A STUDY TO COMPARE INTRATHECAL BUPIVACAINE AND BUPIVACAINE WITH NEOSTIGMINE FOR POST OPERATIVE ANALGESIA IN PATIENTS UNDERGOING VAGINAL HYSTERECTOMY

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ABSTRACT
Addition of neostigmine to bupivacaine intrathecally helps anesthesiologists to alleviate intraoperative and post operative discomfort by providing better analgesia in continuation of surgical anaesthesia to patients without prolonging recovery. This study was conducted to study the effects of adding low dose of neostigmine to bupivacaine intrathecally on onset of sensory block, duration of analgesia, onset and duration of motor block and associated side effects. Fifty healthy female subjects , aged between 35-55 years, ASA physical status I & II scheduled for elective vaginal hysterectomy were included in this prospective, randomized, controlled, double-blind study. Patients were randomly divided into two groups of 25 each. Group “A” – Patients who were given local anesthetic – bupivacaine 0.5% -3 ml(hyperbaric) with 0.1ml of normal saline intrathecally to make a total volume of 3.1ml. Group “B” – Patients who were given local anesthetic bupivacaine 0.5% -3 ml(hyperbaric) with 50 microgram of preservative free neostigmine methylsulfate (volume 0.1 ml). All patients were preloaded with 15ml/kg of Ringers lactate solution. No analgesic was given to the subject’s preoperatively. Onset and duration of sensory block and duration of analgesia was recorded along with onset and duration of motor block. Data recording was done during the first hour at 0,1,5,10,15, 30, 60 minutes and thereafter at 4-hour interval for 24 hour postoperative period. Development of any adverse effect was also watched during the study. Patients above score 5 received rescue analgesia in the form of Inj. diclofenac 75mg intramuscular in the post operative period. Time of first rescue analgesic required and visual analogue scale score at that time was noted. Duration of surgery was also noted. The data was analysed using appropriate statistical tests. The two study groups were comparable in terms of age, body weight, height and duration of surgery. The onset of motor block was comparable in the two groups. Duration of sensory and motor block was prolonged in group B patients. Duration of analgesia was significantly longer in Group B (340.40±38.43 min) in comparison to Group A(179.20±21.04 min.). This result showed that spinal neostigmine had significant effect on analgesia along with bupivacaine. Vital parameters were well maintained during intraoperative and postoperative period. No significant difference in vital parameters was seen in the two groups. Few minor side effects like nausea, vomiting, hypotension and bradycardia were found.

Keywords: Bupivacaine, Neostigmine, Spinal Anaesthesia, Postoperative Analgesia, Vaginal Hysterectomy

INTRODUCTION
Perioperative pain management is one of the paramount goals of anaesthetic technique. Various drugs have been tried in the subarachnoid space along with local anaesthetics with the aim of improving the quality of post-operative pain relief. Intrathecal neostigmine is one of the promising methods of providing prolonged postoperative analgesia. It blocks the activity of both true and pseudocholinesterase and thereby enhancing the accumulation and binding of acetylcholine at various cholinergic sites.
Neostigmine offers several advantages such as easy availability and cost effectiveness, reliable and durable postoperative analgesia, availability of preservative free drugs, no untoward side effects like respiratory depression, pruritus and drowsiness as experienced with intrathecal opioids. When it is used in lower doses along with local anaesthetics like lignocaine or bupivacaine, it provides prolonged and effective postoperative analgesia. The aim of this study was to evaluate onset of sensory block and duration of analgesia, to evaluate the onset and duration of motor block, to assess any side effects during the study period.

