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Comparison of nalbuphine and morphine as intrathecal adjuvant to 0.5% bupivacaine for post-operative analgesia in lower abdominal surgeries – A randomized and control study

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ABSTRACT

Background: The use of a higher volume of 0.5% bupivacaine, however, is associated with hemodynamic instability. Adjuvants such as morphine and other opioids are added in with the local anesthetic to reduce this adverse effect and extend the duration of sensory block, hence extending the length of analgesia. However, opiates are associated with a high risk of respiratory depression and other side effects. Nalbuphine has been used to counteract these adverse effects. Thus, we decided to compare the analgesic effect of intrathecal (IT) nalbuphine with IT morphine. **Aims and Objectives:** The aim of the study was to compare IT morphine with nalbuphine as adjuvant to a spinal anesthetic agent. The primary objective was to compare between the time of onset of sensory and motor blockade and the post-operative analgesic duration between the two adjuvants, while hemodynamic variables and side effects were studied as secondary variables. **Materials and Methods:** This randomized controlled study was conducted after Ethical Committee approval for a period of 1 year on 100 patients who fulfilled the inclusion criteria. They were randomized into two groups to receive sub-arachnoid block: Group A: 3 mL of 0.5% Hyperbaric Bupivacaine and 0.2 mg morphine and Group B:3 mL of 0.5% Hyperbaric Bupivacaine and 0.5 mg nalbuphine. The following parameters were monitored – Height, Weight, blood pressure, American Society of Anesthesiologists grading, time of onset, maximum duration and regression of Motor and sensory blocks, and total duration of analgesia. **Results**: The onset of sensory blockade was comparable in both groups while the onset of motor blockade was significantly longer in the morphine group ($P \leq 0.001$). The duration of analgesia in the morphine group was longer as compared to nalbuphine group and was statistically significant ($P < 0.05$). The incidence of side effects was 26% in the morphine group and 6% in the nalbuphine group, which was statistically significant ($P < 0.05$). Fourteen patients in the morphine group had pruritus and four patients in the nalbuphine group experienced nausea. **Conclusion:** IT nalbuphine with 0.5% bupivacaine produces rapid onset of anesthesia and early post-operative analgesia with minimal side effects, but the total analgesic duration was more with IT morphine.

Key words: Sensory block; Local anesthetic adjuvants; Intrathecal; Nalbuphine; Morphine

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INTRODUCTION

Ever since the discovery of spinal anesthesia by August Bier, it is the preferred technique for most of the surgeries below the umbilicus as it allows the patient to remain awake and minimizes or completely avoids problems associated with airway management. In the recent years, 0.5% bupivacaine has replaced 5% lignocaine for spinal anesthesia.[1] However, hemodynamic instability is observed with higher volumes of 0.5% bupivacaine. To minimize, this side effect and to maximize the duration of the sensory block thus prolonging the duration of analgesia,

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adjuvants like opioids can be added to the local anesthetic. They augment the analgesia produced by local anesthetic through direct binding with spinal opioid receptors.[2]

Intrathecal (IT) morphine has the benefit of being delivered into the subarachnoid space, where it has direct access to opiate receptors and ion channels. However, the adverse effects include dose-dependent respiratory depression, vomiting and/or nausea, bradycardia, hypotension, pruritus, and urinary retention. IT nalbuphine is considered to have less side effects.[3]

A systematic review by Seki et al., in 2021 confirmed that IT opioids benefit post-operative analgesia. Although morphine seems to be the most appropriate agent, some results were inconsistent, and the evidence confidence was often moderate or low, especially for adverse outcomes.[3] Nalbuphine is a morphinan semisynthetic agonist-antagonist opioid, which exerts pharmacological effects mainly by activating kappa (κ)-receptors and antagonizing mu (μ)-receptors providing analgesia of visceral nociception.[4] It has a strong analgesic effect and can antagonize nausea and vomiting caused by some μ receptors.[5] It has been observed to have lower incidence of nausea, vomiting, and respiratory depression compared to Morphine.[6,7] It does not cause any significant hemodynamic or respiratory complications.[8] When administered systemically, nalbuphine has been used to counteract the adverse effects of spinal opiates and has been shown to have a lower incidence of respiratory depression.[9] Thus, we undertook this study to compare the effects of 0.2 mg morphine and 0.5 mg nalbuphine as an adjuvant with 15 mg of 0.5% hyperbaric bupivacaine intrathecally in lower abdominal and lower limb surgeries regarding duration of analgesia and adverse outcomes.

