Evaluation of the Effect of Intrathecal Nalbuphine as an Adjuvant to Spinal Bupivacaine for Postoperative Analgesia in Patients Undergoing Abdominal Hysterectomy: A Randomized, Double-Blinded Control Trial

Shahedha Parveen¹, P Krishna Prasad², B Sowbhagya Lakshmi³

¹Assistant Professor, Department of Anaesthesia, Pain and Critical Care, Rangaraya Medical College, Kakinada, Andhra Pradesh, India, ²Associate Professor, Department of Anaesthesia, Pain and Critical Care, Rangaraya Medical College, Kakinada, Andhra Pradesh, India, ³Professor and Head, Department of Anaesthesia, Pain and Critical Care, Rangaraya Medical College, Kakinada, Andhra Pradesh, India

Abstract

Background: Nalbuphine is a synthetic mixed agonist-antagonist opioid, which produces k receptor mediated analgesia to control mild to moderate pain without producing μ receptor mediated side effects when used intrathecally (IT) with bupivacaine.

Aim: To evaluate the onset, quality and duration of sensory, motor blockade, post-operative analgesia, and its side effects if any when nalbuphine is added as an adjuvant for spinal anesthesia in the abdominal hysterectomies.

Methodology: 60 patients of ASA Grades I and II in the age group of 30-60 years were randomly allocated to one of the two groups. Group B (n = 30) received 0.5% hyperbaric bupivacaine {3cc (15 mg) + 0.5 ml sterile water} IT; Group N (n = 30) received 0.5% hyperbaric bupivacaine {3cc (15 mg) + 0.5 ml (1 mg) nalbuphine} IT.

Observations: The characteristics of onset of sensory and motor blockade, duration of effective analgesia (visual analog scale [VAS] score), perioperative hemodynamics, respiratory parameters, and side effects were recorded, tabulated, and statistically analyzed.

Results: The onset of sensory and motor blockade was faster in Group N. The two segment regression time was significantly prolonged in Group N compared to Group B. The total duration of effective analgesia (time from IT drug injection to the point of time when VAS ≥4) was also significantly prolonged in Group N compared to Group B. The hemodynamic, respiratory parameters and intraoperative complications were comparable in both the groups.

Conclusion: IT nalbuphine improved the quality of intraoperative and post-operative analgesia with minimal side effects.

Key words: Nalbuphine, Post-operative analgesia, Spinal anesthesia

INTRODUCTION

Spinal anesthesia is in existence since more than a century, and it is still very common regional anesthesia technique done even today. The local anesthetic drugs used had limited duration of action, hence the need for adjuvants such as opioids, alpha 2 agonists, neostigmine, and magnesium. Among them, the intrathecal (IT) opioid administration has been found to provide superior quality of analgesia after a variety of surgical procedures.

The reason for mixing of opioids and local anesthetics is that this combination will eliminate the pain by acting at two different locations, local anesthetics acting at the nerve axon and the opioids at the receptor site in the spinal cord.
Nalbuphine is a highly lipid soluble opioid with an agonist action at the kappa and an antagonist activity at the mu opioid receptors. Nalbuphine and other kappa agonists had provided reasonably effective analgesia in some models of visceral nociception. As Nalbuphine is an agonist-antagonist, it is unlikely to cause side effects such as respiratory depression, urinary retention, pruritus, and excessive sedation, due to its action at kappa receptors.

There are very few studies of IT nalbuphine for post-operative analgesia, and because of this reason, we have decided to take up this randomized study to evaluate the effects of IT nalbuphine 1 mg added to 0.5% hyperbaric bupivacaine in patients undergoing an abdominal hysterectomy.

**METHODOLOGY**

After getting approval from Institutional Ethics Committee and written consent, 60 patients, ASA I and ASA II, in the age range of 30-60 years, posted for abdominal hysterectomy were selected.

**Exclusion Criteria**

Patients with a respiratory disorder and those with a prior history of opioid and other substance abuse, history of drug allergy, and also those unwilling to participate in the study, ASA Grade III and IV and any contraindication to spinal anesthesia were omitted from the study.

All the selected patients were explained about the assessment of pain with the help of visual analog scale (VAS), and then their written and informed consent was taken.

