Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomised case control study

Shadangi B K, Garg R, Pandey R, Das T

ABSTRACT

Introduction: Subarachnoid block with local anaesthetics and adjuvants has been extensively used for surgery. Intrathecal midazolam produces antinociception and potentiates the effect of local anaesthetics. We compared intrathecal bupivacaine with and without midazolam to assess its effect on the duration of sensory block, motor block and pain relief.

Methods: A total of 100 patients scheduled for elective lower abdominal, lower limb and gynaecological procedures were selected to participate in this prospective, randomised, double-blind study. Patients were randomly allocated into two groups for intrathecal drug administration. Group B received 3 mL 0.5 percent bupivacaine with 0.4 mL saline, and group BM received 3 mL 0.5 percent bupivacaine and 0.4 mL (2 mg) midazolam mixture. The onset, duration of sensory/motor block, time to first rescue analgesia and side effects were noted.

Results: Demographic profile and duration of surgery were comparable between the two groups. The onset of sensory (4.8 versus 4.6 min) and motor block (5.9 versus 6 min) was also comparable between the groups. The duration of sensory blockade was prolonged in the midazolam group (90.8 versus 115.8 min, p-value is 0.001), while the duration of motor blockade was comparable (151.8 versus 151.3 min, p-value is 0.51). The duration of effective analgesia was significantly longer in the midazolam group compared to the control group (121.3 versus 221.1 min, p-value is 0.001). Sedation score was comparable in the two groups.

Conclusion: The addition of preservative-free midazolam to bupivacaine intrathecally resulted in prolonged postoperative analgesia without increasing motor block.

Department of Anaesthesiology, All India Institute of Medical Scences, Ansari Nagar, New Delhi 110029, India

Shadangi BK, MD
Ex-Senior Resident

Garg R, MD, DNB
Ex-Senior Resident

Pandey R, MD
Associate Professor

Department of Anaesthesiology, SCB Medical College and Hospital, Cuttack 753007, Orissa, India

Das T, MD
Associate Professor

Correspondence to:
Dr Bijaya Kumar Shadangi
Tel: (91) 11 98103 94950
Fax: (91) 11 2654 4861
Email: drrgarg@hotmail.com

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INTRODUCTION

Spinal anaesthesia with local anaesthetics has been extensively used for lower abdominal and lower limb surgeries. Various intrathecal adjuvants such as opioids, ketamine, clonidine and neostigmine are often added to enhance the duration of spinal anaesthesia.[1-4] However, their use is limited due to adverse effects such as pruritis, urinary retention, respiratory depression, haemodynamic instability, nystagmus, severe nausea and vomiting.[3-5] Midazolam is known to produce antinociception and potentiate the effect of local anaesthetic when given in neuraxial block, without having significant side effects. We compared intrathecal midazolam plus bupivacaine with bupivacaine alone in order to assess their effect on the duration of sensory block and to correlate it with the duration of postoperative pain relief in patients undergoing lower abdominal or lower limb surgeries.

METHODS

After obtaining approval from the institutional ethical committee and written informed consent, 100 American Society of Anesthesiologists (ASA) physical status I/II patients aged 18–60 years who were scheduled for elective lower abdominal, lower limb or gynaecological procedures were selected to participate in this prospective, randomised, double-blind case control study. Patients with contraindications to regional anaesthesia, or sensitivity to study drugs and who were on chronic analgesic therapy were excluded from the study. Patients were premedicated with oral diazepam (0.3 mg/kg) and ranitidine (3 mg/kg) the night before surgery. In the operating room, standard monitors (electrocardiogram, non-invasive blood pressure and pulse oximeter) were attached to the patient, and baseline vitals were recorded. An 18G intravenous line was secured and preloaded with Ringer's lactate 10 mL/kg. Patients were randomly allocated into two groups in a double-blinded manner using a sealed envelope. Group B (n = 50) patients

Table I. Demographic profiles of the two groups.

Demographic	Mean ± SD		p-value
	Group B (n = 50)	Group BM (n = 50)	
Age (yrs)	36.4 ± 8.4	36.8 ± 9.5	0.824
Gender (M:F)	28:22	22:28	0.230
Weight (kg)	61.7 ± 8.9	60.3 ± 7.3	0.392
Duration of surgery (min)	56.3 ± 20.8	52.9 ± 18.2	0.386

SD: standard deviation; M: male; F: female

Table II. Nature of surgeries in the two groups.

