm$ 7.15	169.32 $\pm$ 7.97	0.240
Male/female	9/16	10/15	<sup>b</sup> 0.771

a = Standard deviation; b = Chi-square test. (Student's t-test for the rest of the variables).

The addition of 2 mg midazolam to intrathecal bupivacaine prolongs the duration of postoperative analgesia (p-value 0.001) (see Table II).

**Table II:** Total duration of analgesia (minutes)

	Group M	Group S	P-value
	(n = 25)	(n = 25)	
	Mean $\pm$ <sup>a</sup> SD	Mean $\pm$ SD	
Total duration of analgesia (minutes)	399.40 $\pm$ 88.11	301.60 $\pm$ 110.14	0.001 <sup>b</sup> VHS

A = Standard deviation; b = Very highly significant. (Student's t-test).

The pain score using the VAS between two groups (see Table III) was clinically significant, and statistically very highly significant (p-value 0.001).

**Table III:** Pain Visual Analogue Scale scores (mm)

	Group M	Group S	P-value
	Mean $\pm$ <sup>a</sup> SD	Mean $\pm$ SD	
VAS scores (mm)	33.6 $\pm$ 4.68	56.6 $\pm$ 8.64	0.001 <sup>b</sup> VHS

a = Standard deviation; b = Very highly significant. (Student's t-test).

The two-segment regression time comparison (see Table IV) indicated a significantly prolonged regression in Group M. The difference between the groups was statistically very highly significant (p-value 0.001).

**Table IV:** Two-segment regression time (minutes)

	Group M	Group S	P-value
	Mean $\pm$ <sup>a</sup> SD	Mean $\pm$ SD	
Two-segment regression time (minutes)	120.12 $\pm$ 7.26	90.20 $\pm$ 4.51	0.001 <sup>b</sup> VHS

a = Standard deviation; b = Very highly significant. (Student's t-test)

The peak sensory levels achieved in both the groups were comparable without any statistical difference (see Table V). The addition of 2 mg midazolam to intrathecal bupivacaine did not have any effect on the peak level of sensory blockade achieved.

**Table V:** Peak level of sensory blockade

Peak level of sensory blockade	Group M	Group S	Total number of patients
	(n = 25)	(n = 25)	
T4	5	3	8
T6	8	9	17
T8	5	7	12
T9	0	2	2
T10	5	4	9
T12	2	0	2
	<b>25</b>	<b>25</b>	<b>50</b>

Chi-square test; p-value = 0.415

P-value = 0.248 for systolic blood pressure; p-value = 1 for diastolic blood pressure, mean blood pressure and heart rate. Therefore, there was no difference between the haemodynamic changes ( $\geq 20\%$  change) when comparing the two groups (see Table VI).

Student's t-test: p-value = 1, so no statistical significant difference is present between the two groups regarding adverse effects (see Table VII).

**Table VI:** Twenty per cent change of haemodynamic parameters from the baseline

	Group M (n = 25)	Group S (n = 25)
Mean blood pressure (mmHg) (Yes/no)	20/5	20/5
Heart rate (Yes/no)	21/4	20/5
Systolic blood pressure (mmHg) (Yes/no)	13/12	17/8
Diastolic blood pressure (mmHg) (Yes/no)	14/11	14/11

$\chi^2$  test

**Table VII:** Adverse effects

	Group M (n = 25)	Group S (n = 25)
Shivering	2	3
Nausea and vomiting	0	0
Desaturation	0	0
Urinary retention and neurological sequelae	0	0

## Discussion

In this study, it was found that the analgesic effect of intrathecal heavy bupivacaine 0.5% was augmented by the addition of intrathecal preservative-free midazolam. The addition of 2 mg midazolam prolonged the anaesthetic duration after knee arthroscopy by approximately 1.5-3 hours, without an increase in the sensory level of blockade compared to the control group. In addition, the midazolam-treated group did not exhibit an increased incidence of haemodynamic instability, or observable adverse effects.

Spinal anaesthesia is the most commonly used regional anaesthetic technique. Local anaesthetic agents used for this purpose provide good intraoperative analgesia. However, they provide a very limited postoperative duration of action. In order to overcome this problem and to maximise the duration of analgesia, many adjuvants, for example opioids,<sup>1</sup> neostigmine,<sup>1</sup> ketamine<sup>2</sup> and clonidine,<sup>3</sup> have been tried increasingly in the last two decades to relieve postoperative pain. However, side-effects in the postoperative period such as nausea, vomiting, pruritus, urinary retention and respiratory depression, render most adjuvants as less than ideal.

