Original Article

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A Prospective Randomized Double-Blind Study to Evaluate the Effects of Intrathecal Nalbuphine in Patients of Lower Abdominal Surgeries under Spinal Anaesthesia

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Abstract

Introduction: Various adjuvants are used for the prolongation of anesthesia during the subarachnoid block. Opioids are very commonly used, and it is commonly associated with many benign risks, although nalbuphine proposed to be a safer alternative as it is an opioid receptor agonist-antagonist. We designed this randomized study to evaluate the effects of intrathecal (IT) nalbuphine in patients of lower abdominal surgeries under spinal anesthesia.

Materials and Methods: A total of 70 patients of either sex, aged between 18 and 60 years, American Society of Anaesthesiologists physical status Grade I and II undergoing elective lower abdominal surgeries under spinal anesthesia were enrolled in this study. Patient was randomly assigned to two groups (35 patients each); Group B, injection heavy bupivacaine 0.5% (2.5 ml) + normal saline (0.5 ml) administered IT and in Group N, heavy bupivacaine 0.5% (2.5 ml) + nalbuphine 0.8 mg (diluted to 0.5 ml normal saline) administered IT. Patients hemodynamic/sensorimotor variables were noted.

Results: The onset time of sensory in Group B was 3.78 ± 1.31 min whereas in Group N was 1.29 ± 0.43 min ($P < 0.05$). The duration of sensory block in Group B and Group N was 123.65 ± 21.23 min and 166.24 ± 29.84 min ($P < 0.05$) while similar statistical significance was observed in between groups for duration of motor blockade (Group B; 178.67 ± 28.34 min and Group N; 256.41 ± 33. 41 min). Duration of analgesia in Group B (201.31 ± 34.31 min) and Group N (298.43 ± 30.92 min) was statistically significant among groups ($P < 0.05$). The patients recorded a mean visual analog scale score of 2.87 ± 0.29 min at 180 min (Group B) while 2.89 ± 0.47 min at 270 min (Group N) after starting of spinal anesthesia.

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 a very popular and common technique for lower abdominal surgeries. However, due to the short duration of action and early arising post-operative pain the role of various adjuvants has been proposed and evaluated. Post-operative pain and tissue injury associated with surgery initiate a systemic stress response that has neuroendocrine, immunological, and hematological responses.[1] Intrathecal (IT) administration of adjuvants drugs to local anesthetics improves quality and duration of the spinal blockade, and prolongs post-operative analgesia. Moreover, the dose and amount of local anesthetic drugs are also reduced during the subarachnoid block (SAB).

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IT opioids (morphine, fentanyl and sufentanil), alpha 2 adrenergic agonists (clonidine and dexmedetomidine) are the most commonly utilized to improve the quality and duration of neuraxial anesthesia. The common problems encountered with the use of intraspinal opioids are their side-effects that include nausea/emesis, pruritis, constipation, undesirable sedation, respiratory depression and the development of tolerance/dependence.[2] However, nalbuphine (a mixed opioid agonist-antagonist) can prove to be particularly advantageous because of the potential to maintain or even enhance opioid-based analgesia while simultaneously eliminating the common μ-opioid side-effects.[3,4] Kappa receptors are distributed throughout the brain and spinal cord involved in nociception. Nalbuphine binds avidly to kappa-receptors in these areas to produce analgesia.[5]

Limited literature regarding the use of IT nalbuphine with hyperbaric bupivacaine is found and thus the aim of our study is to observe the possible prompt onset of sensory/motor block and the duration of action with the use of this drug. Our primary outcome is the duration of analgesia. We also evaluated the side-effects with the addition of nalbuphine IT.

MATERIALS AND METHODS

After taking due consent from 70 patients of either sex, aged between 18 and 60 years, American Society of Anaesthesiologists physical status Grades I and II, we designed a prospective, randomized, double-blinded study to be performed in a Teerththanker Mahaveer Medical College and Research Center, undergoing elective lower abdominal surgeries (*viz*. urological and general surgical procedures) under spinal anesthesia. Patients not given consent, infection at the injection site, prior history of spine surgery, hypovolemia, coagulopathy, spinal deformities, increased intracranial pressure, indeterminate neurologic disease, communication problems, known hypersensitivity to local anesthetics and opioids are excluded from our study.

