Comparison of Safety, Efficacy and Duration of Analgesia of Intrathecal Ropivacaine Alone Versus Ropivacaine with Midazolam for Lower Abdominal and Lower Extremity Surgeries

ABSTRACT

Background Spinal anaesthesia is a common anaesthetic technique for lower abdominal and lower extremity surgeries. Many adjuvants have been tried to prolong the duration of analgesia provided by the 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.

Aim This study was designed to evaluate the effect of 5% preservative-free midazolam when added to 0.75% isobaric ropivacaine intrathecally in patients undergoing lower abdominal and lower extremity surgeries.

Methods Hundred patients ASA I or II of either gender aged between 18 and 70 years, were randomly allocated to two groups (fifty each). Group I received 3.5 ml of 0.75% isobaric ropivacaine and 0.5 ml of 0.5% preservative free midazolam while Group II received 3.5 ml of 0.75% isobaric ropivacaine and 0.5 ml of normal saline for spinal anaesthesia. Sensory and motor blocking properties, haemodynamics, postoperative analgesia and side effects were evaluated.

Results The total duration of analgesia observed was significantly higher in Group I as compared to Group II, and also the pain score was lower in the Group I. Time for first rescue analgesic required was also significantly delayed in Group I. Sedation level was higher in Group I and cardiovascular changes were comparable in both groups.

Conclusion The addition of preservative-free 5% midazolam to isobaric 0.75% ropivacaine prolonged the duration of analgesia without any adverse effects in patients undergoing lower abdominal and lower extremity surgeries.

KEYWORDS Analgesia, cardiovascular, transient neurologic symptoms, Midazolam, Ropivacaine

INTRODUCTION

The spinal subarachnoid block is one of the most versatile regional anaesthesia techniques available today. Regional anaesthesia offers several advantages over general anaesthesia—blunts stress response to surgery, decreases intraoperative blood loss, lowers the incidence of postoperative thromboembolic events and provides pain relief in early postoperative period. Pain has been defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” Despite the obviously simple nature of surgical incision, however, perioperative and specifically postoperative pain remain under evaluated and poorly treated. So, providing intraoperative and postoperative pain relief has become very important aspect of anaesthesiology.

Spinal anaesthesia has greatly progressed since 1885 and is used in a number of surgical procedures. However, the choice of local anaesthetic is based on the
potency of the agent, onset & duration of anaesthesia, and side effects of the drug. Two distinct groups of the local anaesthetic drugs are used in spinal anaesthesia, Esters and Amides. Esters contain an ester link between the aromatic portion and the intermediate chain, examples include Procaine, Chloroprocaine and Tetracaine. Amides contain an amide link between the aromatic portion and the intermediate chain, examples include Lidocaine, Etidocaine, Mepivacaine, Bupivacaine and Ropivacaine. Bupivacaine is a viable alternative to Lidocaine for spinal anaesthesia with very little incidence of transient neurologic symptoms (TNS). Onset of action occurs in 8 minutes with duration of action lasting for 120–240 minutes appropriate for intermediate to long cases. It is available as 0.5% with or without dextrose and 0.75% without dextrose. It is reported to have a high incidence of cardiotoxicity due to its nature of interaction with sodium channels. Midazolam, a benzodiazepine, interacts with GABA receptor complex, which are present abundantly in dorsal horn ganglia of the spinal cord. Its action is mediated through benzodiazepine and GABA-A receptor complex, which are present abundantly in dorsal horn ganglia of the spinal cord. Ropivacaine was approved for the intrathecal route, in the European Union in February 2004. It has low lipid solubility, which blocks nerve fibers involved in pain transmission (Aβ fibers). A more rapid post-operative recovery of sensory & motor function seen in Ropivacaine compared to Bupivacaine.

Post-operative pain relief is an unresolved issue. One of the methods of providing post-operative analgesia is by prolonging the duration of intrathecal ropivacaine by adjuvants such as Opioids, Clonidine, Ketamine, Midazolam etc. However each drug has its limitations and a need for alternative methods or drugs always exists. Discovery of benzodiazepine receptors in spinal cord triggered the use of intrathecal midazolam for analgesia. Several investigations have shown that intrathecal or epidural administration of midazolam produces a dose-dependent modulation of spinal nociceptive processing in animals and humans and is not associated with neurotoxicity, respiratory or depression.

Midazolam, a benzodiazepine, interacts with GABA (gamma amino butyric acid) system. GABA enhances the binding of benzodiazepines to their receptors and causes more free GABA to be available. Its mode of action is mediated through benzodiazepine and GABA-A receptor complex, which are present abundantly in dorsal horn ganglia of the spinal cord. This study was formulated to compare the intrathecal administration of Ropivacaine alone versus Ropivacaine with Midazolam for lower abdominal and lower extremity surgeries.

