Original Research Paper

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"A COMPARATIVE CLINICAL STUDY OF SPINAL ANAESTHESIA WITH BUPIVACAINE (HEAVY) PLUS NALBUPHINE OR BUPIVACAINE (HEAVY) PLUS FENTANYL, IN PATIENTS UNDERGOING LOWER LIMB SURGERY."

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ABSTRACT **Background and Aims:** Nalbuphine is a synthetic, lipid soluble, mixed agonist-antagonist opioid that binds to both μ and receptors. Nalbuphine has been used intrathecally by various investigators to enhance the postoperative analgesia. Fentanyl, a synthetic and lipophilic opioid, acts through $\mu_1$and $\mu_2$receptors.

To compare peri-operative quality of anaesthesia and analgesia with two drug combinations when used for spinal anaesthesia, Bupivacaine (heavy) with Fentanyl and Bupivacaine (heavy) with Nalbuphine in patients undergoing lower limb surgeries.

Methods and Materials: In this prospective, comparative, randomized, double blind study, 126 patients of ASA grade I/II between age18-60 yrs undergoing lower limb surgery, were randomly allocated into two groups of 42 each; Group C, Group N and Group F, given 0.5ml of normal saline, 0.8mg (0.4ml) Nalbuphine and 25μg (0.5ml) Fentanyl to 2.5ml of 0.5% Bupivacaine (heavy) in L_3-L_4 interspinous space respectively.

Results: On the basis of observations and statistical comparison following conclusions were made: The mean duration of sensory block in Group F (143.45±4.48 minutes), Group N (145.36±4.86 minutes) and Group C (139.05±6.17 minutes), ($p<0.001$). The mean duration of effective analgesia was Group F (210.71± 15.52 minutes), Group N (222.86±17.71minutes) and Group C (170.71±15.52minutes), ($p<0.001$).The mean post-operative VAS score at 30minutes in Group F (2.76±0.43minutes), Group N (2.19±0.40 minutes) and Group C (3.45±0.83 minutes), ($p<0.001$). The mean post-operative VAS score at 60 minutes in Group F (3.12± 0.33 minutes), Group N (2.79±0.52 minutes) and Group C (4.46±0.64 minutes), ($p<0.001$).

Conclusion: It can be concluded that addition of both drugs, nalbuphine or fentanyl, were effective to improve duration of sensory blockage and duration of effective analgesia than in cases given spinal anaesthesia with bupivacaine heavy alone. However, complications associated were lesser in bupivacaine-nalbuphine combination group. Therefore, it is safe option to use Nalbuphine as adjuvent to Bupivacaine heavy in spinal anaesthesia.

KEYWORDS : Intrathecal, Nalbuphine, Fentanyl, spinal anesthesia.

INTRODUCTION

Regional anaesthesia in the form of central neuraxial blockade remains the most commonly used technique for lower limb surgeries.The properties of anaesthetic agent used for day care surgeries in spinal anaesthesia should have fewer incidences of anaesthesia related complications, should provide adequate postoperative analgesia and allow early patient discharge[1]. Early postoperative mobilisation and rehabilitation without postoperative pain and discomfort is the most desirable feature in proper selection of anaesthesia for any surgery.

Subarachnoid anaesthesia produces satisfactory operating conditions for lower abdominal, pelvic and lower limb surgeries. Most subarachnoid anaesthetic drugs have specified duration of action. Lower incidences of failed block, less drug doses and decreased incidence of aspiration pneumonitis are added advantages of spinal anaesthesia[2].

Bupivacaine (heavy) is commonly used local anaesthetic agents used for subarachnoid block since it provides good quality anaesthesia without any complications. It is an amide type of local anaesthetic with high potency, slow onset (5-8 minutes) and long duration of action (1.5-2 hours)[3]. It acts by diffusion through nerve axons in the spinal cord. The degree of nerve blockade with local anaesthetic agents depends on concentration and volume of the agent.