Nature of surgery	No. of patients	
	Group B (n = 50)	Group BM (n = 50)
Lower abdominal	22	21
Gynaecological	11	12
Orthopaedics	17	17

received 3 mL 0.5% bupivacaine (heavy) with 0.4 mL saline, while group BM (n = 50) received 3 mL 0.5% bupivacaine (heavy) and 0.4 mL (2 mg) midazolam (5 mg/mL, preservative-free) mixture. Patients and treating anaesthesiologists were blinded to the test drug.

The drugs were administered intrathecally in lateral position in L3–4 or L4–5 space with a 25-gauze spinal needle. The study solution, prepared by another researcher who was not involved in the patient's care, was injected through the spinal needle over a period of ten seconds with no barbotage. After injecting the drug, the patient was turned to supine position, and the onset time (defined as the time interval between the completion of intrathecal drug injection to the onset of complete loss of pinprick sensation at T8), level of sensory block (defined as the highest dermatomal level of sensory blockade by pinprick testing), time to achieve maximum sensory block level, duration of sensory block (defined as the time interval from completion of intrathecal drug injection and 2-segment regression of sensory block by pinprick method), duration of motor block (defined as the time taken from onset of complete motor block, score 3 to complete recovery of motor block, score 0) and time for rescue analgesia (defined as the time interval between administration of intrathecal drug to the time of administration of first rescue analgesia) were noted.

Pain was assessed using the Visual Analogue Score (VAS) (0: no pain, 10: maximum pain). Pulse rate and blood pressure were monitored every five minutes intraoperatively and every ten minutes subsequently till 2-segment regression of block. Hypotension (> 20% decrease in systolic blood pressure from baseline) was managed with intravenous fluid (20 mL/kg) initially and then with mephenteramine 3 mg in incremental boluses. Adverse effects such as nausea, vomiting, sedation, pruritis and urinary retention were recorded. Intraoperative rescue analgesia was administered with fentanyl (1 μg/kg) intravenously, when required. If the pain was not relieved, the patient was given general anaesthesia and excluded from the study. Postoperatively, rescue analgesic medication with diclofenac sodium (1.5 mg/kg) was administered intramuscularly, if VAS was found to be ≥ 4.

The level of sensory anaesthesia was recorded at two-minute intervals for 15 minutes after completion of intrathecal injection, and every ten minutes thereafter. A dermatomal sensory block up to T10 was considered adequate for surgery. The maximum height of the sensory blockade was noted at 20 minutes. Motor block was assessed by the Bromage score (0: no motor loss, 1: inability to flex the hip, 2: inability to flex the knee joint, 3: inability to flex the ankle) at one-minute intervals until complete motor blockade occurred. Onset of motor block was defined as time taken from injection of drug to development of complete motor block (Bromage score 3). The level of sedation of the patients was assessed by the Ramsay sedation score (1: anxious, agitated and restlessness, 2: oriented and cooperative, 3: responds to command only, 4: brisk response to loud voice and light glabellar tap, 5: sluggish to no response to light glabellar tap or loud auditory stimulus, 6: no response even to pain). All patients were followed up after surgery for up to 24 hours for any behavioural side effects, confusion, dizziness, nystagmus, nausea, vomiting or any neurological complications like pain or numbness in the leg, incontinence, retention of urine or genital dysaesthesias. The sample size was based on first rescue analgesia requirement and a power of 90% and alpha 0.05.[6] Interval data was expressed as mean and standard deviation. Student's *t*-test was used for comparing the two groups, while the chi-square test was used to analyse categorical data. Data was analysed using the Minitab Statistical Software version 13 for PC (XT) (Minitab®, State College, PA, USA). A p-value < 0.05 was considered to be statistically significant.

RESULTS

The two study groups were comparable with respect to age, weight, gender, ASA physical status and duration of surgery (Table I). Both groups involved similar types of surgical procedures (Table II). All patients had successful spinal anaesthesia, and none required general anaesthesia. The onset of sensory and motor block as

Table III. Study parameters in the two groups.

