

The effect of intrathecal midazolam on the characteristics of bupivacaine spinal block and postoperative analgesia in gynaecological procedures

Sidiq S, MD, Senior Resident; Waheed A, MD, Senior Resident
Department of Anaesthesiology, Sher-i-Kashmir Institute of Medical Sciences, India
Correspondence to: Arfat Waheed, e-mail: arafatahraf01@gmail.com
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Abstract

Objectives: The present study was undertaken to determine the onset of sensory block, the time to achieve the maximum level of sensory block and the analgesic efficacy of intrathecal midazolam when given in combination with bupivacaine, and also to observe any undesirable side-effects produced by the midazolam-bupivacaine combination.

Setting and subjects: One hundred patients [American Society of Anesthesiologists (ASA) I and ASA II] aged 45-60 years and posted for elective gynaecological surgery, were randomly allocated to two groups of equal size. Group 1 (n = 50) received 12.5 mg of 0.5% hyperbaric bupivacaine with 0.4 ml of normal saline in the L3-L4 interspace, while Group 2 (n = 50) received 12.5 mg (2.5 ml) of 0.5% hyperbaric bupivacaine with 0.4 ml (2 mg) of preservative-free midazolam. Standard monitoring of haemodynamic parameters was recorded throughout the procedure.

Outcome measures: The onset of sensory block, the time to achieve maximum sensory block and the level of block were also chronicled. The sedation scores were noted every two minutes for 20 minutes and then every 10 minutes until the end of surgery. Pain assessment was carried out according to the visual analogue scale (VAS) score. The duration of the pain-free period up to rescue analgesia, or a VAS score greater than 40 mm, was documented. Unwanted side-effects were also recorded.

Results: There was no significant difference in the demographic distribution of the patients. There was no statistically significant difference in the onset of the sensory block (p-value = 0.735) and time to achieve maximum level of sensory block in both groups (p-value = 0.45). The sedation score was comparable in both groups. There was a significantly higher duration of pain-free period in Group 2 (274.9 ± 18.07 minutes) than in Group 1 (187.2 ± 16.8 minutes) (p-value < 0.05). The number of rescue medications that were required was also significantly lower in the study group than in the controls. The number of patients who developed bradycardia and hypotension was comparable.

Conclusion: The addition of midazolam to intrathecal bupivacaine prolonged the duration of postoperative analgesia in this study, without affecting the onset of block and without increasing the risk of side-effects.

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Introduction

Postoperative pain relief can improve functionality, reduce physiological and emotional morbidity and improve quality of life.¹ Neuraxial blocks not only reduce the incidence of venous thrombosis, pulmonary embolism, cardiac complications, bleeding, transfusion requirements and respiratory depression, but also provide effective postoperative analgesia.² One of the methods of providing postoperative analgesia is to prolong the duration of

intrathecally administered bupivacaine using additives such as opioids, clonidine and ketamine.³ The discovery of benzodiazepine receptors in the spinal cord triggered the use of intrathecal midazolam.⁴ Intrathecal administration of midazolam produces antinociceptive effects in rats and humans.⁵ γ -aminobutyric acid A (GABA_A) receptors in the spinal cord have been reported to be involved in nociceptive mechanisms.⁶ To date, following the intrathecal or epidural administration of midazolam to human beings, no adverse or

irreversible effects have been observed.⁷ The present study was undertaken to evaluate the additive analgesic effects of intrathecal midazolam in combination with bupivacaine in gynaecological procedures and to compare the results with the use of bupivacaine alone.

Materials and method

After approval was granted by the institutional ethical committee, written informed consent was obtained from the patients for participation in this study. One hundred patients [American Society of Anesthesiologists (ASA) I and ASA II] aged 45–60 years and posted for elective gynaecological procedures (vaginal hysterectomy and anterior and posterior colpoproctography), were enrolled in this double-blinded, randomised study. The patients were evaluated. Those with contraindications to regional anaesthesia were excluded from the study. A visual analogue scale (VAS), consisting of a 100 mm-long line, with “0 mm” representing no pain and “100 mm” the worst possible pain, was explained to the patients at the preoperative visit.

The patients were randomly allocated to two equal groups of 50 patients each:

- Group 1 (n = 50): received 12.5 mg (2.5 ml) of 0.5% hyperbaric bupivacaine with 0.4 ml of normal saline.
- Group 2 (n = 50): received 12.5 mg (2.5 ml) of 0.5% hyperbaric bupivacaine with 0.4 ml (2 mg) of preservative-free midazolam (5 mg/ml).