AIMS AND OBJECTIVES
1. To compare the safety and efficacy of intrathecal Ropivacaine alone versus Ropivacaine with Midazolam for lower abdominal and lower extremity surgeries.
2. To study the duration of analgesia with intrathecal Ropivacaine as compared to that of Ropivacaine alone.

MATERIALS AND METHODS
The study was carried out in 100 ASA grade I and II adult patients of either sex between the age group of 18 and 70 years undergoing lower abdominal and lower limb surgery, under spinal anaesthesia at Grecian Hospital, Mohali after taking written informed consent from every patient.

All patients were selected randomly and divided into two groups containing 50 patients each.

- **GROUP I (n = 50)** received an intrathecal injection of 3.5 ml of 0.75% Ropivacaine and 0.5 ml of 0.5% (2.5 mg) preservative free Midazolam (1 ml ampoule).
- **GROUP II (n = 50)** received an intrathecal injection of 3.5 ml of 0.75% Ropivacaine and 0.5 ml of normal saline.

Total volume injected intrathecally was 4 ml.

EXCLUSION CRITERIA
- Patient’s refusal
- Any contraindication for regional anaesthesia like spinal abnormality, skin infection at puncture site or blood coagulopathies
- Patient having a pre-existing neurological disorder
- Patient with any cardiovascular disease or respiratory disease.

PRE-ANESTHETIC CHECK UP (PAC)
Pre-anesthetic check-up including a detailed history and medical examination of each patient was done a day before surgery. All patients were thoroughly investigated as per the requirement of the surgery apart from the routine investigations. Technique of procedure of spinal anaesthesia was explained to all the patients, and the Visual Analogue Score for pain assessment was explained. The patients were educated to note down the time of first pain sensation at the site of surgery.

TECHNIQUE OF ANAESTHESIA
Pre-operatively, an intravenous line was secured with an 18G intravenous cannula & preloading with Ringer’s Lactate solution 10 ml/kg body weight was done before the initiation of the intrathecal injection. A baseline reading of all the vital parameters was recorded before anaesthesia.
For patients falling under group I, 0.75% Ropivacaine 3.5 ml was mixed with 0.5 ml of normal saline. For patients in group II, 0.75% Ropivacaine 3.5 ml was mixed with 0.5 ml of 0.5% (2.5 mg) Midazolam (preservative free).

Under all aseptic precautions, lumbar puncture was performed with 25 G Quinckie’s needle by using the midline approach at L₁ – L₂/L₂ – L₃ interspace in lateral decubitus position. Once the free flow of CSF was seen, the drug was injected and the patient was turned supine.

Subsequent readings of blood pressure, pulse rate, arterial oxygen saturation and respiratory rate were taken every 5 minutes till 30 minutes and then every 10 minutes till the completion of surgery.

Sensory blockade using a pin-prick test was recorded at dermatomal level. Time of onset of sensory blockade is defined as the time between the injection and maximal blockade. Duration of blockade is defined as the period between the injection and recovery from blockade. Assessment of the level of sensory blockade was done every 2 minutes till it stabilised.

Motor block was assessed by Modified Bromage Score (Table 1).

Onset of motor blockade is defined as the time between the injection and maximum Bromage score. Duration of motor block was assessed by recording the time elapsed from the maximum to the lowest Bromage score. Assessment of motor block was done every 2 minutes till 20 minutes.

The quality of anaesthesia was evaluated by the surgeon at the end of the surgery as given in Table 2.

The quality of intraoperative analgesia was judged at the end of the surgery by the investigator as given in Table 3.

Table 1  Modified bromage score.

<table>
<thead>
<tr>
<th>S. no</th>
<th>Level of block &amp; movement</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Complete block (unable to move feet or knees)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Almost complete block (able to move feet only)</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Partial block (just able to move knees)</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Detectable weakness of hip flexion while supine (full flexion of knees)</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>No detectable weakness of hip flexion while supine</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>Able to perform partial knee bend</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2  Quality of anaesthesia.

<table>
<thead>
<tr>
<th>Quality of anaesthesia</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>No disturbing muscle strain</td>
</tr>
<tr>
<td>Satisfactory</td>
<td>Disturbing but acceptable muscle strain</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>Unacceptable muscle strain</td>
</tr>
</tbody>
</table>

Intraoperatively, side effects like hypotension, bradycardia, myocardial infarction, cardiac arrest, arrhythmias, restlessness, paraesthesias, dizziness, drowsiness, convulsions, nausea & vomiting were noted and treated accordingly.

Hypotension defined as the fall in mean arterial blood pressure <30% from the baseline was treated with boluses of i.v. mephentamine 3 mg every 3 minutes after vascular loading with crystalloid/colloid solution.