Parameter (min)	Mean ± SD; range		p-value
	Group B (n = 50)	Group BM (n = 50)	
Onset of sensory block	4.8 ± 0.6; 4–6	4.6 ± 0.7; 3–6	0.13
Onset of motor blockade	5.9 ± 0.4; 4–7	6.0 ± 0.8; 3–8	0.126
Duration of sensory blockade: 2-segment regression	90.8 ± 4.1; 85–98	115.8 ± 8.1; 100–140	0.001
Duration of motor blockade	151.8 ± 4.4; 142–162	151.3 ± 3.2; 144–158	0.51
First rescue analgesia	121.3 ± 5.4; 110–135	221.1 ± 15.6; 195–255	0.001
Ramsay sedation score*	2; 1–3	3; 1–4	0.08

* Data for Ramsay sedation score shows median; range.
SD: standard deviation

well as maximum sensory block level were comparable between the two groups (Table III). The duration of sensory blockade, as assessed by 2-segment regression, was prolonged in the midazolam group, while the duration of motor blockade was comparable between the two groups. No patient required intraoperative analgesia (fentanyl). The duration of effective analgesia was significantly longer in the midazolam group compared to the control group. Sedation score, mean arterial pressure and heart rate were comparable in the two groups. Respiratory rate and oxygen saturation did not differ between the groups. No significant differences in the incidence of adverse effects were observed between the groups (p = 0.09) (Table IV), and no neurological deficit was observed in any patient receiving midazolam.

Table IV. Complications/adverse effects in the two groups.

Complication	No. (%)	
	Group B (n = 50)	Group BM (n = 50)
Bradycardia	4 (8)	6 (12)
Drowsiness	0 (0)	2 (4)
Hypotension	6 (12)	9 (18)
Nausea and vomiting	2 (4)	3 (6)
Total	12 (24)*	20 (40)*

* p = 0.09

DISCUSSION

Intrathecal midazolam has been shown to have analgesic properties and potentiates the effects of intrathecal local anaesthetics.[7] The mechanism by which midazolam provides analgesia has been explored in several recent studies,[7-11] some of which suggest that intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal delta receptors.[12] Therefore, adding intrathecal midazolam may potentiate the antinociceptive effect of morphine-like agents.[8]

In a cohort study, Tucker et al evaluated 574 patients who received intrathecal midazolam and observed the patients for one month for a wide range of symptoms related to neurotoxicity. They concluded that the administration of up to 2 mg intrathecal midazolam did not increase the occurrence of neurological symptoms.[13] We used 2 mg midazolam as an additive to bupivacaine for intrathecal administration, as most studies agree that 1–2 mg intrathecal midazolam is safe and efficacious.[10,14] Intrathecal midazolam 2 mg provided a moderate prolongation of postoperative analgesia as compared to 1 mg midazolam when used as an adjunct to bupivacaine in patients undergoing caesarean delivery.[6]

Bharti et al, however, found that the postoperative pain scores were lower in patients who received intrathecal midazolam (1 mg) along with bupivacaine.[11] Kim and Lee[10] as well as Prakash at al[6] administered intrathecal bupivacaine along with midazolam in either 1-mg or 2-mg doses. The latter observed that the duration of postoperative analgesia was significantly prolonged with the addition of intrathecal midazolam and that the effect was dose-dependent.[6] The duration of sensory blockade in our study, as assessed by 2-segment regression, was prolonged in the midazolam group, which is comparable to the results of previously reported studies.[6,11] Our results, however, contrasted with those of earlier studies, which found the duration of motor blockade to be prolonged in the midazolam group compared with the control group.[10,11]

In an study of subarachnoid block with intrathecal bupivacaine (2 mL) with 2 mg midazolam for caesarean section, Prakash et al found that the mean duration of postoperative analgesia was 3.8 ± 0.5 hours in the group of patients administered bupivacaine alone as compared to 6.1 ± 1.0 hours in the midazolam group.[6] In our study, time to block regression was longer in the midazolam group (182 ± 30 min) compared to the bupivacaine group

(126 ± 20 min), but onset of block was comparable in the two groups (7.2 ± 1.9 min in bupivacaine group vs. 7.6 ± 1.9 min in midazolam group). Similar to our findings, no significant difference in sedation levels has been reported in the intrathecal midazolam group as compared to the control group without intrathecal midazolam.[11] Although 1 mg and 2 mg intrathecal midazolam has been reported to decrease postoperative nausea and vomiting,[6] our study found no difference in the two groups.

There are limitations to this study. Firstly, our study was not adequately powered to comment conclusively on the side effects in the two groups; a larger study that is adequately powered to study the side effect profile of intrathecal midazolam is required. Secondly, different types of surgical procedures were selected in our study; however, as the cases were randomly distributed and the types of surgery in the two groups were comparable, bias due to differences in surgical procedure was prevented. In conclusion, the addition of preservative-free midazolam to bupivacaine in spinal anaesthesia resulted in prolonged postoperative analgesia without an increase in the duration of motor block.

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