Aims and objectives

The aim of the study was to compare Intrathecal morphine with nalbuphine as adjuvant to a spinal anesthetic agent. The primary objective was to compare between the time of onset of sensory and motor blockade and the post-operative analgesic duration between the two adjuvants, while hemodynamic variables and side effects were studied as secondary variables.

MATERIALS AND METHODS

This prospective and randomized study was planned in a tertiary care hospital among patients undergoing lower abdominal surgeries. After getting the approval of the Institutional Ethics Committee, (Institutional Ethics Committee of ESIC Medical College and PGIMSR - No - 04-17/04/2017), the study was conducted for a period of 1 year in accordance with the Helsinki Declaration of 1975, as revised in 1983. Written, informed consent was obtained for all patients before enrolling for the study.

Inclusion criteria

Patients who were in the age group of 30–60 years, belonging to either sex, weighing 50–70 kg, with a height of 150–180 cm, and American Society of Anesthesiologists (ASA) 1 and 2 statuses were explained about the procedure and its complications. Patients who were willing for the procedure were enrolled into the study after getting written informed consent.

Exclusion criteria

The exclusion criteria were as follows: Patients with a history of pre-existing cardiac or pulmonary disease, renal or hepatic derangements, metabolic or neurological disorders; spinal column deformity or cutaneous infection at the lumbar puncture site; bleeding or coagulation disorder; known hypersensitivity or allergy to local anesthetics/opioids; and uncooperative patients or refusal to the technique.

In Group A, 15 mg of hyperbaric 0.5% bupivacaine (3 mL) with 0.2 mg morphine (3.5 mL) and in Group B, 15 mg of hyperbaric 0.5% bupivacaine (3 mL) with 0.5 mg nalbuphine (3.5 mL) were used. Morphine and nalbuphine (1 mL = 10 mg) were diluted with 9 mL of normal saline. One hundred patients were randomly divided into two groups by slips in the box technique. A standard anesthesia protocol was followed, and routine monitoring was applied. An intravenous line was started with 18G cannula and crystalloid infusion at 10 mL/kg. Oxygen was administered through a face mask at 3 L/min. The patient was positioned in right lateral decubitus; subarachnoid puncture was performed in the L3-L4 intervertebral space with a 25G Quincke needle using the midline approach. After free flow of cerebrospinal fluid, 15 mg of hyperbaric 0.5% bupivacaine with 0.2 mg morphine at 0.2 mL/s was injected in Group A and 15 mg of hyperbaric 0.5% bupivacaine with 0.5 mg nalbuphine at 0.2 mL/s was injected in Group B. Patient was placed in dorsal decubitus position after the subarachnoid block. The assessor was blinded for the drug used as an adjuvant. Sensory and motor assessment was performed immediately after positioning supine. The level of sensory blockade was measured by pin prick in the mid-clavicular line on both sides with a blunt 27 G needle, every minute until the block reached T6 dermatome. Thereafter the level was checked every 2 min until the maximal height of the sensory block is achieved. Onset and recovery of motor assessment were performed by modified bromage scale.

The onset of sensory blockade is defined as the time taken from the completion of the injection of the study

drug till the patient did not feel the pin prick at T10 level. The surgical incision was commenced when the sensory level is at or above T6 dermatome. Time taken for maximum sensory blockade is defined as the time taken from the completion of the injection of the study drug to the maximum sensory blockade attained. Thereafter, the block was assessed until recovery of motor function and sensation at the L1 dermatome. Duration of analgesia is taken as the time from the onset of sensory block to the time when the patient requires the first dose of analgesic for post-operative pain or recovery of T10 dermatomal sensory level whichever was earlier. Quality of motor blockade in the lower limb was graded by a modified Bromage scale until the return of normal motor functions. The maximum Bromage score achieved was noted. Onset of motor block is defined as the time from spinal injection until Bromage 1 score was registered. Duration of motor blockade is taken as the time from onset of motor block till the patient attained slight motor recovery to Bromage 1.

Heart rate and blood pressures (BP) were recorded before the procedure and immediately after the subarachnoid block, then at 2 min interval for 10 min, later at 5 min interval until 30 min and then after every 10 min till completion of the surgery. The last reading is taken 10 min after the completion of the procedure. Postoperative BP and heart rate were measured every 2 h until 24 h. Bradycardia (heart rate <60 beats/min or if hemodynamically unstable) was treated with Inj. Atropine 0.6 mg.