A sample size calculation was done using the standard deviation of the time to the first request for analgesics. To find a 30 min difference in the mean duration of the first request for analgesics (two sided - alpha of 5% and beta of 10%), 23 subjects enrolled per group. We decided to include 35 patients per group to allow for possible dropouts.

Patients were divided into two groups (35 patients each) using computer generated randomization. In Group B, injection heavy bupivacaine 0.5% (2.5 ml) + normal saline (0.5 ml) administered IT. In Group N, heavy bupivacaine 0.5% (2.5 ml) + nalbuphine 0.8 mg (diluted to 0.5 ml normal saline) administered IT.

All patients were premedicated with injection ondansetron (4 mg intravenous [IV]) and preloading was done by Lactate Ringers (10 ml per kg). Standard monitors (pulse oximeter for SpO_2, heart rate (HR), non-invasive blood pressure, respiratory rate and EKG) were applied. Preparation of IT drugs was done by an independent anesthesiologist not involved in the study and the drug mixture to be administered by another anesthesiologist who will be blinded and performing spinal anesthesia. The volume of the drug, the size of the syringe and color of the drug of interest would be similar in both groups.

Spinal anesthesia would be performed in all patients in the sitting position. Under strict aseptic precautions, using 25G Quincke needle mid-line spinal puncture was performed at the L3 L4/L4-L5 level. After observing the free flow of cerebrospinal fluid, a total volume of 3 ml of spinal solution was administered to each patient over approximately 10-15 s. Patients were moved to the supine position immediately after administering the spinal block. The completion of the injection was taken as zero time of the induction of anesthesia.

Hemodynamic variables in the form of systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR were noted every 3 min up to 15 min and then every 15 min up to 300 min irrespective of the duration of surgery. Hypotension (SBP <90 mm Hg or >30% fall from the baseline value) was treated by injection mephentermine 6 mg IV and an extra bolus of 100 ml of Ringer lactate. Bradycardia (HR <50 beats/min or >30% decrease from the baseline value) was treated with IV atropine (0.5 mg). Surgery would be allowed to proceed when T10 block level achieved.

Sensory block level (loss of pain sensation to pinprick test in the midclavicular line) was measured every 1 min until it reached T10 level, and the surgeons were asked to start. Duration of sensory block defined as the time to two segment regression time from the highest level of the sensory blockade. Modified Bromage scale[6] was used to assess the degree of motor block and the duration of motor blockade as the time required for motor blockade return to Bromage's Grade I from the time of onset of motor blockade was measured. Post-operatively, sensory level, and motor block, pain was evaluated every 30 min during the first 2 h, every 60 min for the next 6 h, and at 12 and 24 h after entrance in the recovery room.

The intensity of pain was assessed by visual analog scale (VAS)[7] at every 10 min for 60 min and then after every

30-min intervals till 300 min after injection or until rescue analgesic was given to the patient. Patients reporting a VAS score (more than 3) received rescue analgesics in the form of injection diclofenac (75 mg im). Nausea and vomiting were managed with injection ondansetron 4 mg IV and pruritus was treated with chlorpheniramine maleate (4 mg IV).

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for windows version 21.0 software, Chicago, SPSS Inc. Student's *t*-test was used for the analysis of parametric data while fisher/Chi-square test for nonparametric data. $P < 0.05$ was considered as statistically significant.

RESULTS

Demographic data (age, weight, height, duration of surgery) of both the groups were found to be comparable ($P > 0.05$) (Table 1). There was no case of failure/inadequate blockade after SAB.

The onset time of sensory block in Group B was 3.78 ± 1.31 min while in Group N was 1.29 ± 0.43 min ($P < 0.05$), but statistically insignificant result was observed in between groups in onset of motor blockade (Table 2). The duration of sensory block in Group B and Group N was 123.65 ± 21.23 min and 166.24 ± 29.84 min ($P < 0.05$) (Table 2) while similar statistical significance was observed in between groups for duration of motor blockade (Group B; 178.67 ± 28.34 min and Group N; 256.41 ± 33. 41 min) (Table 2). Duration of analgesia in Group B (201.31 ± 34.31 min) and Group N (298.43 ± 30.92 min) was statistically significant among groups ($P < 0.05$) (Table 2).

