Intrathecal clonidine versus intrathecal midazolam with hyperbaric bupivacaine for post operative analgesia in abdominal hysterectomy: A randomised study

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Abstract---Objectives: This randomised study was conducted to compare the effects of intrathecal clonidine and midazolam with hyperbaric bupivacaine for postoperative analgesia in patients undergoing abdominal hysterectomy. Materials and Methods: 60 patients of ages between 40 and 60 years of ASA grade I/II undergoing abdominal hysterectomy were randomly divided into two equal groups. Group C and group M received 0.5% hyperbaric bupivacaine 3ml with either clonidine 45µg with 0.2 ml saline or midazolam 2.5mg respectively intrathecally. Onset and duration of sensory blockade, haemodynamic changes, duration of post operative analgesia, number of rescue analgesics and side effects if any, were observed. Results: There was statistically significant difference in the onset and duration of sensory block (p<0.001) between the two groups. Duration of post
operative analgesia was significantly longer in midazolam group (373.33±24.22 minutes) than in clonidine group (328.5±21.78 minutes). Conclusion: Spinal anaesthesia with 2.5 mg midazolam as an adjuvant to 3ml hyperbaric bupivacaine provides longer duration of post operative analgesia compared to 45µg clonidine with 3ml hyperbaric bupivacaine with better haemodynamic stability without any adverse effects.

**Keywords**---Adjuvants, alpha 2 agonist, benzodiazepine, pain relief, spinal anaesthesia.

**Introduction**

The main aim of postoperative pain management is to decrease a patient’s pain to a level which can be tolerated by the patient, with minimal or no associated suffering or distress\(^{(1)}\). It is of utmost importance that the anaesthetic and analgesic technique should be such that it provides optimal conditions for surgery and also reduces postoperative discomfort, morbidity and mortality\(^{(2)}\).

Spinal anaesthesia is frequently used in sub umbilical surgeries like lower abdominal surgeries, lower extremity orthopedic and arthroscopic surgeries\(^{(3)}\). It is used commonly due to simplicity, minimum skill implementation, optimal operative condition, unhampered airway patency, lower risk of aspiration, less intraoperative blood loss, minimal biochemical and metabolic changes secondary to the stress of general anaesthesia, continued analgesia in the post-operative period and minimal post-operative morbidity\(^{(3,4,5)}\).

Intrathecal adjuvants like clonidine, neostigmine, midazolam, magnesium sulphate and opioids are increasingly used for prolongation of postoperative analgesia with local anaesthetic. They also intensify the subarachnoid block and offer hemodynamic stability\(^{(6)}\). Clinical studies have suggested that intrathecal clonidine prolonged sensory block and decreased anaesthetic requirements during surgery and increased postoperative analgesia without any clinically significant side effects\(^{(4,7)}\).

With the discovery of benzodiazepine receptors in spinal cord, midazolam is used intrathecally for prolongation of analgesia along with local anaesthetics. Several studies showed that intrathecal or epidural midazolam produced a dose dependent modulation of spinal noiceceptive processing in animals and humans and was not associated with neurotoxicity, respiratory depression or sedation\(^{(8,9,10)}\).

In this study, the analgesic efficacy of intrathecal clonidine is compared with intrathecal midazolam as an adjuvant to hyperbaric bupivacaine in abdominal hysterectomy.

**Objectives**
- To compare the onset of sensory blockade by both drugs.
- To compare the duration of sensory blockade by both drugs.
To compare duration of analgesia.
To compare the number of rescue analgesia in 24 hours.
To compare side effects/complications if any in both drugs.

Materials and Methods

After permission and clearance from the ethical committee (SVIEC/ON/MEDI/BNPG18/D19189), this randomised study was conducted at Dhiraj (tertiary care) hospital in Department of Anaesthesiology, Vadodara, Gujarat, India. 60 patients between ages 40 and 60 years of Grade I or II of American Society of Anaesthesiologists (ASA) classification, posted for elective abdominal hysterectomy between 2019 to 2021 were included in the study. All the patients who participated in the study were explained clearly about the purpose and nature of the study. Written informed consent was obtained. Sample size is calculated using following formula:

$$n = 2 \left( \frac{z_{1-\alpha/(2\tau)} + z_{1-\beta}}{\mu_A - \mu_B} \right)^2$$

$$1 - \beta = \Phi \left(z - z_{1-\alpha/(2\tau)}\right) + \Phi \left(-z - z_{1-\alpha/(2\tau)}\right), \quad z = \frac{\mu_A - \mu_B}{\sigma \sqrt{\frac{2}{n}}}$$

Table/Figure 1: Sample Size

where:

- $n$ is sample size
- $\sigma$ is standard deviation
- $\Phi$ is the standard Normal distribution function
- $\Phi^{-1}$ is the standard Normal quantile function
- $\alpha$ is Type I error
- $\tau$ is the number of comparisons to be made

$\beta$ is Type II error, meaning $1-\beta$ is power.