Several adjuvants have been studied to prolong the duration of spinal anaesthesia which includes Fentanyl, Nalbuphine, Morphine and Dexmedetomidine. Intrathecal opioids are synergistic with local anaesthetics and intensify the sensory block[2] and reducing their doses, and thereby reducing their complications and offer hemodynamic stability[4]. They also produce postoperative analgesia .Pure opioid agonist acts on mu(μ) receptors which are pre and post synaptic opioid receptor present in dorsal horn in the spinal cord. Fentanyl, a synthetic and lipophilic opioid, acts through μ_1 and μ_2 receptors by opening potassium channels and reducing intracellular calcium which decreases the release of excitatory neurotransmitters from pre-synaptic C fibres. A partial opioid agonist acts principally on kappa() receptors in the substantia gelatinosa of dorsal horn in the spinal cord[5]. Nalbuphine is a synthetic, lipid soluble, mixed agonist-antagonist opioid that binds to both μ and receptors. It has agonist action at receptors and antagonist action on μ receptors which produces analgesia of visceral nociception[6,7,8]. It would ensure better outcome of anaesthesia and also provide comfort and satisfaction to patient by prolonging postoperative analgesia. The amount of opioid drug given should have fewer side effects e.g. nausea, vomiting, respiratory depression and other problem known to occur with parenteral use.

We also propose to compare two combinations- Bupivacaine (heavy) plus Fentanyl and Bupivacaine (heavy) plus Nalbuphine. The outcome will be benefiting the patients undergoing lower limb surgeries.

MATERIAL AND METHOD:

The present study was carried out in Swaroop Rani Nehru Hospital associated to Moti Lal Nehru Medical College, Prayagraj over a period of one year after approval from Institutional Ethical Committee and obtaining written and informed consent from all patients. A comparative, randomized, prospective, double blind study which was carried out on 126 patients undergoing middle ear surgery aged between 18-60 years of either sex of ASA grade I-II.

The Study Includes The Patients Who Confirm The Following:

INCLUSION CRITERIA :

1] Patients with ASA grade I and II
2] Patients scheduled for lower limb surgery in spinal anaesthesia
3] Adult patients between 18-60 years of age, of either sex.
4] Patients weighing between BMI 20-25.

EXCLUSION CRITERIA :

1] Patient refusal for consent.

2] Patient having age <18 or > 60years
3] Patients with known hypersensitivity to any of the study drug.
4] Patients with any relative or absolute contraindication to spinal anaesthesia.
5] Patients with any bleeding or coagulation disorders.
6] Patients having neurological disorder or any mental disturbance.
7] Pregnant and lactating women.
8] Patients with cardiovascular-respiratory disorders and any other systemic disorder or neuromuscular disorder.

Group Allocation, Randomisation and Blinding: Eligible patients were randomly allocated and divided into three groups (42 patients in each group) using Sequentially Numbered, Opaque, Sealed Envelope (SNOSE) technique. Double blinding achieved by three different anaesthesiologists – one for preparation of the study drug, second for administration of the drug and third for data collection. Hence the observer and patient both are unaware of the study.

Group C: Patients will receive 2.5ml of 0.5% Bupivacaine (heavy) in L_3 -L_4 interspinous space + 0.5ml of normal saline, it will acts as control group.

Group N: Patients will receive 2.5ml of 0.5% Bupivacaine (heavy) + Nalbuphine 0.8mg (0.4ml) in L_3-L_4 interspinous space.

Group F: Patients will receive 2.5ml of 0.5% Bupivacaine (heavy) +Fentanyl 25µg (0.5ml) in L_3-L_4 interspinous space.

Statistical Analysis
The results were analyzed using descriptive statistics and making comparisons among the groups. Categorical data were summarized as in proportions and percentages (%) while discrete as mean ± SD. The statistical analysis were calculated using Chi Square test, Arithmetic Mean, Standard deviation (O) One way ANOVA , Tukey Post Hoc Test, Kruskal Wallis Test and Dun's Post Hoc test. Sample size was calculated from previous study with confidence interval 95% and statistical power 90%.(80).A two-sided (α=2) $p<0.05$ was considered statistically significant. Analysis was done by IBM-SPSS ver 23.

METHODOLOGY:
After Pre Anaesthetic Check up and group allocation patients shifted to pre-operative room. After gaining intravenous access, standard monitors were attached and pre spinal anaesthesia vitals noted. Following standard protocol for spinal anesthesia, after positioning the patient, 25G Quincke's spinal needle with beveled tip was used to give intrathecal injection in L3-L4 intervertebral space . Drugs were given according to allocation of Group C, Group N and Group F.

OBSERVATIONS
1. Sensory block assessment
2. Motor block assessment
3. Heart Rate (HR)
4. Systolic Blood Pressure
5. SpO2
6. Duration of anaesthesia
7. Duration of analgesia (patient's complain of pain)
8. Complications ,if any.

