# Intrathecal Midazolam for Postoperative Analgesia in Adults

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## ABSTRACT

**Introduction:** Midazolam produces an analgesic action through the benzodiazepine/γ-aminobutyric acid $(GABA)_A$ receptor complex in the spinal cord. We conducted this study to evaluate postoperative analgesic effects and associated complications of intrathecal midazolam in patients undergoing perineal surgery.

**Material and methods:** 30 subjects belonging to ASA grade I and II scheduled to undergo elective perineal surgery under spinal anaesthesia were randomly allocated to either Group A- 1 ml of 0.5% heavy bupivacaine+saline or Group B- - 1 ml of 0.5% heavy bupivacaine+preservative free midazolam. The duration of postoperative analgesia, postoperative visual analogue scores for pain, and perioperative side effects were noted.

**Results:** The basic demographic characteristics were similar between the two groups. The mean duration of surgery was 22.33 ± 14.96 in group A, and it was 16.8 ± 12.55 in group B. The mean time to first pain medication was 4.93 ± 3.32 hours in group A, and it was 8.63 ± 6.17 in group B. The mean VAS at first pain medication was 40.00 ± 00 mm, and it was 40.00 ± 00 mm in group B. the mean difference in the postoperative analgesia between group was statistically significant (P value <0.02). Hemodynamic parameters did not differ between the groups. The complications included urinary retention among 5 (33.33%) in group A and 6 (40.00%) in group B.

**Conclusion:** The addition of preservative-free midazolam to bupivacaine intrathecally resulted in prolonged postoperative analgesia without any significant side effects.


**Keywords:** Midazolam, Bupivacaine, Analgesia, Intrathecal

## INTRODUCTION

Midazolam, synthesised by Walsar and colleagues in 1976, was the first clinically used water-soluble benzodiazepine, it is also the first benzodiazepine that was produced primarily for use in anaesthesia.[1,2] Midazolam exerts its effect by occupying benzodiazepine receptor that modulates γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. The hypnotic effects of benzodiazepine are mediated by alterations in the potential dependent calcium ion flux. Hypnotic, sedative, amnesic, and anticonvulsant effects are mediated by α1 GABA receptors and anxiolysis and centrally acting muscle relaxant properties are mediated by α2 GABA receptors.[3-5]

By administrating intrathecal combinations of drugs, targeting different spinal cord receptors; prolonged and superior quality analgesia can be achieved by relatively small concentrations of individual drugs. The dose reductions may avoid drug-related side effects. In addition, the simultaneous targeting of several different receptor sites in the spinal cord may lead to improved pain relief.[6] Midazolam is known to produce antinociception and potentiate the effect of local anaesthetic when given in neuraxial block, without having significant side effects.[7] Intrathecal midazolam also causes the release of an endogenous opioid, acting at spinal delta receptor.[8]

There has been growing emphasis on the advantages of combined pharmacological approach for pain relief. Discovery of analgesic effects of spinally administered opioids and other drugs such as benzodiazepines and alpha-2 adrenoreceptor agonists has opened the possibilities of optimising on useful drug interactions at the level of spinal cord in the management of pain.[9-11]

This study was conducted to evaluate postoperative analgesic effects and associated complications of intrathecal midazolam and bupivacaine in patients undergoing perineal surgery.

## MATERIAL AND METHODS

The current study was conducted in the Department of anaesthesiology, Civil Hospital, Aizawl during the period July 2017 to June 2018. A total of thirty adult patients belonging to ASA grade I and II scheduled to undergo elective perineal surgery under spinal anaesthesia were selected for the study. After obtaining approval from the Hospital Ethical Committee and written informed consent, patients were randomly allocated to two groups of fifteen in each group. Group A patients received 1 ml of 0.5% heavy bupivacaine and 0.4 ml of 0.9% saline intrathecally while Group B received 1 ml of 0.5% heavy bupivacaine and 0.4 ml (2mg) of preservative-free midazolam intrathecally.

The pre-anaesthetic evaluation was done for all the patients. Age, sex, weight, height, pre-anaesthetic medication, arterial blood pressure, heart rate, respiratory rate and haemoglobin oxygen saturation ($SPO_2$) were documented. All the patients were premedicated with oral diazepam 0.2 mg $kg^{-1}$ and ranitidine 150 mg the night before surgery.