(According to the above formula the sample size is 56 patients, but to make the study convenient we took the sample size as 60 patients)

Inclusion criteria:

- Patient willing to participate in the study.
- ASA I, II patients.
- Age of patients: 40-60 years.
- No past history of allergic reaction, sensitivity or other form of reaction to local anaesthetics of the amide type.

Exclusion criteria:

- Refusal of patient.
- Patients allergic to any drugs.
- History of seizure disorder.
- Patients with renal, hepatic, cardiovascular and respiratory diseases, neurological disorders and neuropathies.
Using chit method, 60 patients were randomly distributed into two equal groups of 30 each.
Group C received Inj 3.0ml bupivacaine (0.5% hyperbaric) + 0.3ml clonidine (45µg) and 0.2ml normal saline intrathecally.
Group M received Inj 3.0ml bupivacaine (0.5% hyperbaric) + 0.5ml midazolam (2.5mg) intrathecally.

Preoperative preparation

Pre – anaesthetic check-up was done one day prior to the surgery. Patients were evaluated for any systemic diseases and laboratory investigations were noted. All patients were kept nil by mouth for atleast 8 hours before the surgery. The procedure of spinal anaesthesia and visual analogue scale was explained to all the patients. On the day of surgery, intravenous (i.v.) line was secured with 20 gauge cannula and preloading with 10ml/kg ringer lactate was done. On arrival of patient in the operating room standard monitors were attached. Echocardiography (ECG), non-invasive systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR) and arterial oxygen saturation (SpO₂) were monitored and recorded. Patients were pre-medicated with Inj. glycopyrrolate 0.2mg and Inj. ondansetron 4mg intravenously.

Patients were positioned in the sitting position. After painting with povidone-iodine and alcohol under aseptic and antiseptic precautions and draping, 23 gauge spinal needle was inserted in the midline at L₃-₄ interspace. Drug was injected over 10-15 seconds after free flow of clear cerebrospinal fluid. The patient was placed in supine position immediately after injection.

Time of onset of sensory and motor block was recorded. HR, SBP, DBP, SpO₂ and sedation was monitored every 5 minutes up to 15 minutes and then every 15 minutes till the surgery ended. Onset of sensory block was noted as the time
taken to loss of pinprick sensation at L1 after intrathecal injection. The level of sensory block was determined using pin prick test by checking at 2 minutes interval until two consecutive levels of sensory block was identical (i.e., fixation of the level).

Sedation was assessed by ‘four point sedation scale’ (Modified Wilson sedation scale). Table/Figure 3.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spontaneous eye opening [awake and alert]</td>
</tr>
<tr>
<td>2</td>
<td>Drowsy, responsive to verbal stimuli</td>
</tr>
<tr>
<td>3</td>
<td>Drowsy, arousable to physical stimuli</td>
</tr>
<tr>
<td>4</td>
<td>Unresponsive</td>
</tr>
</tbody>
</table>

**Table/Figure 3: Four point sedation scale**

Side effects and complications were noted and treated. Bradycardia defined as fall in heart rate < 60/minute and it was treated with Inj. atropine sulphate 0.6mg i.v. Hypotension defined as the fall in SBP ≥20% from the base level and was treated with Inj. mephentermine 6mg i.v. Respiratory depression was defined as respiratory rate ≤10 breath/minute. After the patients were shifted to recovery room, HR, SBP, DBP, SpO2, sedation and complications, if any was monitored for 24 hours. Duration of sensory was noted. Patient’s pain score was assessed by visual analogue scale (VAS) (1)– Figure/Table 4. Duration of analgesia was considered from the time of intrathecal injection to when VAS ≥4. Inj diclofenac sodium 1.5mg/kg i.v. was given for analgesia. Number of rescue analgesic in 24 hours were recorded.

