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Two Different Doses of Nalbuphine as an Adjuvant to Bupivacaine Intrathecally in Lower Abdominal and Lower Limb Surgeries- A Comparative Study

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Abstract:
Background:*Nalbuphine is a synthetic opioid with mixed agonist-antagonist action, when added as adjuvant to intrathecal bupivacaine acts on kappa receptors in the dorsal horn of the spinal cord producing analgesia.*
Aim:*To evaluate the onset of sensory block, hemodynamicchanges, duration and quality of analgesia, and adverse effects of different doses of nalbuphine with bupivacaine for spinal anesthesia.*
Materials and Methods:*Randomized double blind study done on 90 patients undergoing lower abdominal and lower limb orthopedicsurgeries under subarachnoid block. Patients were randomly allocated to three groups receiving either intrathecal 12.5 mg of bupivacaine + 0.5 mL normal saline alone or 12.5 mg of bupivacaine with either of nalbuphine 0.4 or 0.8 mg.*
Conclusion:*Addition of 0.4 mg of nalbphine to 0.5% bupivacaine for subarachnoid block provides excellent analgesia with long duration of action compared with 0.8 mg of nalbuphine with minimal side-effects.*
Key words: *Bupivacaine hydrochloride, nalbuphine hydrochloride, subarachnoid block.*

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I. Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (International Association for Study of Pain). Pain is usually protective and warns of tissue damage prompting treatment.Post-operative pain management can thus improve functionality and reduce the in-hospital stay and also improve the quality of life[1]. Because aggressive treatment of acute postoperative pain is considered to be so beneficial, "The Joint Commission on Accreditation of Healthcare Organizations" has recognized that "pain is the fifth vital sign".The aim of good pain management is to reduce it to a tolerable or comfortable level, not necessarily to eliminate it completely. A multi-disciplinary approach to pain management combining regional anaesthesia, centrally acting analgesics like paracetamol, peripheral nonsteroidal anti-inflammatory drugs and opioids leads to improved pain relief, better patient outcomes, improved efficacy and reduced side effects, including the long-term benefit of reduced risk of developing chronic pain[2,3].

Neuraxial block for lower abdominal and lower limb surgeries are becoming popular as it has many advantages over general anaesthesia. Once administered, it provides an unvarying dense analgesia unlike general anaesthesia (GA), where both the sedation and the analgesia are dynamic, keep varying and require constant manipulations[3].The first spinal anesthesia was administered in 1885 by Leonard Corning, a neurologist in New York[4]. The first report on the use of intrathecal opioids (ITO) for acute pain treatment was in 1979 by Wang and colleague Use of ITO as adjuncts has a definite place in the present regional anesthesia practice. Various opioids have been used along with bupivacaine to prolong its effect, to improve the quality of analgesia and minimize the requirement of postoperative analgesics.Nalbuphine is a semisynthetic opioid with mixed mu antagonist and k agonist properties[5].Nalbuphine when added as adjunct to intrathecal local anesthetics has the potential to provide good intraoperative and postoperative analgesia with decreased incidence and severity of mu receptor side effects[5]. In contrast to other centrally acting opioid analgesics, nalbuphine has minimal respiratory depressant effect and low potential abuse; it can be used as an alternative to other opiates[6].

II. Materials and Methods

Following ethical committee approval, a double-blind randomized controlled clinical study was conducted on 90 adult patients admitted for lower abdominal andorthopedic procedures under subarachnoid block.

2.1 Inclusion Criteria

1. American Society of Anaesthesiologists (ASA) I and IIpatients
2. Age group of 25-70 years
3. Patient with written valid consent
4. Weight between 45 and 95 kgs,
5. Height between 145 and 170 cms

2.2 Exclusion Criteria

1. Infection at the site.
2. Bleeding disorder.
3. Allergic reaction to any anesthetic drug.
4. ASA III and IV grade.
5. Patients on tranquilizers, hypnotics, sedatives, andother psychotropic drugs.

Patients were randomly allocated into three groups. Each group consists of 30 patients. They received either ofdrugsolution as below .