In the operating room, each patient was preloaded with Ringer's lactate 15 ml/kg, before the induction of spinal anaesthesia. Baseline heart rate, noninvasive blood pressure, respiratory rate, arterial oxygen saturation (SPO₂) and the electrocardiogram results were recorded before the induction of spinal anaesthesia, and thereafter during the procedure. Spinal anaesthesia was performed in the lateral position, using a 25G Quincke needle at the L3–L4 interspace and the patients were positioned supine for surgery. The onset of sensory block by loss of sensation to a pinprick was noted. The anaesthesiologist and the researchers who mixed the medications and performed the subarachnoid block were not involved in the assessment of the patients. Observers were also blinded. Time to achieve maximum sensory block and the level of block were also documented. Surgery was started following confirmation of spinal block.

The sedation score, as detailed below, was recorded every two minutes for 20 minutes, and thereafter every 10 minutes until the end of surgery.

The sedation score⁸ that was used was:

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

Intraoperatively, any discomfort experienced by the patient in the form of sweating, nausea and vomiting, were recorded, as well as any significant alterations in vital signs.

Postoperatively, the VAS score was logged half-hourly for six hours. The duration of postoperative analgesia, defined as the time taken in the postoperative period for the patient to demand analgesia, or when the VAS score was ≥ 40 mm, was noted. Rescue analgesia was provided by diclofenac sodium 75 mg intramuscularly for the first 24 hours. The duration of the pain-free period, from the completion of spinal injection to the time of rescue analgesia administration or a VAS score greater than 40 mm, was recorded in both groups.

The obtained results were subjected to statistical analysis. A two-sample independent t-test was used. A p-value of < 0.05 was taken to be significant.

Results

There were no significant differences with respect to age, body weight, height, duration of surgery and ASA status (Table I).

There was no statistical difference in the onset of sensory block (p-value > 0.05), and the time to achieve maximum level of sensory block (p-value > 0.05), between the two groups.

However, there was a significant difference in the duration of the pain-free period, as substantiated by the VAS score. The duration of the pain-free period in Group 1 was 187 ± 16.8 minutes, while in Group 2 it was 274.94 ± 18.07 minutes (p-value < 0.05). The VAS at first medication for rescue analgesia was comparable between the two groups (p-value > 0.05), although the mean VAS in the first six hours was significantly lower in Group 2 (p-value < 0.05). The number of rescue medications in the form of injected diclofenac was also significantly lower in Group 2 than in Group 1 (see Table II).

Six patients (12%) in Group 1 developed bradycardia (heart rate < 60), while seven patients (14%) with bradycardia were observed in Group 2. Hypotension was observed in 18 patients (36%) and 17 patients (34%) in Groups 1 and 2 respectively. There was no significant difference between the two groups in terms of an alteration in vital signs or the side-effects profile (Table III). The sedation score was comparable in both groups.

Discussion

Benzodiazepine receptors have been demonstrated in humans. They are found throughout the central nervous system, including the spinal cord, and also in many other tissues, e.g. the kidney, liver and lungs.⁹ Benzodiazepines

Table I: Demographic distribution and duration of surgery of the studied patients

Description	Group 1	Group 2	p-value
Age	51 ± 4.75	50.2 ± 3.5	0.341
Body weight	49.92 ± 8	51.96 ± 3.45	0.123
Height	148 ± 5.56	149.82 ± 5.5	0.104
Duration of surgery (minutes)	90 ± 10.6	93.36 ± 9.71	0.103
American Society of Anesthesiologists I and II	27/23	25/25	

Table II: Characteristics of the spinal blockade

	Group 1	Group 2	p-value
Onset of sensory block (minutes)	3.4 ± 0.94	3.53 ± 0.93	> 0.05
Time to achieve maximum block (T6-T8) (minutes)	8.91 ± 1.5	9.41 ± 1.67	> 0.05
Duration of pain-free period (minutes)	187 ± 16.8	274.94 ± 18.07	< 0.05
Visual analogue score at first medication (mm)	35 ± 8.4	36 ± 9.1	> 0.05
Mean visual analogue score in first 6 hours (mm)	38 ± 9	33 ± 9	< 0.05
Number of diclofenac injections required in 24 hours	2.89 ± 0.60	1.93 ± 0.63	< 0.05

Table III: Comparison of side-effects in the two groups (%)