**Table/Figure 4: Visual Analogue scale**

**Statistical Analysis**

The collected data were analysed by unpaired student – t test, chi square test and results obtained in the form of range, mean and standard deviation. The probability value ‘p’ of less than 0.05 considered statistically significant.
Results

This study was conducted to compare the effects of intrathecal clonidine and midazolam as an adjuvant to bupivacaine to assess the postoperative analgesia in total abdominal hysterectomy. 60 patients posted for total abdominal hysterectomy between the ages of 40 years and 60 years were divided equally into two groups. The demographic variables such as distribution of age, weight and ASA grading was statistically insignificant between both the groups (p>0.05).

Table/Figure 5: Onset and duration of sensory blockade.

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group M</th>
<th>p-Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sensory block at L1</td>
<td>Mean ± SD (in minutes)</td>
<td>Mean ± SD (in minutes)</td>
<td>p &lt; 0.001</td>
<td>Highly significant</td>
</tr>
<tr>
<td></td>
<td>2.47 ± 0.90</td>
<td>1.63 ± 0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of sensory block</td>
<td>258 ± 17.45</td>
<td>281.17 ± 14.30</td>
<td>p &lt; 0.001</td>
<td>Highly significant</td>
</tr>
</tbody>
</table>

Table/Figure 6: Duration of analgesia

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group M</th>
<th>p-Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>328.50±21.78</td>
<td>373.33±24.22</td>
<td>p &lt; 0.0001</td>
<td>Highly significant</td>
</tr>
</tbody>
</table>

The mean duration of analgesia was statistically significantly longer in group M than group C (p < 0.0001) as seen in Table/Figure 6.

Table/Figure 7: No of rescue analgesics

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group M</th>
<th>p-Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>2.77±0.58</td>
<td>1.87±0.73</td>
<td>p &lt; 0.0001</td>
<td>Highly significant</td>
</tr>
</tbody>
</table>

Table/Figure 7: No of rescue analgesics

The mean number of rescue analgesics given in 24 hours was more in Group C than in group M (p< 0.0001) as seen in Table/Figure 7. Intraoperative sedation score, respiratory rate, arterial oxygen saturation was within normal limits and comparable between the two groups (p >0.05) intraoperatively and post operatively.

Table/Figure 8: Intraoperative complications

<table>
<thead>
<tr>
<th>Intraoperative Complications</th>
<th>Group C</th>
<th>Group M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>33.3%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>10%</td>
<td>nil</td>
</tr>
</tbody>
</table>
Intraoperatively, significant hypotension and bradycardia was noted in group C compared to group M (Table/Figure 8). Postoperatively, the difference in mean systolic blood pressure, diastolic blood pressure and mean heart rate was statistically not significant (p>0.05) between the groups. No side effects were observed post operatively.

**Discussion**

Clonidine is centrally acting partial alpha 2 adrenergic agonist. It inhibits voltage gated Na+ channels and when administered intrathecally it potentiates post-operative analgesia by hyperpolarizing A-delta and C fibre in the substantia gelatinosa of the spinal cord \(^{(17)}\).

Intrathecal midazolam is a benzodiazepine agonist which binds to GABA A receptor leading to enhancement of GABA activity. There is a high density of GABA A receptors in lamina II of the dorsal horn of human spinal cord, possibly explaining the pain modulation effect of midazolam. Benzodiazepines suppress afferent evoked excitation in the substantia gelatinosa and motor horn. Benzodiazepines agonists exert an inhibitory effect on spinal sensory and motor excitability \(^{(18)}\).

In our study, it was found that the difference in demographic variables was statistically insignificant between both the groups (p>0.05) which was in accordance with Suchita A Joshi et al (2011)\(^{(13)}\), Anjali Bhure et al (2011)\(^{(8)}\), Pingley et al (2012)\(^{(14)}\), Piyush Kumar Sengar et al (2016)\(^{(15)}\), Dr. T.chandra Kumar et al (2018)\(^{(5)}\), Gandhi Gunjan P et al (2018)\(^{(16)}\).

**Onset of sensory block:** In our study, it was observed that the mean onset of sensory block at L1 was earlier in group M than in group C (p<0.05). Our findings correlated with the findings of Suchita A Joshi et al (2011)\(^{(13)}\), Gandhi Gunjan P et al (2018)\(^{(16)}\) (Depicted in Table/Figure 5).