Bradycardia (decrease in the heart rate <50 bpm) was treated with 0.01 mg/kg of i.v. atropine.

POST-OPERATIVE MONITORING

After the surgery was over, the motor and sensory levels were again noted for regression of the block and vitals were also recorded. The patients were observed post-operatively in the ward half hourly for the first 3 hours and hourly subsequently to note down the regression of sensory and motor block and degree and duration of post operative analgesia.

The regression of the sensory block was noted with the pin prick test and the time taken for regression of sensory block by two levels and the time taken for sensory block to regress to L₁ level was noted down. The duration of motor block was taken as reversion of Bromage score 3 to score 0.

SEDATION

Sedation was assessed using the following sedation score

0 – awake. Opens eyes spontaneously.

1 – mild. Opens eyes on command.

2 – moderate. Opens eyes when shaken.

3 – deep. Opens eyes on giving painful stimulus, with difficulty.

ANALGESIA

The degree of analgesia was determined by the Visual Analogue Scale (VAS). It is a 10 cm scale with the marks from 0 to 10 with 1 cm spacing. The mark 0 denotes no pain and the mark 10 denotes worst possible pain (Fig. 1). The patients were asked to mark a point on the scale which corresponded with their intensity of pain they are felt.
RESCUED ANALGESIA

When VAS was ≥ 4 inj. Diclofenac Sodium 1.5 mg/kg (max 75 mg) was given intramuscularly as rescue analgesia. Inj. Diclofenac Sodium was repeated intramuscularly if the patient complained of pain (VAS = 4) in the next 24 hours. The total no. of doses of rescue analgesic required in 24 hr. were recorded.

Patients were observed for other complications such as dry mouth, nausea vomiting. Nausea/vomiting was treated with inj. Ondensetron 4 mg iv. In case of dry mouth sips of water were given.

OBSERVATION AND RESULTS

The study was carried out in 100 ASA grade I and II adult patients of either sex between the age group of 18–70 undergoing lower abdominal and lower limb surgeries, under spinal anaesthesia at Grecian Hospital, Mohali after taking written informed consent from every patient.

Table 4 shows the distribution of cases according to age. Maximum number of patients 19(38%) in group I were between the age group of 51 and 60 years and in group II, maximum number of patients 23(46%) were in the age range of 51–60 years. The mean age of the patients in group I is 45.6 ± 9.7 years and in group II is 47.2 ± 9.5 years. On statistical analysis the groups were comparable and statistically non significant (P value > 0.05).

Table 5 shows the mean distribution of various pre-operative vitals in both groups. As shown in Table 5, pre-operative vitals were comparable in both the groups which were non significant (P value > 0.05).

Table 6 shows the mean onset time of sensory block in group I was 1.98 ± 0.64 min and in group II mean onset time was 2.05 ± 0.76 min. On statistical analysis the difference between the mean time of group I and group II was not significant (P value > 0.05).

Table 7 shows the time of two segment regression of level in both the groups. In group I, two segment regression upto 40–60 min was not found in any patient while in group II, it was in 19(38%).

![Visual Analogue Scale](image-url)
In group I, two segment regression up to 60–80 min was not found in any patient while in group II, it was in 17 (34%).

In group I, two segment regression up to 81–100 min was in 20 (40%) patients while in group II it was 10 (20%).

In group I, two segment regression up to 101–120 min was in 30 (60%) patients while in group II, it was in 4 (8%).

The mean regression in group I was 104.9 ± 23.1 min while in group II it was 71.8 ± 19.3 min. It was significant on statistical analysis (P value < 0.001).

Table 8 shows the duration of sensory block in minutes in both the groups.

In group I, two segment regression up to 120–160 min was in 26 (52%) patients while in group II, no patient had sensory block up to 120–160 min.

In group I, two segment regression up to 161–200 min was in 20 (40%) patients in group II while in group I no patient has sensory block up to 160–180 min.

In group I, two segment regression up to 201–240 min was in 15 (30%) patients while in group II, no patient in group I had achieved such level.

In group I, two segment regression up to 241–280 min was in 34 (68%) patients in group I while no patient in group II had achieved such level.

In group I, two segment regression up to 321–400 min was in 1 (2%) patients in group I while no patient in group II achieved such level.

The mean duration of sensory block was 252.7 ± 21.6 min in group I while in group II it was 158.7 ± 24.9 min. On statistical analysis it was significant (P value < 0.05).

Table 9 shows the comparison of duration of motor block in both the groups.

In group I, 17 (34%) patients had duration of motor block up to 120–180 min while in group II, 50 (100%) patients had duration between 120 and 180 min.

In group I, 33 (66%) patients had duration of motor block up to 181–240 min while no patient in group II attained the same level.