Sensory and motor block characteristics will be assessed in the normal lower limb. All time intervals will be calculated from the time of end of intrathecal injection.

Sensory level was assessed by loss of sensation to pinprick[17] bilaterally. Onset of sensory block was taken as the time interval between the end of intrathecal injection to the time to reach sensory block level of T10 on the operating side. Further testing was performed at every 5 minutes interval till 15 minutes and then at every 15 minutes till the regression of segments to S2 level and this was considered as the duration of sensory blockage. The time of onset of sensory block and duration of sensory block was noted.

Motor block was assessed based on a **Modified Bromage scale** [18]. Onset of motor block is defined as time taken from completion of subarachnoid injection of drug till patient unable to flex ankle i.e. Bromage 3 grade. Recovery of motor block is defined as ability of patient flex hip. Further testing was performed at every 5 minutes interval till 15 minutes and then at every 15 minutes till the recovery of motor block. Duration of motor block was calculated from time 0 minute upto recovery of motor block.

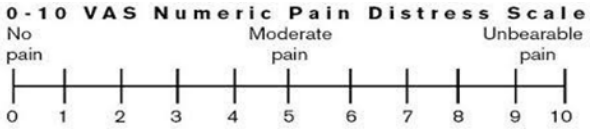
Bromage 0	**No motor block**
Bromage 1	Inability to raise extended leg, able to move knees and feet.
Bromage 2	Inability to raise extended leg and move knees, able to move feet.
Bromage 3	Complete block of motor limb.

The surgical anesthesia was considered to be achieved when the levels of sensory block were reached to T10 thoracic dermatome level with attainment of complete motor block (Bromage-3).

Postoperatively, the sensory and motor block levels were assessed at every 30 minutes for 1 hours.

Visual Analogue Scale (VAS) [19] given by Revill in 1976 was used for recording the intensity of pain of the patients. It is an imaginary straight line of 10 cm from 0 to 10. Patients were asked to point out the scale after test drug was given. "0" indicates no pain while "10" denotes worst pain imaginable.Pain scores were measured at the time of incision and every 5minutes for 15 min thereafter every 15 minutes till the end of surgery in the operation room and every 30 minutes postoperatively in the recovery room using visual analogue scale.

However, patients were instructed to report pain score of 4 or more at any point of time. Pain score more than or equal to 4 was considered inadequate analgesia/ anesthesia. The duration of effective analgesia were taken as the time from completion of intrathecal injection to the time of administration of first rescue analgesic for postoperative pain. At this time, intravenous opioid infusion was started after a bolus dose of opioid.



Sedation score was assessed using **Ramsay sedation score** [20]**:**

SCORE	FEATURES
1	Patient is anxious & agitated or restless or both
2	Patient is cooperative, oriented & tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response (unarousable)

Heart rate, Systolic blood pressure (SBP), Respiratory Rate (RR) and peripheral O2 saturation (SpO2) at baseline (i.e. 5 min after stabilization of patient in the operation room), at the time of institution of spinal anesthesia i.e. 0 minute, at every 15 min interval for the rest of surgery were recorded.

All the patients were shifted to post anaesthesia recovery room for the next 1 hour and were observed.

At any point of time during the study period hypotension was defined as 20% decrease in SPB below the baseline level, and was treated with 100-200 µg of intravenous Phenylephrine. Bradycardia (HR <60 bpm) was treated with 0.4-0.6 mg of intravenous Atropine Sulphate. Respiratory depression (Respiratory rate<8 breaths/min or SpO2<90% on room air) was treated with Oxygen supplementation or ventilatory support, if required. The need for these drugs was noted.

OBSERVATION AND RESULTS :
Table–1: Distribution of Cases according to Age and Anthropometric Characteristics

Group	Group F		Group N		Group C		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F-value	p-value
Age (years)	38.02	11.00	38.71	10.70	38.69	10.01	0.06	0.944
Height (cm)	164.50	8.00	163.81	8.70	163.93	7.74	0.09	0.918
Weight (Kg)	61.95	7.66	60.57	10.62	63.14	7.61	0.91	0.406
BMI (Kg/m_2)	22.88	1.98	22.42	2.07	23.50	2.07	2.96	0.056

Above table shows P value of ANOVA for Age (in years) was 0.944 (>0.05), for Height (in cm) was 0.918 (>0.05), for Weight (in kg) was 0.406 (>0.05) and for BMI (in kg/m2) was 0.056 (>0.05), distribution of patients among the groups was similar and no statistical significant difference was four.