(i) Group A(n=30): Patients received intrathecal 0.5% hyperbaric Bupivacaine 2.5 ml plus 0.5 ml Normal Saline(control).

(ii) Group B(n=30): Patients received intrathecal 2.5 ml of 0.5% hyperbaric Bupivacaine plus Nalbuphine hydrochloride 0.4 mg(0.5 ml).

(iii) Group C(n=30): Patients received intrathecal 2.5 ml of 0.5% hyperbaric Bupivacaine plus Nalbuphine hydrochloride 0.8mg(0.5 ml).

Preanesthetic evaluation was done to all patients underinclusion criteria. All relevant investigations were done and patient was kept 6 hours fasting overnight. Tablet Alprazolam 0.25 mg and tablet Pantoprazole 40 mg were advised at bedtime on night before surgery.

On the day of surgery, in the recovery room, an intravenous line with 18-gauge (G) cannula was secured. Each patient was given injection Ondansetron 0.1 mg/kg on day of surgery. After receiving the patient in the operating room, all routine monitoring namely, non-invasive blood pressure (NIBP), peripheral oxygen saturation by pulse oximetry (SpO2), and electrocardiogram (ECG) were started. Baseline values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxygen saturation (SpO2) were recorded. The patient was placed in sitting position. Under all aseptic precautions, after painting the area and draping the back, skin overlying L3-L4 inter-vertebral space was infiltrated with 2% Lignocaine. A 25 G Quincke spinal needle was inserted and after free flow of cerebrospinal fluid, drug was injected slowly. Injection Midazolam 0.5 mg intravenously(i.v), was given to the patient to allay the anxiety and apprehension.The onset of sensory block was assessed by Gromely and Hill scale. Onset of motor blockade was assessed by Modified Bromage scale. The time to reach T10 dermatome sensory block, peak sensory level and Modified Bromage 3 motor block was recorded before the start of the surgery. For recovery of block, time to two dermatome regression of sensory block and time to complete motor recovery was recorded. Intra-operative non-invasive monitoring of vitals(HR, NIBP and SPO2) was done at 2, 5, 10 ,15 minutes and then every 15 min till the completion of the surgical procedure or till 120 minutes.

Duration of effective analgesia [i.e., time of onset of sensory block to the first request of analgesia] was calculated from Visual analogue scale (VAS) score. VAS score was checked at 30 minute interval till the requirement of analgesia. Patient with score ≥ 3 received injection Diclofenac 75 mg as rescue analgesia. Postoperatively vitals (HR, SPO2, NIBP) were recorded at baseline, 30 minutes, 1 hour, hourly interval till 4 hours and then 4 hourly interval till 24 hours. Hypotension was categorized as fall in SBP to less than 90 mmHg or decrease in MAP of more than 20% from the baseline. Bradycardia was when a decrease in heart rate greater than 20% from the baseline present. Respiratory depression defined as SpO2 < 90% on room air. Other side-effects like pruritus, nausea, vomiting, sedation also recorded. Hypotension was treated with intravenous crystalloid/colloid and bolus dose of intravenous Mephentermine 6 mg was given. Bradycardia episodes were treated with injection Atropine 0.6 mg as bolus dose. Nausea and vomiting was treated with injection Ondansetron 4 mg intravenously and pruritus with anti-histaminics.

III. Statistical Methods

Statistical analysis of the data was done using ANOVA and Chi-square test. Continuous variables were summarized in the form of means and standard deviations and categorical variables were expressed as frequencies and percentages. Graphically, the data was presented by bar and lie diagrams. Analysis of variance (ANOVA) with least significant difference(LSD) test was employed for comparing continuous variables.

IV. Results

The effects of intrathecal 0.5% hyperbaric bupivacainewith nalbuphine hydrochloride at two different doses(0.4 mg, 0.8, mg) was studied and compared with0.5% hyperbaric bupivacaine alone in 90 patientsbelonging to ASA grade I and II who underwent lowerlimb orthopedic and lower abdominal procedures.