The mean duration of motor block was 187.3 ± 26.4 min in group I while in group II it was 137.7 ± 3.05 min. On statistical analysis the difference between the two groups was significant (P value < 0.05).

Sedation was assessed using the following sedation score 0 – awake. Opens eyes spontaneously.

1 – mild. Opens eyes on command.

2 – moderate. Opens eyes when shaken.

3 – deep. Opens eyes on giving painful stimulus, with difficulty.

Table 10 shows the comparison of sedation score in both the groups.

In group I, 9 (18%) patients achieved score 0 while 50 (100%) patients achieved the same score in group II.

In group I, 28 (56%) patients had sedation score 1 while in group II no patient had the same score.

In group I, 13 (26%) patients had sedation score 2 while in group II no patient had the same score.

On statistical analysis it was significant between both the groups (P < 0.05).

Table 11 shows the comparison of duration of analgesia in both the groups. In group I, the mean duration of analgesia was 363.8 ± 21.82 minutes, while in group II, it was 220.7 ± 30.6 minutes. The duration of analgesia in two groups was highly significant (P value < 0.05).
Table 11: Comparison of duration of analgesia in both the groups.

<table>
<thead>
<tr>
<th>Duration (in minutes)</th>
<th>Group I</th>
<th>Group II</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Mean</td>
<td>363.8</td>
<td>21.82</td>
<td>20.7</td>
</tr>
<tr>
<td>Analgesia</td>
<td>0.018</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Table 12: Number of rescue analgesics in 24 hours in both the groups.

<table>
<thead>
<tr>
<th>No. of Rescue Analgesics</th>
<th>Group I</th>
<th>Group II</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.7</td>
<td>1.9</td>
<td>0.4</td>
</tr>
<tr>
<td>SD</td>
<td>0.5</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Table 12 shows the comparison of number of rescue analgesia given in 24 hours in both the groups. In Group I the number of rescue analgesics was $1.7 \pm 0.5$ as compared to in Group I $1.9 \pm 0.4$ and the statistical difference was significant (P value < 0.05).

No patients had any complication like bradycardia, hypotension, nausea/vomiting, retention of urine in the postoperative period in either of the group and the statistical difference is not significant (P value > 0.05).

**DISCUSSION**

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, neostigmine, ketamine and clonidine, 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-A receptor. Agonist occupancy of the benzodiazepine binding site enhances the activity of GABA at the GABA-A 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. 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. 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.

The characteristics of sensory and motor block, duration of analgesia, duration of block, vitals and various side effects were recorded and compared in both the groups.

**ONSET OF SENSORY BLOCK**

As seen in Table 8, the duration of sensory block was measured by regression time to L-1 Level. It was 4.2 hrs in Group I, whereas it was 2.6 hrs in Group II. The difference in duration was significantly prolonged in group I as compared to group II.

**DURATION OF MOTOR BLOCK**

The duration of motor block was taken, when bromage grade became 0. It was 2.29 hrs in Group II, while it was 3.12 h in Group I. So it was prolonged in group I compared to group II and the difference was statistically significant.

**Sedation Score**

Sedation score was evaluated by using 4 point sedation score. We also observed the sedation scores between the two groups at various time intervals. 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 ropivacaine was associated with sedation and tranquility.

Table 10 shows the sedation score in both the groups. In Group I 56% patients had sedation score 1 and 26% patients had sedation score 2 whereas all the patients in Group II had sedation score 0. Midazolam has a mild sedative action which is helpful when given as an adjuvant in the spinal anaesthesia.

**Duration of analgesia**

The duration of analgesia in Group II was 3.67 hrs, while in group I, it was 6.06 hrs. So the duration of analgesia was prolonged in group I than in group II and the difference was statistically significant.
**Number of rescue analgesics in 24 hours**

Table IX illustrates the number of rescue analgesics consumed in 24 hours in both groups. In Group I the number of rescue analgesics was $1.7 \pm 0.5$ as compared to in Group I $1.9 \pm 0.4$ and the statistical difference was significant ($P$ value < 0.05).

**Post-operative side effects**

No post operative complications like bradycardia, hypotension, nausea, vomiting, retention of urine and neurological sequel seen in either of the group.

The addition of 2 mg midazolam to intrathecal bupivacaine causes no significant haemodynamic disturbances, and is relatively free from common side-effects.

**CONCLUSION**

The conclusion from the above study reveals that the addition of 2.5 mg midazolam to intrathecal ropivacaine 0.75% significantly prolongs the duration of analgesia with synergistic analgesic effect, without causing any significant side effect, except slight bradycardia, hypotension and sedation. Hence, mixture of midazolam and ropivacaine is an attractive solution for intrathecal anaesthesia.

**REFERENCES**