Table -2: Intergroup Comparison of Mean of Duration of Sensory block and Motor Block

Variable	Group F		Group N		Group C		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F-value	p-value
Duration of sensory block (segment regression to S2 level) (min)	143.45	4.48	145.36	4.86	139.05	6.17	16.12	**<0.001**
Duration of motor block (min)	132.14	4.70	131.67	6.12	131.79	6.61	0.07	0.928

Above table shows the significant difference in mean duration of sensory block between the groups (p<0.001) and no significant difference in mean duration of motor block between the groups (p=0.928).

Table – 3 : Intergroup Comparison of Duration of Surgery and Effective Analgesia

Variable	Group F		Group N		Group C		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F-value	p-value
Duration of surgery (min)	105.00	11.94	105.36	11.23	106.43	13.98	0.15	0.861
Duration of effective analgesia (min)	210.71	15.52	222.86	17.71	170.71	15.52	117.91	**<0.001**

Above table shows no significant difference in mean duration of surgery between the groups (p>0.05) and the significant difference in mean duration of effective analgesia between the groups (p<0.001).

Table –4: Intergroup Comparison of VAS Scores :

VAS	Group F		Group N		Group C		Kruskal Wallis Test	
	Mean	SD	Mean	SD	Mean	SD	chi sq-value	p-value
30min post op	2.76	0.43	2.19	0.40	3.45	0.83	61.59	**<0.001**
60min post op	3.12	0.33	2.79	0.52	4.46	0.64	73.21	**<0.001**

Above table shows the significant difference in mean VAS score between the groups at 30 min post operative was (p<0.001) and at 60 min post operative was (p<0.001)

Table – 5 : Intergroup Comparison of Complications :

Complications	Group F		Group N		Group C		Chi sq	p-value
	No.	%	No.	%	No.	%		
Bradycardia	0	0.0%	0	0.0%	2	4.8%	4.07	0.131
Hypotension	2	4.8%	2	4.8%	3	7.1%	0.30	0.860
Respiratory Depression	0	0.0%	0	0.0%	0	0.0%	NA	NA
O2 Desaturation	0	0.0%	0	0.0%	0	0.0%	NA	NA
Shivering	0	0.0%	0	0.0%	0	0.0%	NA	NA
Pruritus	4	9.5%	0	0.0%	0	0.0%	8.26	**0.016**
Nausea	3	7.1%	2	4.8%	7	16.7%	3.87	0.145
Vomiting	0	0.0%	0	0.0%	0	0.0%	NA	NA

Above table shows complications, Bradycardia, Hypotension and Nausea were in maximum proportion in group C (4.8%, 7.1% and 16.7% respectively) while Pruritus showed proportions significantly different among the groups **(p=0.016).**

DISCUSSION

Opioids as adjuvants to local anesthetics provide better perioperative sensory blockade with prolongation of postoperative analgesia and hemodynamic stability helps early ambulation and recovery of the patients. By reducing the local anesthetic dosage, they decrease their toxicity and the side effects associated with higher level of blockade. Hyperbaric Bupivacaine is the most popular among all local anaesthetics being used for spinal anaesthesia but it has the drawback of shorter duration of block and lack of postoperative analgesia.[9] Fentanyl in a dose range of 10–30 µg and nalbuphine of 0.8 mg have shown to provide better perioperative analgesia with less hemodynamic changes.[14,22,23,24] Henceforth, we choose 25 µg of fentanyl and 0.8 mg of nalbuphine for our present study.

The groups were similar in respect to mean age, mean weight, sex, mean height and BMI were statistically not significant with p >0.05. By including only ASA–I and ASA–II patients, it was tried to eliminate any systemic problems confounding our results. The mean changes in heart rate, Systolic blood pressure, saturation and duration of surgery during intra-operative period between groups F,N and C were statistically not significant (p <0.05)

This study demonstrated no statistically significant difference between fentanyl and nalbuphine regarding duration of motor block and which was found to be comparable to plain bupivacaine as observed in the previous study[29]. The synergism is characterized by enhanced somatic analgesia without effect on degree or level of local anesthetic induced sympathetic or motor blockade [25,26,27,28].