Patients were randomly allocated into two groups of 30 each. Patients in Group B were given 0.5% bupivacaine heavy (3 cc) + 0.5 ml sterile water while patients in Group N were given 0.5% bupivacaine heavy (3 cc) + 0.5 ml (1 mg) nalbuphine for spinal anesthesia.

Patients were premeditated with injection atropine 0.6 mg I.M and injection Rantididine 50 mg I.V, both ½ h before surgery. Preloading was done with ringer lactate 10 ml/kg body weight 20 min before spinal anesthesia was given by taking into consideration all aseptic and antiseptic precautions, using 25 g Quincke type spinal needle. Patients were turned supine immediately at the end of the injection and observations were recorded as shown below:

**Sensory Block - Assessed by Using “Pin-Prick” Method**

1. The onset of sensory block: Immediately after the spinal injection was given, patients were checked for loss of pinprick sensation at L1 dermatome, and that time was taken as an onset of sensory block.
2. The highest sensory level achieved
3. Two segment regression time: The time interval from highest sensory level to two segment regression of the sensory block
4. Duration of sensory block: The time interval from the onset of sensory block to regression of sensory level to L1 dermatome again.

**Motor Block- Assessed by the Bromage Scale**

1. Grade 0 - No muscular weakness
2. Grade I - Unable to flex the hip
3. Grade II - Unable to flex the knee
4. Grade III - Unable to flex the ankle.

Following things were observed in motor block:

1. The onset of motor block: The time interval from IT injection to achievement of motor block of Bromage Grade I
2. Maximum motor block achieved
3. Duration of motor block: The time interval from the onset of motor block to regression of motor block to Bromage Grade 0.

Recordings of pulse rate, blood pressure, SPO2, respiratory rate were done at 1, 3, 5 min and then every 5 min until 15 min and every 15 min until the end of the procedure.

Intraoperative sedation scores were defined by Ramsay sedation score. After the operation, pain, sensory level, and motor block were evaluated at every 30 min during the first 2 h, and at every 60 min for the next 6 h, and at 12 and 24 h after arriving in the recovery room. Visual analog scale was used to evaluate the pain intensity. Side effects of pruritus, post-operative nausea and vomiting (PONV), sedation, urinary retention, euphoria or dysphoria, and respiratory depression were recorded for 24 h. The durations of complete analgesia (time from the IT injection to the first pain report, VAS score >1) and effective analgesia (time from the IT injection to the first analgesic requirement, VAS score >3) were noted. At this time, patients were given rescue analgesic- injection diclofenac sodium 1.5 mg/kg. Intramuscular Patients were monitored for various intra and post-operative complications. All the recorded data were statistically analyzed, and the significance was measured as a probability of occurrence by the t-test.

1. $P > 0.05$ - Not significant
2. $P < 0.05$ - Significant
3. $P < 0.001$ - Highly significant.

**RESULTS**

The two groups are nearly similar to each other demographically in age, weight, and ASA physical status.
No major difference was found in various hemodynamic or vital parameters between the two groups. However, there was a significant difference in $P<0.001$ between mean onset and a complete sensory block in Group N and Group B. The mean onset and complete motor block in Group N and Group B also showed statistical significance in $P<0.05$. Group N has shown a faster onset compared to Group B in both the cases. The distribution of sensory level in both the groups was similar; the maximum was reached up to T8 level. The mean regression in sensory (taken as regression up to L1 level) and motor block in Group N and Group B showed statistical significance ($P<0.001$). Similarly, mean duration of requirement of first rescue analgesia in Group N and Group B showed significant difference in $P<0.001$, this has highlighted the fact that Group N had prolonged post-operative analgesia. Group N showed a significantly higher median Ramsay sedation score than Group B, $P<0.001$ (Table 1).

There was a drop in the systolic blood pressure, but it was not statistically significant. There was no change in the mean respiratory rate as well as mean oxygen saturation as measured by pulse oximeter during intra, as well as post-operative periods ($P>0.05$). Side effects, such as nausea, vomiting, and urinary retention, were observed in Group N in one patient each. In Group B, two patients had nausea, and another two had urinary retention.

**DISCUSSION**

Spinal anesthesia is the preferred technique for gynecological surgeries. Pain and stress-free post-operative period bring about early mobilization and recovery thereby reducing the morbidity and mortality of any surgical operation. It has been well-documented that the combination of opioid and local anesthetics administered IT has a synergistic analgesic effect thus providing powerful potentiation of analgesia by local anesthetic. Opioids, however, act through various receptors. Spinal opioids can provide profound post-operative analgesia with fewer central and systemic adverse effects than with opioids administered systemically. Most commonly used IT opioids are mu agonist drugs that provide excellent analgesia but carry along with them various mu-mediated side effects. Eventually, it was established that significant analgesia can be obtained by kappa binding sites as well with the added advantage of bypassing mu related side effects.