Table 1: Demographic data (mean±SD)

Variable	Group B (*n*=35)	Group N (*n*=35)	*P* value
Age (years)	42.67±13.93	44.63±12.81	0.54
Weight (kg)	69.45±9.65	71.71±10.82	0.36
Height (cm)	166.36±7.59	163.47±8.89	0.14
Sex (M:F)	14:21	18:17	
Duration of surgery (min)	107.35±18.11	111.15±20.17	0.41

SD: Standard deviation

Table 2: Block characteristics (mean±SD)

Variable	Group B (*n*=35)	Group N (*n*=35)	*P* value
Onset of sensory block (min)	3.78±1.31	1.29±0.43	0.0001*
Onset of motor block (min)	4.91±1.50	5.45±1.32	0.11
Duration of sensory block (min)	123.65±21.23	166.24±29.84	0.0001*
Duration of motor block (min)	178.67±28.34	256.41±33.41	0.0001*
Duration of analgesia (min)	201.31±34.31	298.43±30.92	0.0001*

SD: Standard deviation, *: <0.05

After SAB, the results were comparable with respect to the intraoperative mean HR, systolic/DBP, SpO_2, respiratory rate between the groups.

The patients recorded a mean VAS score of 2.87 ± 0.29 min at 180 min (Group B) while 2.89 ± 0.47 min at 270 min (Group N) after starting of spinal anesthesia and were given rescue analgesics when VAS was 3 or more (Table 3 and Figure 1). Only two patients reported nausea/vomiting in Group B, but five patients complaint about the same in Group N, thereby injection ondansetron (4 mg IV) given and patients were relieved (Table 4).

DISCUSSION

SAB is a more popular technique of anesthesia for lower abdominal surgeries. Bupivacaine added to various adjuncts prolongs the duration of analgesia and hence take care for better post-operative analgesia. Reduction in the dosages of local anesthetics holds the key for better anesthesia and to prevent high spinal blocks. With the addition of various adjuncts, the local anesthetic toxicity and the chances of dreadful high spinal blocks are minimized.

Culebras *et al*.[8] conducted a study where they compared IT morphine with different doses of nalbuphine and concluded that 0.8 mg dose of nalbuphine was appropriate for effective analgesia without any side effects. Based on similar results we also incorporated similar dose (0.8 mg of nalbuphine) for our study.

The onset of sensory block was significant among patients receiving nalbuphine as compared to Group B, because

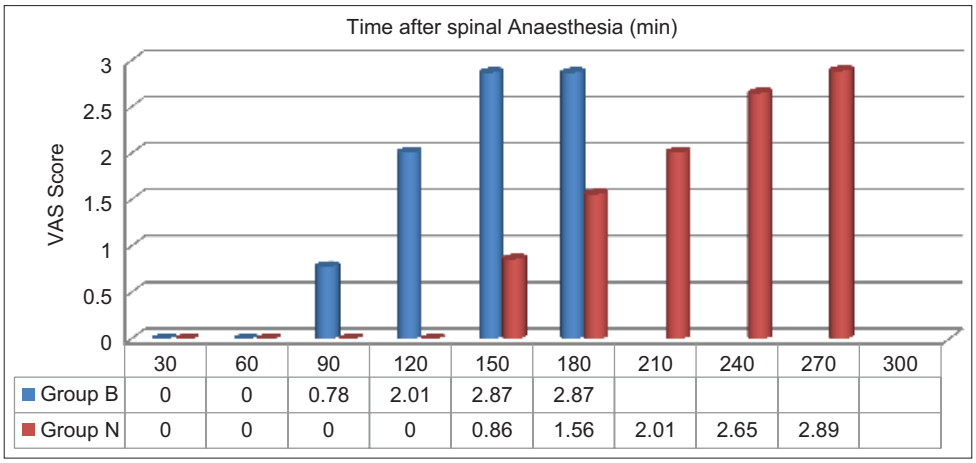
Table 3: VAS scores comparison (mean±SD)

