Effect Of Intrathecal Midazolam On Quality And Duration Of Spinal Anaesthesia With Bupivacaine In Perineal And Lower Limb Surgery

I Punjabi, Waqar-ul-Nisa, A Farooqi, A Ahmad, A Maqbool

INTRODUCTION

Adequate analgesia is the hallmark and basic requirement of every anesthetic technique. Post-operative pain management can improve functionality and reduce physiological and psychological morbidity and in turn hospital stay and also improve quality of life (1). Various anaesthetic techniques have been used for perineal and lower limb surgeries but regional anaesthesia is considered the anaesthesia of choice for procedures like trans-urethral resection of prostate (2), bladder tumour and lower extremity surgeries. Spinal anaesthesia is widely used for perineal and lower limb surgeries. Various drugs like lidocaine, tetracaine and bupivacaine have been used so far in spinal anaesthesia (3). Bupivacaine has gained popularity because of its longer duration of action. It was the first local anesthetic that produced adequate pain relief without a major effect on motor fibres (4). However, in high doses intrathecal bupivacaine may produce a high level of sensory and motor block and arterial hypotension and therefore delay the discharge from hospital (5). Besides, margin of safety may be less with bupivacaine. Intravascular absorption has resulted in seizures and cardiac arrest and eventually death (6). Therefore in order to keep the dose of bupivacaine to the minimum possible and to reduce its side effects, the need was felt to use an adjuvant that would prolong its duration of action and analgesia. Various drugs like opioids (7), ketamine (8), neostigmine (7), clonidine (9) etc have been added to local anaesthetics to prolong the duration of spinal anaesthesia, prominent amongst them being the opioids. However, their use is limited because of the side effects such as nausea, vomiting, pruritis, urinary retention, respiratory depression and haemodynamic instability (10,11). The discovery of benzodiazepine receptors in spinal cord (12,13) triggered its use as an adjuvant to local anaesthetic in spinal anaesthesia. Therefore, the present study was undertaken to evaluate the effects of midazolam added to bupivacaine on onset and duration of motor and sensory block and postoperative analgesia following intrathecal block in patients undergoing perineal and lower limb surgery.

MATERIAL & METHODS

This prospective, double blind, randomized control study...
was conducted in the department of Anaesthesiology SK Institute of Medical Sciences, Srinagar, India.

After the institutional ethical committee approval and written informed consent, 100 patients of ASA grade I and II, aged 25 to 60 years, scheduled for perineal and lower limb surgeries under spinal anaesthesia were included in the study. Patients with history of congestive cardiac failure, ischemic heart disease, motor/sensory nerve disturbances, diabetes mellitus, known sensitivity to study drugs used, spinal deformity or any other standard contraindication to spinal anaesthesia were excluded from the study.

All patients were thoroughly evaluated preoperatively at least 24 hours before surgery. Complete medical history was elicited. History about previous anesthetic exposure, medications, allergy to any drug, personal habits were asked for. General physical examination, systemic examination of cardiovascular system, respiratory system, central nervous system and local examination of spine was carried out.

Airway assessment was also done to predict difficult intubation (in case need for intubation arose). All investigations as per the proforma protocol were checked and asked for if not available. VAS (Visual Analog Scale) consisting of a 10 cm line with 0 = no pain and 10 cm = maximum imaginable pain, was explained to patients at preoperative visit. Patients were randomly allocated to two equal groups of 50 patients each.

Group I (control, n = 50): These patients received 2.5ml of 0.5% hyperbaric bupivacaine and 0.5ml of normal saline to make a total volume of 3ml.

Group II (study, n = 50): These patients received 2.5ml of 0.5% hyperbaric bupivacaine and 0.5ml (1mg) of preservative free midazolam in normal saline to make a total volume of 3ml.

All drug solutions were prepared by an anesthesiologist who was not involved in administration of spinal anesthesia or in observation of the patient. No premedication was given to any patient. On arrival in operation theatre, an 18 gauge cannula was secured in a peripheral vein and each patient was preloaded with 500ml of Ringers lactate. Patients were connected to an ECG monitor. Baseline systolic arterial pressure, diastolic arterial pressure and heart rate were recorded with the patient in semi-recumbent position.

Patients were placed in the sitting position and under all aseptic precautions a lumber puncture was performed with a 25 G Quinckes spinal needle at L3 – L4 intervertebral space. Free flow of cerebrospinal fluid was established. Patients randomly allocated to either control or study group received either 2.5ml of 0.5% hyperbaric bupivacaine plus 0.5ml of normal saline or 2.5ml of 0.5% hyperbaric bupivacaine plus 0.5ml (1mg) of preservative free midazolam in normal saline intrathecally respectively so as to make a total volume of 3ml in both the groups. After withdrawal of spinal needle an antiseptic seal was applied at the site of lumbar puncture.

The time of injection was noted and patient was placed in supine position immediately.