MATERIALS AND METHODS
The present work was carried out after the approval of the Institutional Ethical Committee of Burdwan Medical College and Hospital, Burdwan and permission of the West Bengal University of Health Sciences (WBUHS). This prospective, randomized, double blind, parallel group study was done under the Department of Anaesthesiology, Burdwan Medical College and Hospital. Fifty adult patients of female gender, ASA physical status I and II, aged between 35-55 years, admitted in the department of Gynaecology & Obstetrics of this hospital for elective vaginal hysterectomy were included as study subjects. The exclusion criteria were patients with systemic (cardiovascular, respiratory, hepatic, renal or CNS) disorders, patients with disease and deformity of the spine, patients with bleeding diathesis, patients having skin disease or local sepsis at the site of lumbar puncture. Patients with hypersensitivity to local anaesthetics and lastly patient refusal. For the purpose of sample size calculation, the duration of effective post-operative analgesia was taken as the primary outcome measure. It was estimated that 23 subjects (recruitment target being 25 subjects per group) were required per group in order to detect the difference of 1 hour in this parameter between the 2 groups with 90% power and 5% probability of type-I error. The calculation assumes a standard deviation of 1 hour. Subjects were divided into 2 groups equal in no.(n=25) Sample was designed as per computerized randomized table. Patients were provided with a patient information sheet in which details of the study and the procedures were written. They were explained about the study and written, informed consent was obtained from them. Group “A” – Patients who were given local anesthetic – bupivacaine 0.5% -3 ml(hyperbaric) with 0.1ml of normal saline intrathecally to make a total volume of 3.1ml. Group “B” – Patients who were given local anesthetic –bupivacaine 0.5% -3 ml(hyperbaric) with 50 microgram(μg) of preservative free neostigmine methylsulfate (volume 0.1 ml, as 0.5mg or 500 μg neostigmine methylsulfate is present in 1ml of commercial preraration of neostigmine so 50 μg of neostigmine methylsulfate is present in a volume of 0.1 ml ) intrathecally making a total volume of 3.1 ml.

Routine investigations like haemogram, electrocardiogram (ECG), blood sugar, urea/creatinine, BT, CT and urine routine examination was obtained. Patient’s height and weight were recorded. All the patients were kept fasting overnight and premedicated with oral diazepam 10 mg and ranitidine 150 mg at bed time on the day prior to surgery. Patients were explained about the procedure of spinal anaesthesia after an IV access was secured with 18 G cannula. All patients were preloaded with 15ml/kg of Ringers lactate solution. Baseline heart rate, blood pressure (BP) and oxygen saturation (Spo2) were recorded. Patients were also explained about Visual analogue score (VAS) and taught how to express the degree of pain on the scale. Before the procedure we checked the prerequisites of giving neuraxial block like anaesthesia machine, oxygen source, suction apparatus, operating table tilts, availability of drugs (atropine, adrenaline, vasopressors, diazepam, thiopentone), defibrillator. Under strict aseptic precautions through midline approach, intrathecal block was performed between L3-L4 or L4-L5 intervertebral space using 26 G Quincke spinal needle in lateral decubitus position. After free flow of CSF, 3 ml of 0.5% bupivacaine (hyperbaric) with 0.1 ml of normal saline to make a total volume of 3.1 ml for group A patients and 3 ml of 0.5% bupivacaine (hyperbaric)with 0.1 ml of neostigmine (which is equivalent to 50 μg of neostigmine) making a total volume of 3.1 ml for group B patients , were injected into subarachnoid space. The dose of intrathecal neostigmine and normal saline was measured by using insulin syringe. Monitoring of vital signs was continued throughout the procedure. Then the patients were positioned and
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all the necessary monitoring devices were connected namely heart rate, oxygen saturation, blood pressure, ECG. The time of intrathecal injection was noted. No analgesic was given to the subject’s preoperatively. Onset and duration of sensory block and duration of analgesia were recorded. Data recording was done during the first hour at 0.1, 5, 10, 15, 30, 60 minutes and thereafter at 4-hour interval for 24 hour post-operative period. Development of any adverse effect was watched during the study. Patients above score 51 received rescue analgesia in the form of Inj diclofenac 75mg i.m. in the post operative period. Time of first rescue analgesic required an using VAS score at that time was noted. Duration of surgery was also noted. The patients’ pulse rate and blood pressure were recorded throughout intra and post-operative period. Spo2 was recorded throughout the intra-operative period. Hypotension was defined by decrease in mean blood pressure> 30% of baseline and was treated with rapid IV fluid and/or mephentermine. Bradycardia defined by decrease in heart rate> 30% of the baseline.