The three groups of patients A, B, C included inthe study did not differ significantly with respect to age,sex, body weight, height, type, and duration of surgery as shown in Table 1.On intragroup comparison after SAB, there was no statistically significant difference in the intraoperative and postoperative mean pulse rate, systolic blood pressure and diastolic blood pressure, respiratory rate and SpO2 between the groups (Table not provided).

The results regarding the characteristics of sensory block and motor blockare summarized in Table 2.The mean time of onset of sensory blockade and motor blockade and duration of motor blockade betweenthe groups is comparable with the P value >0.05 which is statistically not significant. Two segment regression of sensory blockade is significantly prolonged by additionof intrathecal nalbuphine as seen with Groups B, Cwhen compared with group A with bupivacaine alone.The duration of analgesia was significantly prolongedwith the addition of nalbuphine as compared withbupivacaine alone as shown in Figure 2. Statistical analysis shows thatthere is significant difference between Groups B, C when compared with Group A. The quality of analgesia is good with nalbuphine groups compared with bupivacainealone as shown in Table 2 and Figure 1.

On intergroup comparison of side effects statistical significant difference was seen between group A and C for hypotension, bradycardia, nausea and vomiting and sedation with p value < 0.05 %. Intergroup comparison between group B and C showed statistical significant difference in hypotension and nausea and vomiting (with p value < 0.05%)(Table 3).

Table 1: Demographic Data

PARAMETER	GROUP A	GROUP B	GROUP C	P VALUE
AGE	47.4±7.89	46.6±9.81	48.5±10.58	>0.05
WEIGHT	65.1± 6.76	66.7±7.79	64.3±8.12	>0.05
HEIGHT	158.93±7.45	157.63±7.76	160.97±7.48	>0.05
GENDER(M:F)	63.3 : 36.7	56.7:43.3	66.7: 33.3	>0.05
ASA STATUS(I:II)	76.7:23.3	86.7: 13.3	73.3:26.7	>0.05
DURATION OF SURGERY	92.6 ± 26.02	89.7±27.18	89.3±27.59	>0.05

Table 2: Inter-group comparison of motor block, sensory block and analgesia in the three study groups

PARAMETER	GROUP A	GROUP B	GROUP C	P VALUE
ONSET OF SENSORY BLOCK	1.67 ± 0.274	1.58±0.216	1.55±0.222	>0.05
ONSET OF MOTOR BLOCK	5.97 ± 0.957	5.78±0.916	5.49±0.816	>0.05
TWO SEGMENTSENSORY REGRESSION	119.7 ± 6.40	141.6±6.51	155.4±6.61	<0.001
DURATION OF MOTOR BLOCKADE	155.4±6.61	141.4±8.83	143.9±9.26	>0.05
VISUAL ANALOG SCALE SCORE	180 min	270 minutes	300 minutes	
DURATION OF ANALGESIA	168.4 ± 11.04	245.2±17.73	293.1±13.74	<0.001

Table 3(A): Group comparison of side-effects

SIDE EFFECTS	GROUP A		GROUP B		GROUP C	
	NO.	%AGE	NO.	%AGE	NO.	%AGE
HYPOTENSION	0	0.0	2	6.7	9	30.0
BRADYCARDIA	0	0.0	1	3.3	5	16.7
RESPIRATORY DEPRESSION	0	0.0	0	0.0	0	0.0
NAUSEA AND VOMITING	0	0.0	0	0.0	4	13.3
PRURITUS	0	0.0	0	0.0	0	0.0
SEDATION	0	0.0	1	3.3	4	13.3

Table 3(B): Group comparison of side-effects

SIDE EFFECTS	P-VALUE		
	A VS B	A VS C	B VS C
HYPOTENSION	0.150	0.001*	0.019*
BRADYCARDIA	0.313	0.019*	0.085
RESPIRATORY DEPRESSION	-	-	-
NAUSEA AND VOMITING	-	0.038*	0.038*
PRURITUS	-	-	-
SEDATION	0.313	0.038*	0.161