The rationale for the use of intrathecal midazolam focuses on the awareness that it is an agonist at the benzodiazepine binding site, a subunit of the pentameric gamma-aminobutyric acid (GABA)<sub>A</sub> receptor. Agonist occupancy of the benzodiazepine binding site enhances the activity

of GABA at the GABA<sub>A</sub> receptor. This receptor is a chloride ionophore that, when activated, typically stabilises the transmembrane potential at, or near, the resting potential. In neurons, this typically serves to decrease excitability.<sup>5</sup> Intrathecal benzodiazepine-induced analgesia is spinally mediated. Binding sites are GABA receptors, abundantly present in the dorsal root nerve cells, with the maximum concentration found within lamina II of the dorsal nerve cells, a region that plays a prominent role in processing nociceptive and thermoceptive stimulation.<sup>6</sup> The present cumulative experience with intrathecal midazolam across species broadly confirms the safety thereof, the analgesic activity of the molecule and its benzodiazepine pharmacology, and the lack of irreversible effects.<sup>4</sup>

The reduction in the pain scores observed in this study is comparable to the results of a previous study by Bhattachary et al.<sup>7</sup> In a study by Kim et al, VAS scores were lower in the midazolam group, but this was not found to be statistically significant.<sup>8</sup> We observed the sedation scores between the two groups at various time intervals to be comparable. The sedative effect peaked at 30 minutes, and none of the patients had a sedation score above 2. No clinically significant sedation was recorded postoperatively in either of the groups. In a study by Adam et al, the addition of midazolam to intrathecal bupivacaine was associated with sedation and tranquility.<sup>9</sup>

The paucity of studies on intrathecal midazolam warrants caution in elderly patients, the obese, and those who are already on other sedative medication. When intrathecal midazolam is used, all patients should be closely monitored intra- and postoperatively. The findings of this study are consistent with those of earlier reported studies by Bharti et al<sup>10</sup> and Batra et al,<sup>11</sup> who found that the duration of sensory blockade was significantly prolonged after the addition of midazolam to intrathecal bupivacaine. The addition of intrathecal midazolam did not significantly alter the peak level of sensory blockade that was achieved after the onset of spinal anaesthesia. This is considered a significant finding regarding the safety aspects of the combination of these two drugs, and is consistent with other studies done earlier in this regard.<sup>12</sup>

The duration of motor blockade was comparable in both groups in this study. There is a paucity of and variation in the literature reports with respect to the duration of the motor blockade. Many earlier studies did not find an increased duration of motor blockade after the addition of midazolam to intrathecal bupivacaine.<sup>7,8,11,13</sup> Further studies on larger samples are needed to evaluate and confirm this finding. The present study is consistent with other studies conducted by Goodchild et al<sup>6</sup> and Batra et al,<sup>11</sup> who found

no added haemodynamic changes, such as hypotension and bradycardia, or shivering, respiratory depression, desaturation, pruritus, urinary retention, nausea or vomiting from the baseline when intrathecal midazolam was added to intrathecal bupivacaine.<sup>7, 10,11,14,15</sup> The addition of 2 mg midazolam to intrathecal bupivacaine causes no significant haemodynamic disturbances, and is relatively free from common side-effects.

Erdine et al conducted neurotoxicologic studies in animals by studying histologic and vascular lesions in animal spinal cord samples, indicating the neurotoxic effects of intrathecal midazolam. Therefore, they advised against the use of intrathecal midazolam in humans.<sup>16</sup> Subsequent studies in humans, by Tucker et al,<sup>9</sup> Valentine et al<sup>17</sup> and Anjana et al,<sup>14</sup> found no adverse neurological symptoms in those who had received intrathecal midazolam. In agreement with these studies, the present study observed no significant adverse neurological effects in any patient during the study period.

## Conclusion

The addition of preservative-free midazolam 2 mg to intrathecal 0.5% hyperbaric bupivacaine prolongs the duration of analgesia, without any adverse effects in patients undergoing knee arthroscopies.

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