The parameters used for comparison between two groups are:
1. Onset of sensory blockade.
2. Duration of analgesia using VAS.
3. Onset and duration of motor block.
4. Hemodynamic effects.
5. Side effects such as nausea, vomiting, hypotension, bradycardia, sedation and others in any were noted.

All the observations and particulars of each patient were recorded in a proforma. Onset of sensory block was assessed by the time interval between the drug injected into the intrathecal space and absence of pin prick sensation. Duration of sensory block assessed by pin prick method. Time duration (minute) was assessed from onset of sensory block to regression of dermatome of two segments. The duration of analgesia was calculated by the time gap between the onset of sensory block and administration of subsequent analgesics which was given when visual analogue scale (VAS) score >5. Pain was assessed by Visual Analogue Scale which was measured by 0 to 10 cm score from no pain to worst pain as score of 0 = no pain and 10 = worst pain. The time gap between the intrathecal dose of and first rescue analgesia was recorded. Modified Bromage scale was used for motor block assessment. Onset of motor block was calculated from the time gap between the administration of study drug into intrathecal space to achievement of motor block scoring of 2 or more according to modified Bromage Scale. The duration of motor block was measured from the onset of motor block to the regaining of full motor power and joint movement.

Sedation was assessed by 4 point scale:-
1. Barely arousable (sleeping, needs shaking or shouting to arouse).
2. Asleep (eyes closed, arousable with soft voice or light touch).
3. Sleepy (eyes open but less active and responsive).
4. Awake.

The preparation and administration of study drugs, intra-operative and post-operative assessment were done by anaesthesiologists who were not involved in the study.

RESULTS AND DISCUSSION

Results

Table 1: Demographical data of study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A Mean±SD</th>
<th>Group B Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.92±4.22</td>
<td>44.40±5.04</td>
<td>0.712</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>148.48±3.24</td>
<td>149.16±2.95</td>
<td>0.445</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>44.48±5.57</td>
<td>46.0±4.16</td>
<td>0.293</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>98.60±17.35</td>
<td>103.60±19.76</td>
<td>0.748</td>
</tr>
</tbody>
</table>

SD- Standard Deviation
Total of fifty patients were included in the study. No significant differences were detected among the groups with respect to age, weight, height and duration of surgery [Table 1]. The onset of sensory block was similar in both the groups (P>0.05) [Table 2]. But there was a highly significant difference (P < 0.0001 = significant) between group B and group A in respect to the two dermatomal segments regression of sensory level as shown in table 2. So, the two segment regression of sensory block was significantly prolonged with addition of neostigmine. The duration of analgesia which was assessed using VAS was observed in both the groups for 24 hours of post-operative period. The duration of analgesia for group A was 179.20±21.04 min and for group B 340.40±38.43 min [Table 2]. The statistical analysis showed that the time of duration of analgesia in group B was significantly more when compared to group A (p<0.0001).

**Table 2: Comparison of onset and duration of Sensory block and duration of analgesia between groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A Mean±SD</th>
<th>Group B Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sensory block (in seconds)</td>
<td>136.80±13.45</td>
<td>136.60±12.87</td>
<td>0.422</td>
</tr>
<tr>
<td>Duration of sensory block (in minutes)</td>
<td>85.00±8.00</td>
<td>124.48±8.53</td>
<td>0.000</td>
</tr>
<tr>
<td>Duration of analgesia (in minutes)</td>
<td>179.20±21.04</td>
<td>340.40±38.43</td>
<td>0.000</td>
</tr>
</tbody>
</table>

SD- Standard Deviation

There was no significant difference (P>0.05) among the groups in respect to the time for onset of motor block [Table 3]. The duration of motor block which was assessed using modified Bromage scale was observed in both the groups. The duration of motor block for group A was 98.60±8.48 min and for group B 139.20±9.64 min. The statistical analysis showed that the time of duration of motor block in group B was significantly more when compared to group A [Table 3].