Onset of sensory block was checked by loss of sensation to pinprick. Sensory testing was performed using a blunted 21 G needle in a cephalad to caudal fashion. Dermatome level was tested every 2 minutes until the level stabilized for 3 consecutive tests. A sensory blockade up to T10 was considered adequate. The time taken from intrathecal injection to attainment of the highest level of sensory block was recorded. Later, the time taken for sensory regression to S2 from the highest sensory level was also noted.

Motor block in the lower limbs was assessed as per Bromage scale:

0 - No paralysis
1 - Inability to raise extended legs
2 - Inability to flex the knee
3 - Inability to flex the ankle

Duration of motor blockade was recorded from the onset up to the cessation of grade I block.

Hemodynamic variables such as systolic arterial pressure, diastolic arterial pressure and heart rate were recorded immediately after the injection, at 5, 10, 15, 30, 45, 60 minutes and at the end of the procedure. Hypotension was taken as a fall in baseline systolic arterial pressure by 20%.

Hypotension was treated with bolus doses of intravenous ephedrine 3mg, repeated if required. Bradycardia was taken as heart rate less than 50 beats per minute. Bolus doses of intravenous atropine 0.3 mg were injected to treat the episodes of bradycardia.

Side effects such as sedation levels were assessed after every 15 min intervals using four-point sedation score:

1 - Awake.
2 - Drowsy but responding to verbal commands.
3 - Drowsy but responsive to physical stimulus.
4 - Unresponsive to verbal or physical stimulus.

Bradycardia, any respiratory depression and excessive sedation were recorded. Patients were monitored for 24 hours for dizziness, post-operative nausea and vomiting.

Post-operative analgesia was evaluated using a standard 10 cm linear visual analogue scale (VAS) with 0 corresponding to no pain and 10 to the worst pain possible. Pain score more than 3 on VAS was given rescue analgesia. Duration of analgesia was recorded from its onset up to the time when
pain was first reported. The data was collected, assessed and statistically analyzed using standard statistical tests. A $p \geq 0.05$ was considered statistically non-significant and $p < 0.05$ was considered statistically significant. Statistical analysis of the data was done using ANOVA & students t-test for difference of means (paired samples t-test). For quantitative analysis of nominal data, chi-square test ($\chi^2$-test) was used. These tests were two sided & were referenced for $p$-values for their significance. Any $p$-value less than 0.05 (i.e. $p<0.05$) was taken to be statistically significant.

**RESULTS**

The two groups were comparable in age, weight, gender distribution and the type of surgical procedures performed. There was no significant difference in heart rate, systolic BP and diastolic BP before the subarachnoid block, immediately after injection and 5, 10, 15 and 30 minutes after the injection and at the end of surgical procedure between the two groups. No significant difference was observed in the onset of motor block between the two groups. The time taken from injection of the drug to grade III motor block was 9.3 minutes in control group and 8.2 minutes in study group.

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>SD</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>5</td>
<td>15</td>
<td>8.2</td>
<td>2.9</td>
<td>0.000 (NS)</td>
</tr>
<tr>
<td>Control</td>
<td>5</td>
<td>20</td>
<td>9.3</td>
<td>2.9</td>
<td></td>
</tr>
</tbody>
</table>

Similarly there was no significant difference in the onset of sensory block between the two groups, being 12.5 minutes in control group and 12.0 minutes in study group.

**Table 2**

<table>
<thead>
<tr>
<th>Sensory Level</th>
<th>Study</th>
<th>Control</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T8</td>
<td>24</td>
<td>48</td>
<td>0.320 (NS)</td>
</tr>
<tr>
<td>T10</td>
<td>26</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>T12</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

The duration of sensory block was assessed by time for regression of sensory block to S2 dermatome. It was significantly prolonged in study group as compared to control group. Time for regression of sensory block to S2 dermatome was 237.6 minutes in control group while as it was 260.1 minutes in study group.

**Table 5**

<table>
<thead>
<tr>
<th>Group</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>SD</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>175</td>
<td>310</td>
<td>260.1</td>
<td>25.4</td>
<td>0.000 (NS)</td>
</tr>
<tr>
<td>Control</td>
<td>200</td>
<td>345</td>
<td>237.6</td>
<td>34.5</td>
<td></td>
</tr>
</tbody>
</table>

No statistically significant difference was observed in highest sensory level achieved between the two groups.

The difference in duration of motor block between the two groups was statistically insignificant, being 174.2 minutes in control group and 169.0 minutes in study group.

**Table 3**

<table>
<thead>
<tr>
<th>Group</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>SD</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>132</td>
<td>227</td>
<td>169.0</td>
<td>17.4</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>140</td>
<td>240</td>
<td>174.2</td>
<td>21.5</td>
<td></td>
</tr>
</tbody>
</table>

No statistically significant difference was observed in highest sensory level achieved between the two groups.

The duration of effective analgesia, i.e, time from injection of the drug to first complaint of pain was also significantly longer (312.1 minutes) in study group as compared to 253.7 minutes in control group.
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Table 6
Table 6: Showing time from injection of drug to first complaint of pain.