Immediately after preload and under aseptic precautions, a lumbar puncture was performed with 24-gauge spinal needle at $L_{3-4}$ interspace in the sitting position (Plate – VIII and IX). After the free flow of cerebrospinal fluid was

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obtained, patients were randomly assigned to receive either 1 ml of 0.5% heavy bupivacaine plus 0.4 ml of 0.9% saline intrathecally (Group A), or 1 ml of 0.5% heavy bupivacaine plus 0.4 ml(2mg) of midazolam intrathecally (Group B) (Plate – X). The time of intrathecal injection of these drugs was noted. Once the needle was withdrawn each patient was kept in the sitting position for 5 minutes, tested for sensory loss and then placed in the lithotomy position for surgery.

Electrocardiogram, heart rate, non-invasive arterial blood pressure, respiratory rate and $SPO_2$ of each patient were recorded every 5 minutes for the first 20 minutes, and at 15 minutes interval during surgery and then every 1 hour after surgery till patients demand rescue analgesia. Any adverse event or complication was also recorded.

Injection ephedrine and injection atropine were kept ready for administration to ant patient with fall of systolic arterial pressure by more than 20% below the preoperative value and bradycardia (Heart rate < 60 beats min) respectively.

The anaesthetics performing intraoperative, postoperative assessment and recording the time of rescue analgesia was blinded to the solution administered intrathecally. Duration of pain relief in Group A and B were obtained from the completion of spinal injection to time of rescue analgesic administration. Visual analogue scale (VAS) at first analgesia has also been recorded during the study period. Statistical analysis of the data between the two group was performed by student's 't' test and chi-square/Fisher's exact test for numeric and categorical data respectively. A p value of < 0.05 was considered to be highly significant.

## RESULTS

There was no difference with respect to age, gender, type of surgery and ASA status between the groups (Table 1). The mean duration of surgery was 22.33 ± 14.96 in group A, and it was 16.8 ± 12.55 in group B. Among the group A, 10 (66.66%) had 0-5 hours' pain at operative site after surgery, 4 (26.66%) had 6-10 hours' pain at operative site after surgery and 1 (6.66%) had 6-10 hours' pain at operative site after surgery. Among the group A, 1 (6.66%) had 0-5 hours' pain at operative site after surgery, 11 (73.33%) had 6-10 hours' pain at operative site after surgery, and 3 (20%) had 6-10 hours' pain at operative site after surgery. The difference in the proportion of time to first localisation of pain at operative site after surgery between group was statistically not significant (P value 7.72). The mean time to first pain medication was 4.93 ± 3.32 hours in group A, and it was 8.63 ± 6.17 in group B. The mean VAS at first pain medication

| Parameter | Group | | P value |
|---|---|---|---|
| | Group A | Group B | |
| Age | | | |
| 20-30 | 5 (33.33%) | 9 (60.00%) | 0.249 |
| 31-40 | 7 (46.66%) | 2 (13.33%) | |
| 41-50 | 2 (13.33%) | 3 (20.00%) | |
| 51-60 | 1 (6.66%) | 1 (6.66%) | |
| Gender | | | |
| Male | 12 (80.00%) | 11 (73.33%) | 1.00 |
| Female | 3 (20.00%) | 4 (26.66%) | |
| ASA Status | | | |
| ASA- I | 13 (86.66%) | 13 (86.66%) | 1.00 |
| ASA- II | 2 (13.33%) | 2 (13.33%) | |
| Name of operation | | | |
| Fistulectomy | 13 (86.66%) | 10 (66.66%) | ** |
| Haemorrhoidectomy | 1 (6.66%) | 3 (20.00%) | |
| Sphincterotomy | 0 (0.00%) | 2 (13.33%) | |
| Fistulectomy & Haemorrhoidectomy | 1 (6.66%) | 0 (0.00%) | |
| Duration of surgery | 22.33 ± 14.96 | 16.8 ± 12.55 | 0.282 |
| **No statistical test was performed due to 0 subjects in cells | | | |

**Table-1:** Demographic characteristics and ASA Status of the patients in the group- A and group- B

| Time (hour) to the first localisation of pain at the operative | Group | | P value |
|---|---|---|---|
| | Group A | Group B | |
| 0-5 hours | 10 (66.66%) | 1 (6.66%) | 7.72 |
| 6-10 hours | 4 (26.66%) | 11 (73.33%) | |
| 11-15 hours | 1 (6.66%) | 3 (20%) | |
| Postoperative analgesia | Group | | P value |
| | Group A | Group B | |
| Time to first pain medication (hours) | 4.93 ± 3.32 | 8.63 ± 6.17 | <0.02 |
| VAS at first pain medication (mm) | 40.00 ± 00 | 40.00 ± 00 | |