**Table 3: Comparison of onset and duration of motor block between groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A Mean±SD</th>
<th>Group B Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of motor block (in minutes)</td>
<td>5.08±1.11</td>
<td>4.88±1.01</td>
<td>0.610</td>
</tr>
<tr>
<td>Duration of motor block (in minutes)</td>
<td>98.60±8.48</td>
<td>139.20±9.64</td>
<td>0.000</td>
</tr>
</tbody>
</table>

SD- Standard Deviation

**Table 4: Comparison of VAS score between groups**

<table>
<thead>
<tr>
<th>Time</th>
<th>Group A Mean VAS±SD</th>
<th>Group B Mean VAS±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 hour</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>1.000</td>
</tr>
<tr>
<td>4 hour</td>
<td>2.72 1.27</td>
<td>0.00±0.00</td>
<td>0.000</td>
</tr>
<tr>
<td>8 hour</td>
<td>2.20±1.29</td>
<td>1.88±1.12</td>
<td>0.291</td>
</tr>
<tr>
<td>24 hour</td>
<td>2.28±1.30</td>
<td>2.36±0.99</td>
<td>0.624</td>
</tr>
</tbody>
</table>

VAS- Visual Analogue Scale, SD- Standard Deviation

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Table 4 summarizes the descriptive statistics for pain scores (VAS Score) of patients in both groups at various time points. The VAS score at 4 hrs. was significantly higher in group A patients (Mann-Whitney U test, p<0.001). So, we concluded that duration of analgesia was significantly prolonged in group B patients. There was a significant difference (p<0.05) between group B and group A with respect to total number of rescue doses required by the patient in the first 24 hours of administration of spinal anaesthesia as shown in Table 5. While group A patients required an average of 3.16 doses, the group B patients needed only 2.12 doses in the study.

Table 5: Number of rescue doses required in the first 24 hrs. after administration of spinal anaesthesia

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A Mean±SD</th>
<th>Group B Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rescue doses (number)</td>
<td>3.16 ±0.55</td>
<td>2.12 ±0.60</td>
<td>0.010</td>
</tr>
</tbody>
</table>

*SD- Standard Deviation*

On comparing frequency of individual adverse events (by Fisher’s exact test) there was statistically no significant difference between the two groups except for nausea and/or vomiting. In group A, 2 patients had hypotension and 1 patient had bradycardia while in group B, 4 patients had nausea and/or vomiting which was amenable to treatment [Table 6].

Table 6: Comparison of adverse effects between groups

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Hypotension</th>
<th>Bradycardia</th>
<th>Sedation</th>
<th>Nausea or vomiting</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP A</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GROUP B</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Discussion

Regional anaesthesia is now increasingly used for gynaecological surgery compared to general anaesthesia. Various drugs have been tried in the subarachnoid space along with local anaesthetics with the aim of improving the quality of post operative pain relief. The cholinesterase inhibitor neostigmine is one among such adjuvants. Neostigmine for intrathecal use along with hyperbaric bupivacaine was chosen for the present study, since it represents a novel approach in providing postoperative analgesia in continuation with surgical anaesthesia. Unlike other opioids and α2 adrenergic agonists, neostigmine is not a direct agonist, but inhibits break down of endogenous spinal neuro-modulator acetylcholine which has been shown to have antinociceptive effects. Potency of intrathecal neostigmine is increased in post operative period, because descending noradrenergic or cholinergic antinociceptive spinal system is activated by ongoing pain causing an increase in release of acetylcholine, which, in presence of neostigmine results in augmented selective analgesia.