	Group 1	Group 2	p-value
Patients developing bradycardia	12	14	> 0.05
Patients developing hypotension	18	17	> 0.05
Sedation	6	6	> 0.05
Nausea and vomiting	1	1	> 0.05

produce their sedative, hypnotic, anxiolytic anticonvulsant and antinociceptive effects by interaction with GABA_A receptors.¹⁰ GABA_A receptors in the spinal cord have been reported to be involved in nociceptive mechanisms.⁶ These are found in their highest concentration in lamina II or the dorsal horn ganglia.¹¹ The safety of neuraxial administration of midazolam in humans has been demonstrated by several studies.^{7,12,13} Besides causing analgesia, intrathecal midazolam has also been found to be effective in suppressing the reflex response to visceral pain in Caesarean sections in humans.¹³ A total of 2 mg midazolam intrathecally has been found to be the optimum dose for use in relieving pain without causing any side-effects.^{7,13,14} Bupivacaine, a potent, long-acting amide local anaesthetic,¹⁵ blocks the generation, propagation and oscillation of electrical impulses in the peripheral and central nervous system. The sodium channel is a key target of local anaesthetic activity.¹⁶ Bupivacaine blocks sodium currents and rapidly inactivates potassium currents in the neurons of the spinal dorsal horn.¹⁷

In our study, there was no significant difference in the onset of sensory block between the two groups (Group 1: 3.4 ± 0.94 minutes, and Group 2: 3.53 ± 0.93 minutes, p-value > 0.05). Similarly, there was no difference between the time of onset of maximum sensory block (T6-T8). Our results were similar to those of Yegin et al¹⁸ who studied 44 patients using a bupivacaine-midazolam combination and bupivacaine alone for analgesic and sedative effects. No statistical

difference in the onset of sensory block between the two groups was found. We observed the duration of the pain-free period in Group 1 to be 187 ± 16.8 minutes, while in Group 2 it was 274.94 ± 18.07 minutes. When compared statistically, the values were found to be statistically significant (p-value < 0.05). The VAS score in Group 1 was significantly higher than that in Group 2. Kim and Lee,¹⁹ as well as Prakash et al,²⁰ administered intrathecal bupivacaine, together with midazolam, in either 1 or 2 mg doses, and observed that the duration of postoperative analgesia was significantly prolonged with the addition of intrathecal midazolam, and that the effect was dose-dependent.

In the present study, no significant difference was observed in side-effects such as headaches, nausea, vomiting, hypotension and bradycardia between the two groups (Table III). The incidence of sedation in both groups was comparable. There was no difference in the sedation score between the groups. Doses of 1 and 2 mg intrathecal midazolam have been reported to decrease postoperative nausea and vomiting,²⁰ but our study found no difference between the two groups. Our results are similar to those of Valentine et al¹³ who compared intrathecal bupivacaine, bupivacaine-midazolam and bupivacaine-dimorphine, and found no side-effects attributable to midazolam. None of the patients had neurotoxicity. Tucker et al²¹ evaluated patients who received intrathecal midazolam and observed the patients for neurotoxicity in a cohort study. They concluded that the administration of 2 mg intrathecal midazolam did not increase the occurrence of neurological symptoms.

There were limitations to our study as we concentrated mainly on the analgesic efficacy of the bupivacaine-midazolam combination, and did not compare the efficacy of the motor block in the two groups.

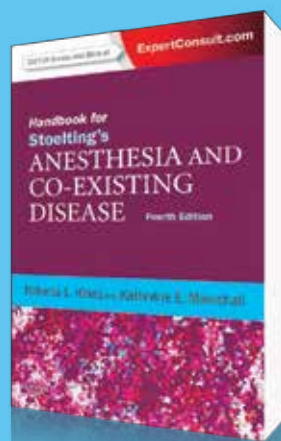
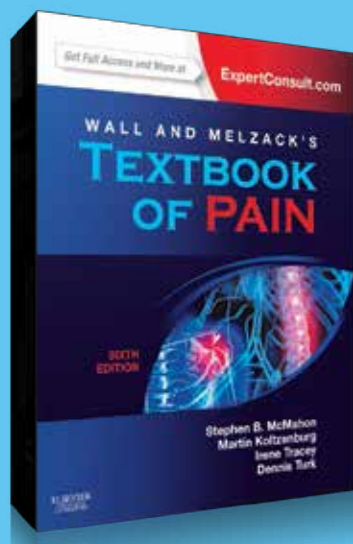
In conclusion, the addition of midazolam to intrathecal bupivacaine prolonged the duration of postoperative analgesia in this study, without affecting the onset of block and without increasing the risk of side-effects.

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