**Table-2:** No of patients and time of the first localisation of pain at operative site after surgery and Postoperative analgesia in group A and group B

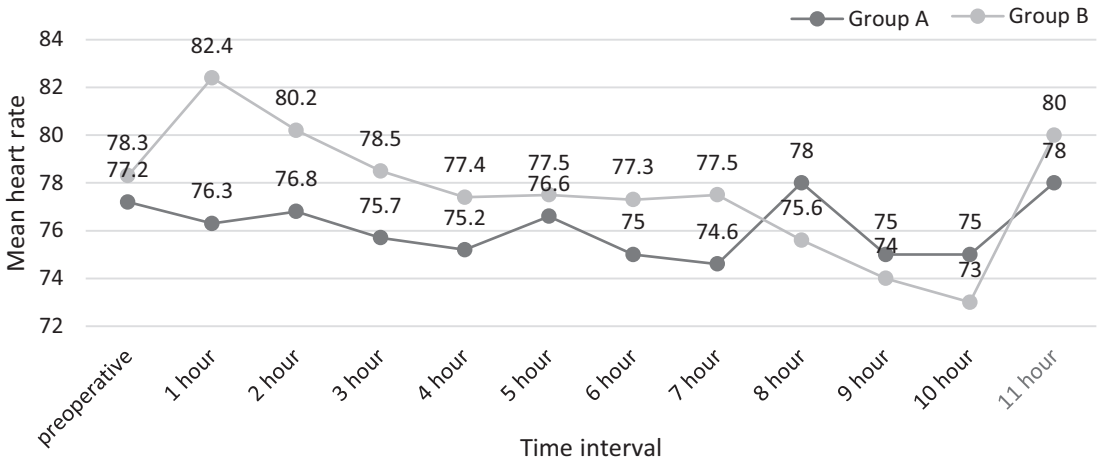


**Figure-1(a):** Trend line diagram for mean changes in heart rate (per min) in the postoperative period in group A and group B

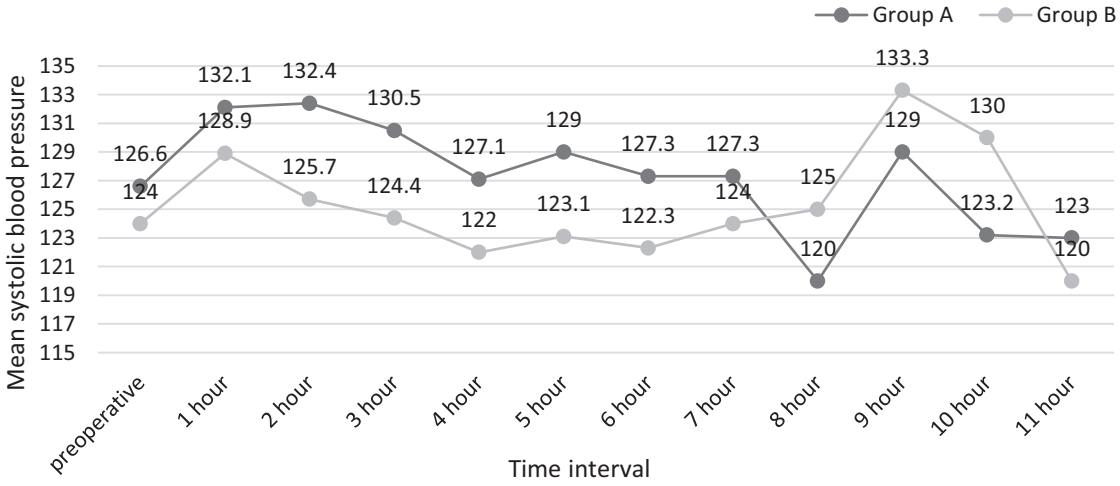


**Figure-1(b):** Trend line diagram for mean changes in systolic blood pressure (mm Hg) in the postoperative period in group A and group B