Nalbuphine is a mixed agonist-antagonist drug, when it binds to kappa receptor, has the agonistic activating effect similar to that of endogenous dynorphins, and it competitively displaces other mu agonists from the mu receptor, thereby exhibiting less respiratory depression.

In the present study, bupivacaine with nalbuphine as an adjuvant to see the duration of analgesia after the operation and side effects was used. After the subarachnoid block was given, there was a significant difference between the onset of sensory and motor block in Group N.

Our results have shown that the onset of sensory and motor block was faster and time taken to attain complete sensory and motor block to occur was shorter in the N Group as compared to B Group. The mean onset of sensory block in Group N was $1.63 \pm 0.57$ min compared to $3.23 \pm 1.03$ min in Group B. The $P<0.001$ is statistically significant (Graphs 1 and 2).

The same type of results were documented by Xavier et al., in their study of 100 female patients posted for elective cesarean section who were given three different doses of nalbuphine (0.2 mg, 0.8 mg, or 1.6 mg) or morphine (0.2 mg) IT. They found that IT nalbuphine provided significantly faster onset of pain relief compared to IT morphine, probably due to its lipophilic nature. Xavier et al., in 2000, performed a comparative study to evaluate post-operative analgesia and adverse effects after using three doses, i.e., 0.2 mg, 0.8 mg, and 1.6 mg of IT nalbuphine or morphine 0.2 mg given for cesarean section along with bupivacaine. The longest durations of complete and effective analgesia among the nalbuphine-treated groups are provided by 0.8 mg added to bupivacaine. Neither pruritis nor PONV was observed with nalbuphine 0.2 and 0.8 mg. IT nalbuphine 0.8-1.6 mg improved the quality of intraoperative analgesia and provided a significantly faster onset of pain relief, compared with IT morphine, probably due to its lipophilic properties. They concluded that 0.8 mg of IT Nalbuphine improves intraoperative analgesia and delays early post-operative analgesia without increasing the risk of any side effects.

In contrast to these studies, Tiwari et al., in their study, have shown that onset of sensory and motor blockade was not affected by adding nalbuphine IT. In a study of 75 patients posted for lower limb and lower abdominal surgeries, who received either 0.2 mg or 0.4 mg nalbuphine or plain bupivacaine IT. This disparity in the onset of the

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**Table 1: Onset, duration of sensory, motor block, and first rescue analgesia (mean±SD)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group N</th>
<th>Group B</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sensory block (min)</td>
<td>1.63±0.57</td>
<td>3.23±1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset of motor block (min)</td>
<td>3.77±1.21</td>
<td>4.87±1.76</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Two segment regression time</td>
<td>99.6±9.86</td>
<td>72.33±9.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of sensory block (min)</td>
<td>362.50±34.71</td>
<td>133.33±25.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of effective analgesia</td>
<td>420.4±25.30</td>
<td>170.83±27.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median Ramsay sedation score</td>
<td>3</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD: Standard deviation
blockade could be related to the lower dose of nalbuphine used in this study. The effect of addition of nalbuphine to bupivacaine used for elderly patients undergoing surgeries under spinal anesthesia and in patients scheduled for lower abdominal and the lower extremity surgeries concluded that nalbuphine provided post-operative analgesia for 8-9 h without any adverse side effects.

We observed that the post-operative regression of sensory and motor block was significantly delayed in Group N than in Group B, (Graphs 3 and 4) and the first rescue analgesic requirement in Group N (420.4 ± 25.3 min) was significantly delayed than in Group B (170.83 ± 27.59 min). (Graph 5) These results are in accordance with the study done by Mukherjee et al. He demonstrated that the longest duration of post-operative analgesia was the group in which 0.8 mg nalbuphine was used as an adjuvant as compared to lower doses of nalbuphine, i.e., 0.2 and 0.4 mg.