Hypotension (systolic BP <100 mmHg or <20% from baseline) was treated with incremental boluses of I.V. ephedrine 6 mg when required. Side effects such as respiratory depression, nausea, vomiting, shivering, and pruritus were recorded. Respiratory depression (respiratory rate <8/min or SPO_2 <90%) if observed, oxygen supplementation was continued. Nausea and vomiting if present were treated with I.V. Ondansetron 4 mg. Shivering was treated with Inj. Tramadol 25 mg in incremental doses.

Pruritus was treated with I.V. Chlorpheniramine 25 mg. Sedation was measured using Ramsay Sedation Scale. When the patients begin to experience pain score of 4 and above, in the visual analog scale, it was considered that analgesic action of the drugs was terminated and rescue analgesic injection paracetamol 1 g was given, and patients not responding were given 50 mg of Intravenous Tramadol. Duration of analgesia is defined as the time from onset of sensory block at T10 to the time when the first rescue analgesic was given. The total analgesic requirement was measured.

The sample size was calculated using nMaster 2.0 software, with a minimum sample size of 45 in each group. Considering the dropouts, the final sample arrived was 50 in each group.

Descriptive statistics were done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analyzed with the Student's unpaired t-test. Categorical variables were analyzed with the Chi-square test and Fisher's exact test. Statistical significance was taken as $P<0.05$. The data were analyzed using SPSS version 17 and Microsoft Excel 2007.

RESULTS

The sample consisted of 50 patients in Group A using Bupivacaine and morphine as adjuvant and 50 patients in Group B using Bupivacaine and nalbuphine as adjuvant. The groups were comparable regarding age, gender, weight, and height. They were also comparable with regard to ASA grading. There was no significant statistical difference between the groups with regard to sociodemographic details. This is shown in Table 1.

The mean time to onset of sensory block to dermatome T10 in the morphine group was 2.72±0.48 min and 2.74±0.22 min in nalbuphine group. In relation to time to onset of sensory block to dermatome T10, no significant statistical difference was seen between the groups ($P=0.777$, Student's unpaired t-test).

The percentage of patients who had attained maximum sensory block-dermatome T4 in the morphine group was 12% (n=8) which was higher as compared to 1% (n=1) in the nalbuphine group. In relation to maximum sensory block attained-dermatome T4 status, both intervention groups were comparable and a significant statistical difference was seen between the groups ($P<0.05$, Chi-square test).

The mean time to attain maximum sensory block in the morphine group was 21.79 min which was slower as

Table 1: Sociodemographic details

Study parameter	Group A (n=50)	Group B (n=50)	P-value
Age (years)	43.32 (±8.7)	43.22 (±8.43)	0.954
Gender			
Male	23 (46%)	33 (66%)	0.054
Female	27 (54%)	17 (34%)	
Height (cm)	159.72 (±3.89)	159.40 (±4.28)	0.697
Weight (kg)	59.28 (±5.90)	56.26 (±6.93)	0.061
ASA			
I	35 (70%)	43 (86%)	0.054
II	15 (30%)	7 (14%)	

*ASA: American society of anesthesiologist

compared to 20.81 min in nalbuphine group. In relation to time to attain maximum sensory block distribution, both intervention groups were comparable, and significant statistical difference was seen between the groups (P<0.05, Student's unpaired t-test). The time to attain maximum sensory block among patients was faster in nalbuphine group compared to morphine group.

The mean time to onset of motor block up to bromage Scale 1 in morphine group was 3.06 min which was slower as compared to 2.98 min in nalbuphine group. In relation to time to onset of motor block up to bromage scale significant statistical difference was seen between the groups (P<0.05, Student's unpaired t-test).

Complete motor blockade (Bromage 3) was observed in all patients in both groups. This was clinically and statistically not significant.

The mean time to attain maximum motor block in morphine group was slower as compared to nalbuphine group. In relation to time to attain maximum motor block distribution, both intervention groups were comparable, and a significant statistical difference was seen between the groups (P<0.05, Student's unpaired t-test).

The mean time for regression of sensory block to T10 dermatome in the morphine group was slower as compared to nalbuphine group. In relation to time for regression of sensory block to T10 dermatome distribution, in both intervention groups were comparable, and a significant statistical difference was seen between the groups (P<0.05, Student's unpaired t-test).

The mean duration of motor block in the morphine group was longer compared to that in nalbuphine group. In relation to the duration of motor block distribution, both intervention groups were comparable and a significant statistical difference was seen between the groups (P<0.05, Student's unpaired t-test).