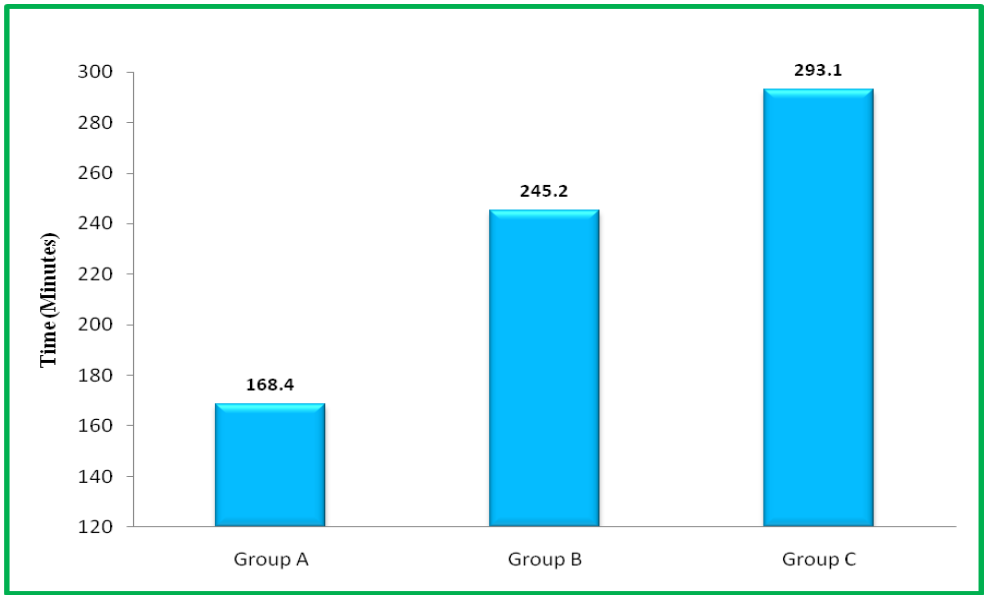

Fig.1: graph showing duration of effective analgesia (minutes) among various groups

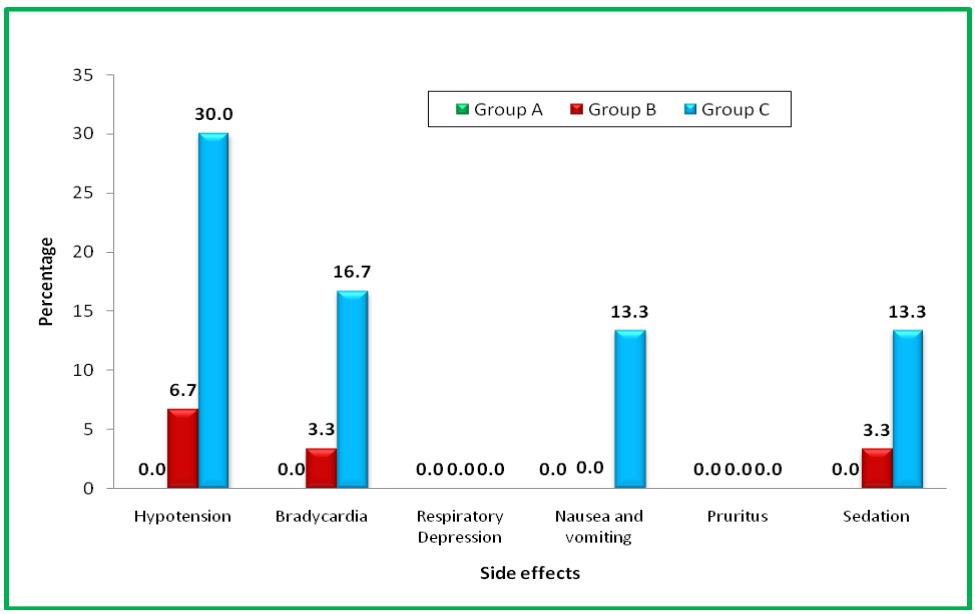

Fig.2: Graph showing group comparison of side effects.