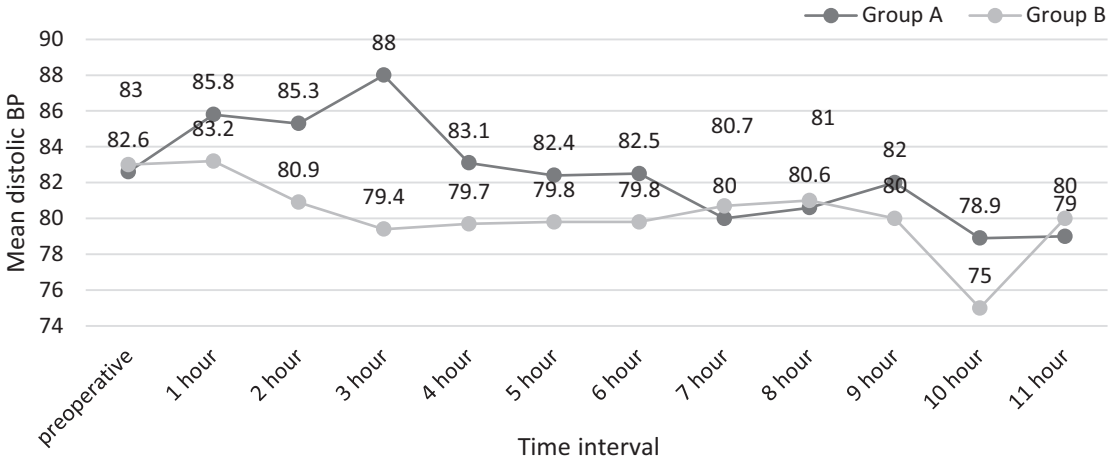


**Figure-1(c):** Trend line diagram for mean changes in diastolic blood pressure (mm Hg) in the postoperative period in group A and group B

was 40.00 ± 00 mm, and it was 40.00 ± 00 mm in group B. The mean difference in the postoperative analgesia between group was statistically significant (P value <0.02) (Table 2). The hemodynamic parameters were similar between the study groups (Figure 1(a)-(e)). The complications included urinary retention among 5 (33.33%) in group A and 6 (40.00%) in the group B. (Table 3)

## DISCUSSION

Midazolam produces an analgesic action through the benzodiazepine/γ-aminobutyric acid $(GABA)_A$ receptor complex in the spinal cord.[12] The administration of a combination of drugs intrathecally targets different spinal receptors resulting in the prolonged and superior quality of analgesia.[13]

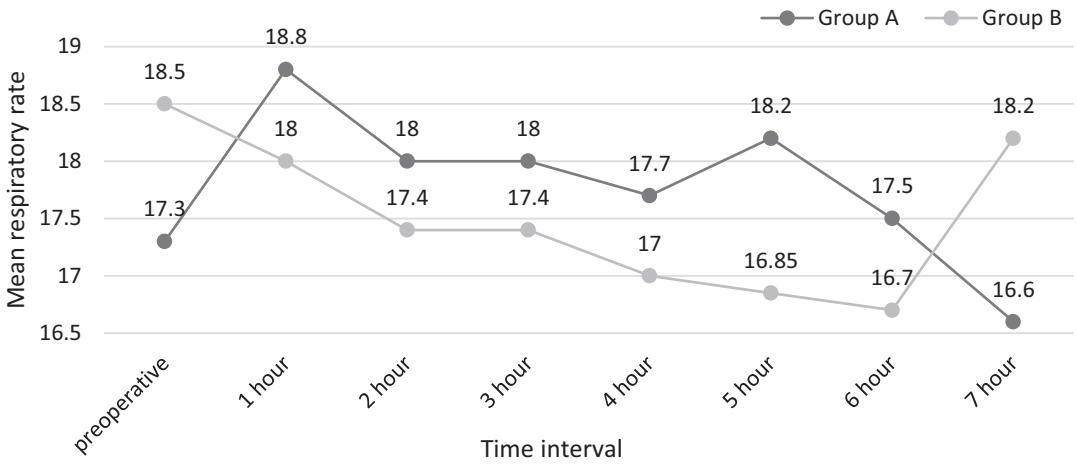


**Figure-1(d):** Trend line diagram for mean changes in the respiratory rate in the postoperative period in group A and group B