In this present study, we observed and compared the onset of sensory block and duration of analgesia, the onset and duration of motor block and any side effects of addition of spinal neostigmine to bupivacaine in patients undergoing vaginal hysterectomy.

The two study groups were comparable in terms of age, body weight, height and duration of surgery. There was no significant difference in onset of sensory block in the two groups. The onset of motor block was comparable in the two groups. Duration of sensory and motor block was prolonged in group B patients. Duration of analgesia was significantly longer in Group B (340.40±38.43 min) in comparison to Group A (179.20±21.04 min). This result showed that spinal neostigmine had significant effect on analgesia along with bupivacaine. Vital parameters were well maintained during intraoperative and...
postoperative period. No significant difference in vital parameters were seen in the two groups. Few minor side effects like nausea, vomiting, hypotension and bradycardia were found. Table 2 shows that there was no significant difference in the time of onset of sensory block in the two groups. In our study addition of 50μg of neostigmine intrathecally in group B patient did not shorten the onset of sensory block and this result correlates with that of Saini et al., (2006). Table 2 shows that there was a highly significant difference (P < 0.0001 = Extremely significant) between group B and group A in respect to the two dermatomal segments regression of sensory level. So, the two segment regression of sensory block was significantly prolonged with addition of neostigmine. The two segment regression of block was prolonged in 50μg neostigmine group as compared to bupivacaine group and this correlates with that of chung et al., (1998) and Saini et al., (2006). We found that there was a highly significant difference between two groups in respect of duration of analgesia. The duration of analgesia in group B was significantly more when compared to group A (p<0.0001). We concluded that addition of 50 μg of intrathecal neostigmine provides a good duration of postoperative analgesia and this correlates with the findings of Pan et al., (1995), Lauretti et al., (1996), Klamt et al., (1997), Krukowski et al., (1997) and Lauretti et al., (1998).

Table 4 shows that VAS score at 4 hrs. was significantly higher in group A patients. So, we concluded that duration of analgesia was significantly prolonged in group B patients. Table 3 shows that there was no significant difference in the time of onset of motor block in the two groups. Table 3 also shows that the duration of motor block in group B was significantly greater when compared to group A (p<0.0001). Table 5 shows that the group B patients needed more rescue doses of analgesics compared to group A patients which was statistically significant (P <0.001). Table 6 shows the comparison of the adverse effects between the two groups. The present study showed nausea and/or vomiting in 4 out of 25 patients belonging to group B with a dose of 50μg on intrathecal neostigmine. Nausea and vomiting incidences were controlled by inj. ondansetron 4 mg i.v. or inj. metoclopramide 10 mg i.v. Bradycardia (Pulse rate fall>30% of the basal value) was noted in 1 patient and hypotension (BP fall > 30% of the basal value) was noted in 2 patients belonging to group A which was amenable to treatment with atropine and i.v fluids respectively.

Krukowski et al., (1997) found that the incidence of nausea and vomiting increases progressively with the increase in dose of intrathecal neostigmine and with 100μg doses, most of their patients had reported nausea and vomiting. It was observed in this study that addition of 50 μg neostigmine to 0.5% bupivacaine administered intrathecally prolongs the duration of analgesia up to 340.40±38.43 minutes compared to 179.20±21.04 minutes with intrathecal 0.5% bupivacaine alone. The total consumption of rescue analgesic was also less in group B compared to group A. There was no significant change in onset of sensory and motor block. Duration of motor block was significantly prolonged in the neostigmine group. There were no significant change in blood pressure, pulse rate and oxygen saturation. There was no significant increase in side effects except nausea and vomiting.

Conclusion
Intrathecal neostigmine in dose of 50μg can be used along with bupivacaine to provide safe, durable and predictable post operative analgesia with minimal adverse effects in patients posted for vaginal hysterectomy. Intrathecal neostigmine in 50μg dose produces minimal nausea and vomiting which can be easily controlled with antimetics.

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