The mean duration of analgesia in the morphine group was 16.08 h which was longer as compared to 6.46 h in nalbuphine group. In relation to the duration of analgesia distribution, both intervention groups were comparable and a significant statistical difference was seen between the groups (P<0.05, Student's unpaired t-test). When statistically comparing the duration of analgesia distribution between the intervention groups, the overall difference in the duration of analgesia among patients was 9.61 h (577 min) longer in the morphine group compared to the nalbuphine group. This trend of significantly longer duration of analgesia in the morphine group was found to be in the range of 60% longer compared to nalbuphine group. This is shown in Table 2.

The results of heart rate and mean arterial pressure distribution showed a decrease in the morphine group from baseline between 2 min and 20 min but were not significant enough to require clinical intervention. No significant hemodynamic variation was noted in nalbuphine group. This is shown in Figures 1 and 2.

The percentage of patients who had side effects in the morphine group was 26% (n=13) which was higher as compared to nalbuphine group. The major side effects observed were pruritus (14%; n=7) in the morphine group and nausea (4%; n=2) in nalbuphine group. In relation to side effects status, both intervention groups were comparable, and a significant statistical difference was seen between the groups (P<0.05, Chi-square test).

DISCUSSION

Surgical pain has a most distressing effect in the recovery of patients. Its management needs prudence and caution.

Table 2: Various variables of sensory and motor block

Study parameter	Group A (n=50)	Group B (n=50)	P-value
Time to onset of sensory block T10 in either group (minutes)	2.72±0.48	2.74±0.22	0.777
Maximum sensory block attained in either group			
T6	42	49	0.015
T4	8	1	
Time to attain maximum sensory block in either group (minutes)	21.79±0.48	20.81±0.28	0.001
Time to onset of motor block bromage 1 in either group (minutes)	3.06±0.10	2.98±0.13	0.001
Maximum motor block attained in either group			
Bromage3	50	50	0.999
Bromage2	0	0	
Bromage1	0	0	
Time to attain maximum motor block in either group (minutes)	5.07±0.21	4.88±0.26	0.001
Time to regression of sensory Block T10 in either group (hours)	4.91±0.34	2.88±0.27	0.001
Duration of motor block in either group (hours)	6.22±0.39	4.71±0.32	0.001
Duration of analgesia in either group (hours)	16.08±0.45	6.46±0.11	0.001

*T10: Thoracic level 10

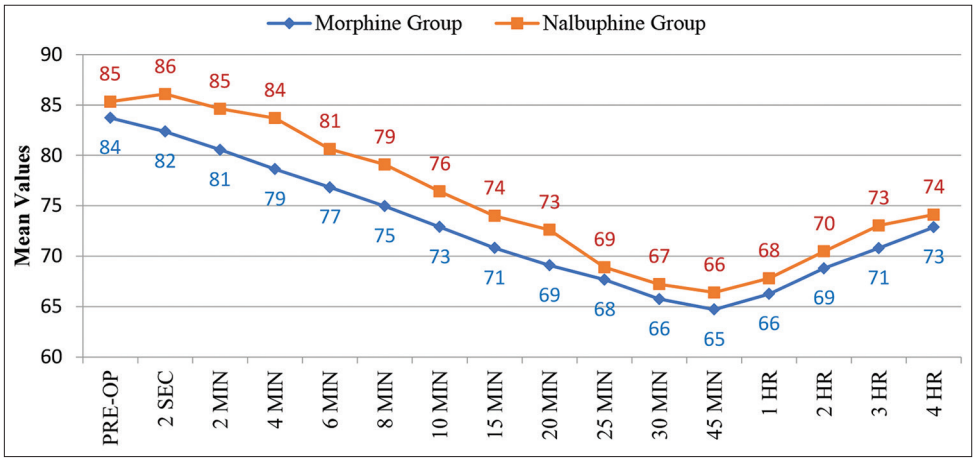

Figure 1: Perioperative heart rate in both groups at various time intervals

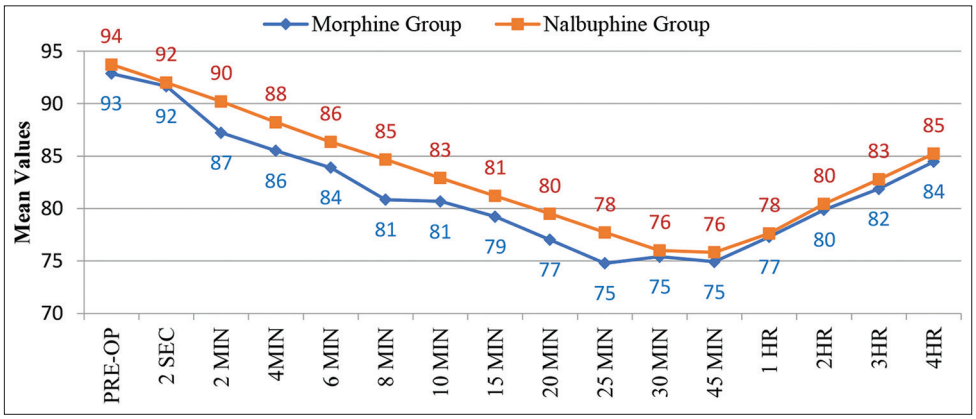

Figure 2: Perioperative mean arterial pressure in both groups at different time intervals