<table>
<thead>
<tr>
<th></th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>255</td>
<td>380</td>
<td>312.1</td>
<td>26.8</td>
<td>0.000 (S)</td>
</tr>
<tr>
<td>Control</td>
<td>220</td>
<td>395</td>
<td>253.7</td>
<td>33.5</td>
<td></td>
</tr>
</tbody>
</table>

No significant difference in sedation levels was observed in midazolam group (9 out of 50 patients had grade 2 sedation score) 15-60 minutes after intrathecal block as compared to control group where 5 patients had grade 2 sedation score.

Table 7
Table 7: Showing sedation scores in the two groups.

<table>
<thead>
<tr>
<th>Sedation Score of the Studied Subjects</th>
<th>Study</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation 15 min</td>
<td>1</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Sedation 30 min</td>
<td>1</td>
<td>47</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Sedation 45 min</td>
<td>1</td>
<td>49</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sedation 60 min</td>
<td>1</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

No significant difference in the incidence of side effects was observed between the two groups.

Table 8
Table 8: Showing incidence of side effects in two groups.

<table>
<thead>
<tr>
<th>Side Effects across the Studied Subjects</th>
<th>Study</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>5</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory Depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shivering</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

DISCUSSION

Neuraxial blocks not only reduce the incidence of deep vein thrombosis, pulmonary embolism, cardiac complications, bleeding, transfusion requirements, respiratory depression but also provide effective postoperative analgesia(3). Intrathecal anaesthesia has improved a lot by availability of newer local anaesthetic drugs and adjuvants. Amongst currently used drugs for spinal anaesthesia, bupivacaine is most widely used, however because of its tendency to produce higher motor and sensory block and hypotension in higher doses(5) various adjuvants have been added to it to prolong its duration of action and analgesic effects in order to keep its dosage requirement to minimum possible. Reduction in dosage of local anaesthetics like bupivacaine with the addition of adjuvants may result in fewer side effects, improved haemodynamic stability, less bladder dysfunction and improved quality and duration of anaesthesia with fewer instances of undesired motor block(14).

An ideal local anaesthetic should provide rapid onset of action and longer duration of sensory block with minimal side effects. At present no sole anaesthetic agent has such characteristics.

Because of the side effects such as pruritis, urinary retention, respiratory depression, haemodynamic instability, nausea and vomiting attributed to the various adjuvants especially opiates, their role has become limited in intrathecal block (10,11).

The development of water soluble benzodiazepine–midazolam and the evidence of its antinociceptive action in spinal cord(15) has led to the use of this agent in intrathecal injections.

In our study, we added 1mg of preservative free midazolam to bupivacaine for intrathecal block. Midazolam upto 2mg has been added without causing any neurological deficit(16). In our study, we found that the analgesic effect of bupivacaine was significantly potentiated by midazolam. Addition of 1mg midazolam to bupivacaine prolonged the duration of sensory block and effective analgesia, (ie, time to the request for first analgesic) significantly as compared to the patients where bupivacaine was used alone. However there was no difference in the onset and duration of motor block between the two groups.

In vitro studies have shown that there is a high density of benzodiazepine (GABA-A) receptors in lamina II of dorsal horn in human spinal cord, suggesting a possible role in pain modulation(13). Animal studies have shown that benzodiazepines have analgesic effect at the level of spinal
The analgesic efficacy of intrathecal midazolam has been demonstrated in humans.(16,18,19). Delta selective opioid antagonist, naltrindole suppresses the antinociceptive effect of intrathecal midazolam(15) suggesting that intrathecal midazolam is involved in release of an endogenous opioid acting at spinal delta receptors. It has been shown that antinociceptive effects of midazolam may be suppressed by opioid antagonist naloxone(20).

Previous studies by Kim and Lee (21) are consistent with our study and have shown that addition of 1-2mg of midazolam to intrathecal bupivacaine produced better post operative analgesia than bupivacaine alone in patients undergoing haemorroidectomy and knee arthroscopy.

Our results are also in accordance with the study conducted by Bharti N, Madan R, Mohanty PR, Kaul HL. (22) in which median sensory level was comparable in groups with or without midazolam as an adjuvant, but the duration of analgesia was significantly longer in midazolam group as compared to bupivacaine used alone.

No significant side effects were observed in our study that could be attributable to midazolam. The side effects studied were nausea, vomiting, hypotension, bradycardia, respiratory depression, shivering and sedation. Although some studies (23) have suggested that intrathecal midazolam may also reduce the incidence of nausea and vomiting when used as an adjunct to other spinal medications, we failed to find any such effect in our study.

In conclusion, addition of 1mg midazolam to intrathecal bupivacaine prolongs the duration of sensory block and effective analgesia (time from injection of the drug to first complaint of pain) without affecting the level of sensory block and the duration of motor block, suggesting thereby that the dose requirement of bupivacaine could be reduced by the addition of midazolam in order to keep its undesired effects at bay. Also no serious adverse effects were observed with dose of midazolam used. However more studies are needed to define the ideal dose of midazolam for better results.

References
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