**Duration of sensory block:** The mean duration of sensory block in group M was significantly longer as compared to group C (p<0.001). Gandhi Gunjan P et al (2018)\(^{(16)}\), also reported longer duration of sensory block in midazolam group than clonidine group(p<0.001) (Depicted in Table/Figure 5).

**Mean duration of analgesia:** In our study, the mean duration of post-operative analgesia was longer in group M as compared to group C which was highly statistically significant (p<0.001). Mean post-operative analgesic consumption in 24 hours in our study was statistically significantly less in group receiving midazolam compared to group receiving clonidine(p<0.001) which correlates with the studies of Suchita A Joshi et al (2011)\(^{(13)}\), Dr. T.chandra Kumar et al (2018)\(^{(5)}\) and Gandhi Gunjan P et al (2018)\(^{(16)}\) (Depicted in Table/Figure 6, 9)

**Mean number of rescue analgesia in 24 hours:** In our study, the mean number of rescue analgesics given in 24 hours was more in Group C than in group M (p<0.0001) which correlated with studies of Suchita A. Joshi et al\(^{(13)}\) and Gandhi Gunjan P et al\(^{(16)}\) (Depicted in Table/Figure 7,9).
<table>
<thead>
<tr>
<th>SR NO</th>
<th>AUTHOR AND TYPE OF STUDY</th>
<th>STUDY POPULATION</th>
<th>TYPE OF SURGERY</th>
<th>DOSES OF DRUGS USED</th>
<th>DURATION OF ANALGESIA (Mean± Standard deviation)</th>
<th>NO OF RESCUE ANALGESICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Suchita A. Joshi et al(^\text{[13]}), Randomized, double blind, prospective, parallel group clinical trial.</td>
<td>n=50 Group BC: 25 Group BM:25</td>
<td>Lower abdominal surgery</td>
<td>Clonidine: 296.60 ± 52.77 min Midazolam :391.64 ± 132.98 min</td>
<td>Less in BM group</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Dr. T.chandra Kumar et al(^\text{[5]}), Double blinded, randomized case control study</td>
<td>n=60 Group BC: 30 Group BM:30</td>
<td>Lower abdominal surgeries</td>
<td>Clonidine: 306.17 mins Midazolam: 486.17 mins</td>
<td>More in BM group</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Gandhi Gunjan P et al(^\text{[16]}), Observational study</td>
<td>n=60 Group BC: 30 Group BM: 30</td>
<td>Hernia surgeries</td>
<td>Clonidine: 252.5±21.1 mins Midazolam: 351.6±39.1 mins</td>
<td>Less in BM group</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Anjali Bhure et al(^\text{[8]}), Prospective, randomized comparative study.</td>
<td>n=120 Group A(control):30 Group B(clonidine):30 Group C(fentanyl): 30 Group D (midazolam):30</td>
<td>Elective caesarian section</td>
<td>Clonidine 75 µg Midazolam 2.5 mg Fentanyl 25 µg</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>P INGLEY et al(^\text{[14]}), Prospective randomized study.</td>
<td>n=75 Group A(control): 25 Group B(clonidine) :25 Group C (midazolam): 25</td>
<td>Lower abdominal and lower limb surgeries</td>
<td>Clonidine: 420.50 ± 130.80 mins Midazolam: 290.54 ± 46.22</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Piyush Kumar Sengar et al(^\text{[15]}), Randomised study.</td>
<td>n=40 Group C: 20 Group M: 20</td>
<td>Lower limb surgeries</td>
<td>Clonidine 75 µg Midazolam 2.5 mg</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Our study Randomised study.</td>
<td>n=60 Group C: 30 Group M: 30</td>
<td>Abdominal hysterectomy</td>
<td>Clonidine: 328.5±21.78 minutes Midazolam: 373.33±24.22 minutes</td>
<td>Less in BM group</td>
<td></td>
</tr>
</tbody>
</table>

* Data not available.

**Table/Figure 9: Comparison of various studies which used intrathecal clonidine and midazolam.**
Study Limitation

We could not measure the plasma level of drug. Study was restricted to only female patients due to the nature of the study. Sample size is limited, so there is scope to study on large group.

Conclusion

It is concluded that addition of 2.5 mg midazolam to 3ml hyperbaric bupivacaine intrathecally, resulted in faster onset of sensory block, longer duration of sensory block as well as prolonged duration of post operative analgesia compared to 45µg clonidine with 3ml hyperbaric bupivacaine without any side effects. Patients in clonidine group had hypotension and bradycardia but was not significant.

References

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