EFFECT OF INTRATHECAL MIDAZOLAM BUPIVACAINE COMBINATION ON POST OPERATIVE ANALGESIA

Dr. Nidhi Agrawal1  Dr. A. Usmani2  Dr. R. Sehgal3  Dr. Rakesh Kumar4  Dr. Poonam Bhadoria5

SUMMARY

A double blind study was carried out on 53 adult ASA grade I/II patients to compare efficacy of intrathecal bupivacaine with intrathecal bupivacaine midazolam combination for post operative pain relief. Patients were randomly divided into two groups. Group B (n=24) received 3 ml (15 mg) of heavy bupivacaine (0.5%) with 0.2 ml of 0.9% saline intrathecally. Group BM (n=25) received 3 ml (15 mg) of heavy bupivacaine (0.5%) with 0.2 ml of preservative free midazolam (1 mg) intrathecally. The two groups did not differ significantly as regards to duration of surgery, time of onset of sensory block and time to achieve maximum sensory block (p>0.05). Time for regression of sensory block to S1 in group B was 164 ± 67 minutes and group BM was 158.6±32.16 minutes. Time to first rescue analgesic in group B was (4 ± 3.5 hours) significantly earlier than in group BM (17.6±8.87 hours). There were no episodes of bradycardia, hypotension, sedation, vomiting, pruritis and urinary retention. In conclusion intrathecal combination of midazolam and bupivacaine provides longer duration of post-operative analgesia as compared to intrathecal bupivacaine alone, without prolonging duration of dermatomal sensory block.

Keywords : Intrathecal, Bupivacaine, Midazolam.

Introduction

Post–operative pain relief is an unresolved issue. One of the methods of providing postoperative analgesia is by prolonging the duration of intrathecal bupivacaine by additives such as opioids,1 clonidine,2 ketamine3 etc. However each drug has its limitations and a need for alternative methods or drugs always exists. Discovery of benzodiazepine receptors in spinal cord4 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 animals5,6 and humans7,8 and is not associated with neurotoxicity,9 respiratory depression or sedation.10 As there are only a handful of studies that have assessed the efficacy of intrathecally administered combination of midazolam and bupivacaine in humans.7,8 We planned this study to further assess the intrathecal midazolam-bupivacaine combination and correlate the duration of dermatomal sensory block with duration of postoperative pain relief.

Material and Methods

After approval from the hospital research committee and a written informed consent this prospective randomized double blind study was carried out on 53 ASA grade I/II patients, aged 18-60 years, scheduled for elective lower abdominal, lower limb and endoscopic urological surgeries. Patients having contraindication to regional anaesthesia, known sensitivity to study drugs or using any drug that modifies pain perception were excluded from the study.

All patients received tab. diazepam 0.2 mgkg-1 orally night before surgery. In the operation theatre, they were preloaded with intravenous Ringer’s lactate solution 15 mlkg-1 before administering subarachnoid block. Patients were randomly allocated to two groups. Group B received 3ml (15 mg) of heavy bupivacaine 0.5% with 0.2 ml of 0.9% saline intrathecally. Group BM received 3ml (15 mg) of heavy bupivacaine 0.5% with 0.2 ml of preservative free midazolam (1 mg) intrathecally.

The anaesthesiologists who performed the spinal block and made observations were blinded to the solution administered intrathecally. Subarachnoid block was performed in sitting position with 23G spinal needle in L3 space. Time of intrathecal injection was noted and the patient was made supine. Standard monitoring was carried out in the form of ECG, pulse oximetry and non invasive arterial blood pressure during the study period. Sensory block was assessed by the loss of sensation to pinprick.

1. D.A., DNB.
2. D.A., Sr. Resident
3. M.D., Director Prof.
4. M.D., Prof.
5. M.D., Prof.

Department of Anaesthesia,
Maulana Azad Medical College, Delhi.

Correspond to:
Dr. Nidhi Agrawal
22, Samachar Apartment, Mayur Vihar Phase–I,
Delhi - 110091
E-mail : lalit_maini@rediffmail.com

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Time of onset of sensory block, maximum level of sensory block achieved and time to achieve maximum sensory block were noted. A dermatomal sensory loss from dorsal eight to sacral fourth was considered satisfactory. Pulse rate, arterial blood pressure and respiratory rate were recorded every five minutes intraoperatively and every thirty minutes during postoperative period till rescue analgesic was administered. Hypotension defined as ≥20% decrease in systolic blood pressure from the baseline values was treated with intravenous fluids and mephenteramine 6 mg intravenous boluses. Bradycardia (pulse rate<60 min⁻¹) was treated with intravenous atropine sulphate. Duration of surgery for each case was noted. The time to regression of sensory block to first sacral dermatome by pinprick method was assessed for each patient. No other sedative or analgesic was given to the patients intraoperatively.