V. Discussion

We conducted this study to compare the efficacy and adverse effects of different doses of nalbuphine as an adjunct to intrathecal bupivacaine and bupivacaine alone in lower abdominal and orthopedic surgeries. Nalbuphine, a mixed agonist-antagonist drug, binds both to u and kappa receptors, but its action on these receptor is divergent[5]. When nalbuphine binds to u receptor, it serves only to competitively displace other u agonists from the receptor without itself displaying any agonist activity similar to those of naloxone. However, when it binds to kappa receptor, it has agonist activating effect. This pattern of binding and effects defines

nalbuphine as a mixed agonist-antagonist. Nalbuphine, administered intrathecally, binds to kappa receptors in the brain and spinal cord areas which are involved in nociception, producing analgesia and sedationwithout mu side effects.Large number of animal studies has been under taken toprove that intrathecal nalbuphine was not neurotoxic. Rawal *et al.*,showed, in a sheep model using histopathological methods that intrathecal nalbuphine, even at large doses15-24 mg were not associated with histopathologicalchanges of the spinal cord. In our study, the dosage of Nalbuphine selected for comparison were 0.4 mg and 0.8 mg intrathecally. The other study comparing the different doses of Nalbuphine was by Xavier Culebras and his colleagues, who studied intrathecal Nalbuphine in doses of 0.2, 0.8 and 1.6 mg in 90 obstetric patients undergoing caesarean section and found 0.8 mg as the most effective dosage [7]**.** We consciously excluded the 1.6 mg dose in our study as they reported that 1.6 mg Nalbuphine did not improve analgesia compared with the 0.8 mg group, exhibiting a ceiling effect, and was associated with higher side-effects. We formulated our study to determine whether Nalbuphine prolongs analgesia by comparing with control and to find out the optimum dose of intrathecal Nalbuphine by comparing the 0.4 and 0.8 mg doses with the control group with Bupivacaine alone, which will provide prolonged post-operative analgesia without increased side-effects. After analyzing the data compiled from our study, we found that there was no statistically significant difference in the age, weight, height and sex of patients in the three groups. ASA grade I and II patients were included in our study with comparable demographic distribution in all the three groups.

In the present study, the onset of sensory block, taken as the time to reach T10 sensory dermatome, when compared between the three groups, showed a mean duration of 1.67 ± 0.274 min in the control group(Group A), while in Nalbuphine group with 0.4 mg dose(Group B), the onset time was 1.58±0.216 min and in Nalbuphine group with dose 0.8 mg(Group C), it was 1.55±0.222 min. The onset of block was faster in the Nalbuphine groups compared to the control group because of the highly lipophilic nature of the drug.However the difference was statistically insignificant, on intergroup comparison, between all the three groups(p-value>0.05).Our results are in accordance with the study done by Tiwari *et al* ,who observed 75 patients posted for surgery under subarachnoid block[8,9]. Time from the injection of intrathecal drug to development of Grade III motor blockade on the Modified Bromage scale was taken as the onset time of motor blockade. The mean duration in the control group with Bupivacaine alone(Group A) was 5.97 ± 0.957 min , while in Nalbuphine group with 0.4 mg dose(Group B) was 5.78±0.916 min and in Nalbuphine group with dose 0.8 mg(Group C) was 5.49±0.816 minutes. The difference observed was statistically insignificant (p-value>0.05), and was in accordance with the study done by Tiwari *et al*[8]. In our study, two segment regression of sensory block in the control group with Bupivacaine alone(Group A) was 119.7 ± 6.40 min , while in Nalbuphine group with 0.4 mg dose(Group B) was 141.6±6.51 min and in Nalbuphine group with dose 0.8 mg(Group C) was 155.4±6.61 min. Two segment regression time of block was prolonged with addition of nalbuphine to intrathecal bupivacaine and this result correlates with that of Tiwari *et al*., who also showed significant increase in two regression time in patients given 0.2 or 0.4mg Nalbuphine intrathecally. The duration of motor blockade was taken as the time to reach grade 0 from grade III on the modified bromage scale.The duration of motor blockade was more in Nalbuphine group compared to the control group but was observed to be statistically insignificant(p-value>0.05)[8]**.**