In the year 2011, Mukherjee et al., formulated a study to determine whether nalbuphine prolongs analgesia by comparing with control and to find out the optimum dose of IT nalbuphine by comparing the 0.2, 0.4, and 0.8 mg doses which prolonged post-operative analgesia without increased side effects. It was observed that effective analgesia increased with increase in concentration, and the
final observation of prolongation of analgesia was with 0.4 mg of nalbuphine with 0.5% hyperbaric bupivacaine without any side effects.

A study by Gear et al.,\textsuperscript{16} suggests that women report higher pain levels or exhibit less tolerance than men for a given stimulus intensities and Kappa opioid analgesia is greater in females than males, that proves that Kappa agonist drugs like nalbuphine can be used to control the visceral pain caused by hysterectomy.

During spinal anesthesia, as the patient is conscious about the surroundings, most of the time it becomes necessary to sedate the patient as this will reduce his anxiety and also minimizes the awareness about routine operating room proceedings. IT nalbuphine has an added advantage of providing intraoperative sedation thus reducing or even abolishing the need for any other sedative drug.

In our study, Group N, 23 out of the 30 patients, had an intraoperative Ramsay sedation score of 3 or 4 as compared to only 3 patients in Group B. Xavier et al., found comparable sedation scores in all four groups in their study, because of the fact that they were comparing sedation scores of nalbuphine with morphine, and morphine in itself has some sedative effects.\textsuperscript{7}

Opioid receptor activation reduces intracellular cyclic adenosine monophosphate formation and opens the potassium channels (mu and delta) or suppresses voltage-gated N-type calcium channels (Kappa receptors). These actions result in neuronal hyperpolarization and reduced availability of intracellular calcium that will lower neurotransmitter release by central nervous system and myenteric neurons,\textsuperscript{10} thereby prolonging the duration of effective analgesia.

In the year 2011, Mostafa et al.,\textsuperscript{11} compared the analgesic effects and duration of analgesia as well as the side effects of 50 mg tramadol or 2 mg nalbuphine, which was administered via the IT route for post-operative pain relief after transurethral resection tumor of the bladder. They concluded that in both the groups there was similar motor block, nearly equal analgesia, delayed first analgesic request, and less analgesic supplement over the first 24 h of operation. No significant post-operative complications, such as itching, respiratory depression, neurological sequelae, were observed among the two groups.

The practice of administering IT nalbuphine for more than ten years did not have any reports of neurotoxicity. The previous studies have been conducted on pregnant patients also but did not reveal any untoward effects.

In the year 1991, Rawal et al.,\textsuperscript{12} has studied the behavioral and histopathological effects following IT administration of butorphanol, sufentanil, and nalbuphine in sheep. They concluded that nalbuphine was the least irritating to neural tissue even when it was used in large doses, and it was associated with minor behavioral and electroencephalogram changes.

On statistical analysis, patients belonging to Group B complained of pain earlier than that of Group N. Patients who received bupivacaine with nalbuphine had significantly longer duration of the first request for analgesia when compared to patients who received bupivacaine alone ($P < 0.001$), and this is highly significant. On inter and intra group comparison, there were no significant changes in pulse rate at any time during the intraoperative period. However, the fall in blood pressure did occur but it was not of the grade of hypotension, i.e., change in blood pressure of <20% of baseline value and hence, this falling blood pressure is considered as physiological fluctuations only.\textsuperscript{13} Intergroup comparison showed no statistically significant value. In our study, there was no significant change in respiratory rate during the intraoperative and post-operative period in both the groups. Nalbuphine exhibits ceiling effect for respiratory depression.\textsuperscript{14,15} Since respiratory depression is predominantly $\mu$ receptor-mediated effect and nalbuphine is a $\mu$ receptor antagonist, respiratory depression effect is expected to be attenuated by nalbuphine. None of the patients had other $\mu$ related side effects such as urinary retention, constipation, and pruritis.

**CONCLUSION**

In conclusion, addition of nalbuphine in the dose of 1mg to IT hyperbaric bupivacaine 0.5%, in patients undergoing abdominal hysterectomy hastens the onset of both the sensory and motor block, prolongs the two segment regression time, duration of sensory block, duration for first rescue analgesic, provides desirable sedation intraoperatively along with maintaining stable hemodynamic, and respiratory parameters without any significant perioperative complications.\textsuperscript{16}

We conclude that nalbuphine can be used as an effective adjuvant along with IT hyperbaric bupivacaine to provide a pain-free post-operative interval.

**REFERENCES**


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