Postoperatively patients were observed for 24 hours and rescue analgesic (diclofenac sodium 1.5 mgkg⁻¹ intramuscular) was given when the patient demanded it. Duration of pain relief was taken as time from onset of subarachnoid block to time of administration of rescue analgesic. Side effects such as nausea, vomiting, sedation, facial analgesia, amnesia, itching and urinary retention were also noted.

**Statistical analysis**

The data are presented as mean±SD. The two groups were compared by unpaired two tailed t-test and P<0.05 was considered significant.

**Results**

There was no significant difference between the two groups with respect to age, weight, height, and sex of the patients (P>0.05) (table 1). The two groups did not differ significantly as regards to duration of surgery, time of onset of sensory block, time to achieve maximum sensory block (P>0.05) and time for regression of sensory block to first sacral dermatome (table 2).

**Table – 1 : Demographic profile.**

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Group BM</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (YEARS)</td>
<td>48.1±18</td>
<td>44.9±18</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>22/7</td>
<td>17/7</td>
</tr>
</tbody>
</table>

**Table – 2 : Summary of results.**

<table>
<thead>
<tr>
<th></th>
<th>Group BM Mean±SD</th>
<th>Group B Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery (min)</td>
<td>99±33.94</td>
<td>89.3±30.13</td>
<td>0.285</td>
</tr>
<tr>
<td>Onset of sensory block (min)</td>
<td>3±1.22</td>
<td>3.1±1.97</td>
<td>0.33</td>
</tr>
<tr>
<td>Time to achieve max. block(min)</td>
<td>7.7±2.69</td>
<td>8.6±2.67</td>
<td>0.24</td>
</tr>
<tr>
<td>Time of regression to S₁ (min)</td>
<td>158.6±32.16</td>
<td>164±67.07</td>
<td>0.69</td>
</tr>
<tr>
<td>Time of rescue analgesic (hrs)</td>
<td>17.56±8.87*</td>
<td>4 ±3.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* All values >24hours were taken as 24 hours for calculations

Time to first rescue analgesic in BM group (17.56± 8.87 hours) was significantly longer than that in B group (4±3.5 hours) (P<0.0001) (table 2). Maximum level of sensory block achieved in both the groups was between T₄ and T₁₀. There were no episodes of bradycardia, hypotension, sedation, and dizziness, vomiting in any of the patients. No neurological deficits were observed in any patients.

**Discussion**

Our study shows that the addition of midazolam to intrathecal bupivacaine significantly prolongs the duration of postoperative analgesia. Time to first rescue analgesic was more than 24 hours in the BM group as compared to 4 hours in the B group. Kim MH et al have reported that time to rescue analgesic was prolonged only by 2 hours and 4.5 hours when midazolam 1mg and 2 mg respectively was added to bupivacaine intrathecally. Administration of benzodiazepene antagonist flumazenil and GABA-A antagonist (Bicuculline) has been reported to reverse the analgesic effect of intrathecal midazolam, suggesting that antinoceptive action are mediated via benzodiazepine/GABA-A receptor complex which are abundantly present in lamina II of dorsal horn ganglia of spinal cord. Intrathecal midazolam probably also causes release of an endogenous opioid acting at spinal delta receptor as naltrindole, a delta selective opioid antagonist suppresses analgesic effect of intrathecal midazolam. Intrathecal midazolam besides causing analgesia has also been found to be effective in suppressing reflex response to visceral distention in rabbits and visceral pain in humans in caesarean section.

Animal studies have shown that intrathecal midazolam causes segmental cord level analgesia. Only one study in humans has reported duration of dermatomal sensory block lasting up to 72 hours which receded at the rate of three dermatomes per day. None of the subsequent studies in humans have noted time to regression of block to first sacral dermatome. They have only noted time of
administration of first rescue analgesic. In our study 18 out of 29 patients in BM group did not require any rescue analgesia for more than 24 hours inspite of the fact that sensory dermatomal block had receded in 2.5 hours (158.6±32.16 min). In the B group time to first rescue analgesic (4 hrs) almost corresponded with time to regression to first sacral dermatome (164±67.07min). Thus our results raise a possibility of another mechanism of action of intrathecal midazolam besides segmental cord level analgesia. There was no difference in the time of onset of sensory block; time to maximum sensory block and maximum level of sensory block in the two groups. None of the other studies in humans have reported this aspect of combination of intrathecal bupivacaine and midazolam.

Intrathecal midazolam has been shown to be free of any neurotoxicity or other side effects in doses upto 2 mg and in continuous infusion with doses £ 6 mg/day for long period in man. In our study also there have been no significant side effects such as nausea, vomiting, sedation, amnesia, itching, urinary retention, hypotension and bradycardia. Our study may be criticized for not assessing motor block but since the purpose of the study was to assess postoperative pain relief, it was left out. Also different types of surgical cases were chosen but this bias could be prevented as cases were randomly distributed. In conclusion, intrathecal midazolam added to bupivacaine prolongs duration of postoperative analgesia without prolonging the duration of dermatomal sensory block with no side effects. However more studies on larger sample of population are needed in humans to evaluate possible mechanisms of analgesia of intrathecal midazolam.

References