Nalbuphine also provided hemodynamic stability. Similar findings are seen in the study conducted by Culebras*et al*., Tiwari *et al*., Mostafa *et al*., where there wasno gross hemodynamic changes throughout their study[7,8,10].Duration of effective analgesia as assessed by VAS score was taken as the time from intrathecal drug administration to the requirement of first rescue analgesia (VAS<3). The duration of effective analgesia was significantly prolonged in the Nalbuphine group compared to the control group and was more with the 0.8 mg dose of Nalbuphine compared to 0.4 mg intrathecal Nalbuphine and was observed to be statistically significant(p-value<0.05) , proving the effectiveness of intrathecal Nalbuphine as adjuvant to 0.5% hyperbaric Bupivacaine in SAB[8]**.**

The incidence of side effects were monitored for 24 hours in post-operative period in the three groups. No hypotension was recorded in the control group. In the Nalbuphine group with 0.4 mg dose (Group B), hypotension was recorded in 6.7% of the patients. With 0.8 mg Nalbuphine(Group C) hypotension was seen in 30% of the patients, the difference being statistically significant (p< 0.05). Group B thus had comparable postoperative analgesia but significantly lower side-effects (*P*<0.05) than Group C. Our results differ from the study by Culebras *et al* as they have not studied the 0.4 mg group, and our study was conducted with a different demographic patient population, in different surgery and with 12.5 mg 0.5% hyperbaric bupivacaine compared with 10 mg 0.5% hyperbaric bupivacaine in their study.

In our study, none of patient had respiratory depression (RR below 10 bpm, SPO2 <90%). Nalbuphine exhibits ceiling effect for respiratory depression[11]. Since respiratory depression is predominantly mu receptor-mediated and Nalbuphine is a mu receptor antagonist, respiratory depression effect is expected to be attenuated by Nalbuphine[7,8,10]

No incidence of bradycardia was recorded in the control group. In the Nalbuphine group with 0.4 mg dose(Group B), bradycardia was recorded in 3.3% of the patients. With 0.8 mg Nalbuphine(Group C) bradycardia was seen in 16.7% of the patients, making the difference statistically significant (p-value<0.05).Sedation was not observed in any patient in the control group and was present in 3.3% and 13.3% patients in group B and C respectively. The difference was statistically significant on intergroup comparison between group A and C and was insignificant in other groups.No incidence of pruritus was observed in all the three groups. For nausea and vomiting, no patient incidence was observed in the control group and 0.4 mg Nalbuphine dose (Group B), but a 13.3% incidence was found with the 0.8 mg dose of Nalbuphine (Group C) for which injection Ondansetron (4 mg IV) was given. The results correlate with the study by Xavier et al (2000) who studied the adverse effects after using three doses i.e. 0.2mg, 0.8mg, 1.6mg of intrathecal Nalbuphine or morphine 0.2mg given for caesarean section along with Bupivacaine[7].

VI. Conclusion

From the present study, we infer that 0.8 mg Nalbuphine intrathecally(Group C) has a significantly prolonged analgesic effect compared to the 0.4 mg dose of intrathecal Nalbuphine(Group B) and control group(Group A) with comparable hemodyanamic variables, onset of sensory and motor block, and duration of motor block in the three groups. Incidence of adverse side effects (like hypotension and bradycardia) were more with the 0.8 mg dose of Nalbuphine(Group C), compared to the 0.4 mg dose of Nalbuphine(Group B) and the control group, with statistically significant difference present.

Based on these data, we conclude that Intrathecal Nalbuphine prolongs the duration of postoperative analgesia when used as an adjunct, and 0.4 mg is the most effective dose that prolongs early postoperative analgesia without increasing the risk of side-effects. We recommend 0.4 mg as the optimal dose of Nalbuphine, if used intrathecally along with 12.5 mg 0.5% hyperbaric Bupivacaine for subarachnoid block in patients undergoing lower abdominal and lower limb surgeries.

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