Time (from induction in min)	Group B (*n*=35)	Group N (*n*=35)
30	0	0
60	0	0
90	0.78±0.67	0
120	2.01±0.34	0
150	2.87±0.29	0.86±0.24
180	2.87±0.29	1.56±0.38
210	R	2.01±0.46
240		2.65±0.39
270		2.89±0.47
300		R

R: Rescue analgesic given, VAS: Visual analog scale, SD: Standard deviation

Table 4: Side-effects

Side-effects	Group B (*n*=35)	Group N (*n*=35)
Nausea/vomiting	2	5
Urinary retention	0	0
Respiratory depression	0	0
Pruritus	0	0



	30	60	90	120	150	180	210	240	270	300
Group B	0	0	0.78	2.01	2.87	2.87				
Group N	0	0	0	0	0.86	1.56	2.01	2.65	2.89	

Figure 1: Vas score after spinal anesthesia

of the high lipophilic nature of nalbuphine.[9] Although, the onset of motor block was found to be comparable in between groups. This observation is further supported by Shakooh and Bhosle[10] as they found the similar better onset of the sensory block of nalbuphine mixed drug in their study. Fournier *et al*.[11] had also demonstrated that after total hip replacement IT administration of nalbuphine through an indwelling catheter resulted in a significantly faster onset of pain relief as compared to IT morphine. Culebras *et al*.[8] observed the similar faster onset of pain relief by using nalbuphine in spinal anesthesia in caesarean patients as compared to morphine. Gomaa *et al*.[12] observed that patients given fentanyl had the more rapid onset of the motor block as compared to nalbuphine as fentanyl has high lipid solubility and rapid tissue uptake. However, Tiwari *et al*.[13] observed on 75 patients posted for lower limb and lower abdominal surgeries that onset of sensory/motor blockade was not affected by adding nalbuphine IT.

We observed that the duration of sensory/motor block was significantly greater in Group N than Group B. The time for first rescue analgesic requirement was 270 min for the nalbuphine mixed drug and 180 min for bupivacaine only group, thereby improving the duration of analgesia. Mukherjee *et al*.[14] also observed the prolongation of the duration of analgesia and similarly found that the patients who received 0.8 mg of IT nalbuphine had longest duration of post-operative analgesia. Shakooh and Bhosle.[10] observed the increase in post-operative analgesia by the use of 0.8 mg IT dose of nalbuphine and Tiwari *et al*. (0.2 mg of IT nalbuphine).

In our study, five patients' complaint of nausea/vomiting for which injection ondansetron (4 mg IV) was given, and the patients were relieved. No other side effect were noted during the study and well tolerated by the patients studied. Yoon *et al*.[15] concluded that post-operative analgesia was prolonged in the morphine group and morphine with nalbuphine group, but the incidence of pruritus was significantly lower in the nalbuphine group, while the incidence of nausea and vomiting did not differ in the different groups. Culebras *et al*.[8] noted increase in complications by the use of 1.6 mg of IT nalbuphine while the duration of post-operative analgesia is statistically insignificant among the groups receiving 0.8 mg and 1.6 mg of IT nalbuphine, again justifying our choice of 0.8 mg dose of IT nalbuphine.

In 2005, FDA advised that nalbuphine should be used judiciously in patients of labor and delivery. No signs of neurotoxicity are reported till now with the use of Nalbuphine. Although this drug is still having issues regarding its safety but Rawal *et al*.[16] reported no psychomotor and histopathologic abnormalities with the use of 0.75 mg/kg of nalbuphine.

CONCLUSION

From our study, we concluded that post-operative analgesia was better taken care off with 0.8 mg IT nalbuphine with minimal side-effects. We recommend 0.8 mg as the optimal dose of nalbuphine if used IT along with 12.5 mg (0.5% heavy bupivacaine) for SAB in patients undergoing lower limb abdominal surgeries.

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