Opioids form an integral part of pain management in the perioperative period; but are limited by their potentially dangerous side effects. Lot of opioids has been used as additives in spinal anesthesia with lesser side effects compared to intravenous, intramuscular routes. In this study, we compared nalbuphine with morphine as an additive in spinal anesthesia with regard to the analgesic effect and side effects.

The time to onset of sensory block was almost equal in both groups. The time to onset of motor blockade and the time to attain maximum sensory and motor blockade was shorter in Group B (nalbuphine) compared to Group A (morphine). This can be explained by lipophilic properties of nalbuphine which leads to rapid intake and rapid onset of action.[10] Furthermore, the previous studies have shown that the duration of motor block is not affected by the administration of nalbuphine.[1] We had similar result from our study too. However, in addition, we found that the duration of motor blockade with nalbuphine and bupivacaine was significantly shorter than that of morphine with bupivacaine.

The analgesic potency of nalbuphine is equivalent to that of morphine on a milligram basis. However, regarding the duration of action, in previous studies, conflicting observations have been made. In their meta-analysis, Zeng et al., had found both morphine and nalbuphine comparable in pain relief.[11] However, various studies have reported that morphine has provided superior pain relief.[1,11] In our study too, morphine outperformed nalbuphine with regard to mean time for regression of sensory block to L1 dermatome and mean duration of analgesia. This trend of significantly longer duration of analgesia in the morphine group was found to be in the range of 60% longer compared to nalbuphine group. This can be explained by ceiling effect seen for analgesic efficacy of nalbuphine when doses above 0.15 mg were used which leads to a shorter duration of analgesia for nalbuphine.[12]

However, in both groups, no intraoperative analgesia was required which demonstrates that nalbuphine can provide comparable equipotent analgesia to morphine.

Earlier studies had demonstrated that the dose of nalbuphine needed for a longer duration of post-

operative analgesia to be 0.8 mg/kg.[10,13] However, in our study, we were able to achieve the same with a lower dose. As discussed by Akshat et al., the analgesic effect of nalbuphine is based on its pharmacodynamic profile rather pharmacokinetic profile, thus explaining the effect at a lower dose.[12]

The hemodynamic parameters such as pulse rate and mean arterial pressure were monitored perioperatively. In our study, the hemodynamic parameters in the morphine group were statistically significant between 2 and 20 min compared to baseline readings though not clinically significant. However, there were no haemodynamic changes observed in the nalbuphine group. A meta-analysis by Yu et al., demonstrated that nalbuphine has a significantly lower incidence of hypotension compared to the potent opioids.[14] This study findings also confirmed the same.

The percentage of patients who had side effects in the morphine group was higher as compared to the nalbuphine group. The major side effects observed were pruritus in the morphine group and nausea in nalbuphine group. All the patients in both groups maintained oxygen saturation. None of the patients in both groups showed evidence of respiratory depression. This is similar to the finding by Zeng et al., that nalbuphine provides a better safety profile than morphine with respect to pruritus and respiratory depression.[11]

Limitations of the study

However, this study has the following limitations. As the study population was restricted to patients referred to our department, a selection bias may have influenced the results. We were unable to use research design like a higher level of blinding due to paucity of time and resources. Further, a multi-centric study design might provide more reliable results.

CONCLUSION

Thus, the study has demonstrated that, although IT administration of nalbuphine with hyperbaric bupivacaine combination produces a rapid onset of anesthesia and effective early post-operative analgesia with minimal incidence of side effects but the total duration of analgesia was more in morphine and hyperbaric bupivacaine combination. Hence, we suggest that morphine can be used in patients who require longer duration of post-operative analgesia and nalbuphine is preferable in high-risk patients who are vulnerable to side effects of morphine.

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Authors Contribution:
SD- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, implementation of the study protocol, data collection, data analysis, manuscript preparation, and submission of the article; **IG-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **RR-** Design of study, statistical analysis, and interpretation; **DD-** Review manuscript; literature survey and preparation of figures; coordination, and manuscript revision.

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