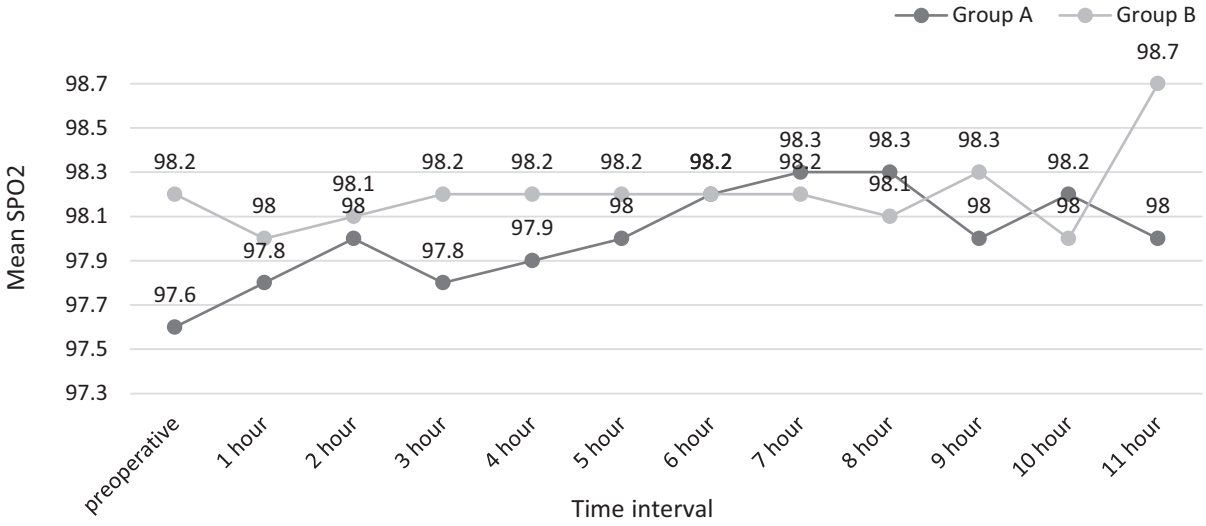


**Figure-1(e):** Trend line diagram for mean changes in SPO2 (%) in the postoperative period in group A and group B

| Side effect | Group | |
|---|---|---|
| | Group A | Group B |
| Nausea/vomiting | 0 | 0 |
| Sedation | 0 | 0 |
| Urinary retention | 5 (33.33%) | 6 (40.00%) |
| Hypotension | 0 | 0 |
| Bradycardia | 0 | 0 |
| Respiratory | 0 | 0 |
| Depression | 0 | 0 |
| Fall in $SPO_2$ | 0 | 0 |
| Others | 0 | 0 |

**Table-3:** Shows side effects found in the study

In current study the patients were equally divided in to two groups with no statistically significant difference of age group, height and weight, duration of surgery all the vital parameters and mean changes in systolic blood pressure (mm Hg), I diastolic blood pressure (mm Hg), SPO2 (per min), $SPO_2$ (%), heart rate. They were comparable with respect to ASA status. In both, the group's patients majorly had undergone Fistulectomy. Similar observations were found in the previous literature.[14-20]

We found that the VAS score of patients in both groups was equal. In the current study we observed that the participants receiving 1 ml of 0.5% heavy bupivacaine and 0.4 ml (2mg) of preservative-free midazolam intrathecally presented prolonged and postoperative effect of bupivacaine as compared to patients in the other group. A meta-analysis by Ho, KM et al[6], confirmed that intrathecal midazolam improves perioperative analgesia and may reduce the risk of postoperative nausea and vomiting. Ajam, AA et al[21], in their study found that the analgesic duration of those patients in midazolam group was significantly longer compared to the control group A for motor as well as sensory with no any substantial difference in hemodynamic status changes. Chattopadhyay, A et al[14], in their study found duration of motor block (median 255 min versus 195 min) and two dermatome regression time of sensory block (median 135min versus 90min) were found to be significantly higher in midazolam group. The duration of analgesia was significantly higher in patients receiving bupivacaine and midazolam in comparison to bupivacaine alone (median 320min versus 220 min). VAS score was found to be significantly higher ($P < 0.05$) among

the patients who received bupivacaine and midazolam which was similar to the current study. In the study by Agrawal, N et al[16], time for regression of sensory block to S1 in group Bupivacaine(B) was 164 ± 67 minutes, and group bupivacaine and midazolam(BM) was 158.6±32.16 minutes. Time to first rescue analgesia in group B was (4 ± 3.5 hours) significantly earlier than in group BM (17.6±8.87 hours). These findings were similar to the current study.

There were no major side effects observed in our study group other than urinary retention. Chattopadhyay, A et al[14], in their study found various side effects in their studies including hypotension, Bradycardia and nausea-vomiting, which was also found in the study by Shadangi, BK et al[7], Salimi, A et al[18], similar to our study did not find significant adverse effect in both groups. Urinary retention was the most common complication in the study by Kim, M et al[22], which was similar to the current study.

Our study contributed significantly to the existing literature. 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.

## CONCLUSION

Our study results conclude that by adding preservative-free Midazolam to Intrathecal Bupivacaine significantly prolonged postoperative analgesia without significant side effects. Hence Midazolam can be considered as advantageous drug to attain prolonged postoperative analgesia which is required after spinal block in adults.

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