There was prolongation of duration of sensory block in nalbuphine and fentanyl group than in the control group. Nalbuphine and Fentanyl increase the intensity of sensory blockade and also prolong its duration. There was more prolongation of sensory block duration in nalbuphine group than fentanyl group the difference was statistically significant.

Ben David et al;(1997)[21] also showed that addition of fentanyl (10mcg) to a small dose of hyperbaric bupivacaine (5mg) enhanced the quality and duration of sensory block without prolonging the intensity or duration of motor block in patients undergoing knee arthroplasty.

Tiwari et al 2013[15] compared the effects of 2 different doses of nalbuphine added to hyperbaric bupivacaine and with bupivacaine alone. They concluded that the duration of sensory block and duration of analgesia was prolonged with nalbuphine without complications.

Duration of effective analgesia was longer in nalbuphine group and fentanyl group as compared to that of control group.

Gomaa et al. showed that fentanyl 25 µg and nalbuphine 0.8 mg as an adjuvant to 10 mg of 0.5% bupivacaine in cesarean section patients produced similar block characteristics.[13] Although duration of analgesia in nalbuphine group was prolonged when compared to fentanyl group, the results were not statistically significant.

Naaz et al. [10]compared the analgesic efficacy of fentanyl (group F: 25 µg) with that of two doses of nalbuphine (group NL: 0.8 mg and group NH: 1.6 mg) when combined with bupivacaine heavy in spinal anesthesia. The study showed that the duration of analgesia was significantly longer in the nalbuphine group when compared with fentanyl group.

The study done by **Thote et al.** in patients undergoing lower abdominal surgeries using 25 µg of fentanyl and 0.5 mg of nalbuphine with 12.5 mg of 0.5% bupivacaine observed longer duration of analgesia with nalbuphine group when compared to fentanyl group.[12] The study also showed the greater intensity of analgesia with nalbuphine group.

Gupta et al.[11] studied intrathecal nalbuphine versus intrathecal fentanyl as an additive with bupivacaine for orthopedic surgery of lower limbs. Patients of fentanyl group were given 25 µg of fentanyl +17.5 mg of hyperbaric bupivacaine, and patients of nalbuphine group were given 2 mg of nalbuphine +17.5 mg of hyperbaric bupivacaine. The total duration of analgesia in patients of nalbuphine group was significantly longer when compared with fentanyl group.

We observed in our study that the early postoperative VAS was lower and also lesser percentage of patients requiring rescue analgesia in early postoperative period in nalbuphine group than compared to fentanyl group. This showed that intensity and quality of analgesia provided by the nalbuphine were better than fentanyl.

Studies done by Jyothi et al., Culebras et al., and Gomaa et al. have showed lesser VAS scores and prolongation of analgesia with nalbuphine group[13,14,16].

Regarding complications, in our study, two cases developed hypotension and three cases reported nausea in the Fentanyl group, whereas in Nalbuphine group, two cases developed hypotension and two cases reported nausea while in control group two cases developed bradycardia, three cases developed hypotension and seven cases developed nausea.

Study done by **Tiwari et al.**, where combination of bupivacaine with

nalbuphine was compared with plain bupivacaine and a study done by **Singh et al.,** where fentanyl was compared to plain bupivacaine group. Both these studies have shown that the incidence of hypotension and bradycardia were lesser in adjuvant groups than compared to plain bupivacaine.[15,30]

Sedation was found in both nalbuphine and fentanyl groups, nalbuphine group had more sedation score than fentanyl and control group. All the patients were arousable and it was not associated with respiratory depression. **Alaaeldin M. Farid et al**[29] compared the effects of intrathecally administered fentanyl and nalbuphine in ASA I or II patients of either sex who underwent lower limb surgeries with spinal anesthesia and concluded that sedation was noticed in the nalbuphine treated group only Pruritis was observed in four cases of Fentanyl group and none reported in Nalbuphine group.

Gomaa et al.[13], who studied 60 female patients, ASA I and ASA II, who presented for elective cesarean deliveries. They found that the incidence of pruritus was higher with addition of fentanyl compared with the nalbuphine group.

CONCLUSION

From our study it can be concluded that addition of both drugs, nalbuphine or fentanyl, were effective to improve duration of sensory blockage and duration of analgesia than in cases given spinal anaesthesia with plain bupivacaine heavy alone.However, complications associated were lesser in bupivacaine-nalbuphine combination group. Therefore, it is safe option to use Nalbuphine as adjuvent to Bupivacaine heavy in spinal anaesthesia.

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