ORIGINAL RESEARCH

Efficacy of 0.8 mg Nalbuphine and 20mcg Fentanyl as adjuvants in Subarachnoid Block for lower limb orthopaedic surgery: A Randomized Controlled Trial

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ABSTRACT

Background: In lower limb orthopedic surgeries there is significant postoperative pain, which is difficult to treat with oral or intravenous analgesics resulting in adverse endocrine, metabolic and inflammatory responses. Morphine, Pethidine, Fentanyl, and other opioids fall under the Narcotics Act whereas nalbuphine does not. So, the accessibility of Nalbuphine is not as major a concern in several hospitals in India as that of morphine and other such opioids. Present study was aimed to compare the effectiveness of 0.8mg nalbuphine with 20 mcg fentanyl as an adjuvant to hyperbaric bupivacaine in lower limb orthopedic surgeries.

Material and Methods: Present study was single-center, prospective, comparative study, conducted in patients of either gender, age group of 18-60 years, belonging to ASA CLASS 1 and 2, With BMI < 30, undergoing elective orthopedic lower limb surgery. Patients were allocated in Group N- Received intrathecal 0.8 mg Nalbuphine & 3 ml 0.5 % H bupivacaine & Group F- Received intrathecal 20 mcg Fentanyl & 3 ml 0.5 % H bupivacaine.

Results: Group F has faster onset of sensory and motor blockade with P values of 0.029 and 0.023 respectively as compared to Group N. However, Group N has longer duration of sensory blockade and motor blockade with p values of <0.0001 each as compared to group F. Ramsay sedation score in Group F was 1.25 and in Group N was 1.18. Both the groups were comparable. The duration of post operative analgesia in group N (200.7min) was significantly prolonged (P< 0.0001) than in group F (154.69min). Postoperative VAS score was comparable at different time (6,12,18 & 24 hrs.) intervals between group N and group F. P value was not statistically significant.

Conclusion: Intrathecal Nalbuphine prolongs the duration of sensory and motor blockade and also has more prolonged postoperative analgesia as compared to 20 mcg intrathecal fentanyl.

Keywords: Intrathecal, Fentanyl, Hyperbaric Bupivacaine, Nalbuphine, postoperative analgesia.

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INTRODUCTION

In lower limb orthopedic surgeries there is significant postoperative pain, which is difficult to treat with oral or intravenous analgesics resulting in adverse endocrine, metabolic and inflammatory responses.[1] Compared to general anesthesia, spinal anesthesia has several benefits comprising of decreased stress response to surgery and postoperative analgesia.[2]

Together with local anesthetics, neuraxial administration of opioids expands the quality of intraoperative analgesia and lengthens the duration of postoperative analgesia without increasing the sympathetic blockade.[3] The rationale for the combination of opioids along with local anesthetics is that these two types of drugs reduce pain by acting at two different sites: local anesthetics act at the nerve axon and the opioids act at the receptors site situated in the spinal cord.[4]

Fentanyl is an opioid agonist, operating on mu opioid receptors. Following intrathecal injection of fentanyl (lipophilic opioid) there is instant onset of action. It does not generate significant side effects but enhances the quality of anesthesia and increases postoperative analgesia and hemodynamic stability.[5,6] Nalbuphine is synthetic opioid prepared by an amalgamation of mu antagonist and kappa agonist properties. Nalbuphine has enhanced the quality of perioperative analgesia when used as an adjunct with a small number of side effects.[2,3] Present study was aimed to compare the effectiveness of 0.8mg nalbuphine with 20 mcg fentanyl as an adjuvant to hyperbaric bupivacaine in lower limb orthopedic surgeries.

MATERIAL AND METHODS

Present study was single-center, prospective, comparative study, conducted in Department of Anesthesiology, at NKP Salve Institute of Medical Sciences and Research centre & Lata Mangeshkar Hospital,digdoh hills, Nagpur- 440019, India. Study duration was of 2 years (January 2018 to October 2019). The present study was carried out after approval of Institutional Ethics Committee

Inclusion criteria

- Patients of either gender, age group of 18-60 years, belonging to ASA CLASS 1 and 2, With BMI < 30, undergoing elective orthopedic lower limb surgery, willing to participate in study.

Exclusion criteria

- Patients with kyphoscoliosis.
- Patients with pre-existing neurological deficit.
- Patients having altered mental status.
- Known allergies to medications used in the study.

Thorough pre–anesthetic check-up was done. Patients were explained about the procedure of spinal anesthesia, they were also explained the use of numeric rating score (visual analogue score) for pain. They were also explained about that they could ask for pain relief postoperatively whenever they felt the need for it.

Informed written consent was taken for anesthesia as well as for participation in the study. NBM guidelines were explained to the patients & kept NBM from midnight 12 am for solids and since 6 am for liquids, on the day of surgery.

In the operation theatre, patients were attached to a multichannel monitor for SpO2, ECG, and NIBP and a large bore i.v. (18G) was secured on the hand. Pre-medication was done with Inj. Ranitidine 1mg/kg i.v. and inj. Ondansetron 0.1mg/kg. Preloading was done with Ringer lactate 10ml/kg.

Subarachnoid block (SAB) was given in sitting position under all aseptic precautions using Quincke's spinal needle of 23 gauge. Anesthesiologist and the patient were blinded to the

drug given which was revealed only once all readings were obtained.

In operation theater, patients were randomly allocated by computer generated randomization table in following groups

- Group N- Received intrathecal 0.8 mg Nalbuphine & 3 ml 0.5 % H bupivacaine
- Group F- Received intrathecal 20 mcg Fentanyl & 3 ml 0.5 % H bupivacaine

Patient were made supine and table was kept horizontal position. In both groups sensory block was assessed by pinprick sensation every minute till same reading was observed thrice & was considered as maximum height of the block. Sensory level and vitals were noted every 2 min till 10 minutes and there after every 15 minutes till end of the surgery. Motor block was judged by Bromage score. It was noted in the non-operative limb every 2 mins for the first 10 mins and there after every 15 min still start of the surgery. Later it was recorded every 15 mins after the surgery was over.

Intraoperative pain if any, was treated with 1gm Paracetamol infusion i.v. and this was recorded. If analgesia became inadequate even after paracetamol, it was converted to General Anesthesia and the patient was withdrawn from the study.

Post-operatively patient were shifted to Post Anesthesia Care Unit (PACU) where they were immediately monitored for level of sedation by Ramsay sedation score. Patients were also for monitored for level of sensory block, Bromage score, vital signs, pain, and side effects like nausea, vomiting, and urinary retention every 15 mins till the patient was shifted to the ward on complete receding of motor block or first demand of analgesia, whichever was later. Duration of postoperative analgesia was measured. Patients were assessed every 6 hours for the first 24 hours for numeric rating score.

The data collected was entered in a master sheet and subjected to statistical analysis by SPSS 23.0 version. Continuous variables were described as mean and variation of each observation from the mean value (Standard deviation) represented as mean ± SD. Categorical variables were described by taking percentages. Analysis between the two groups was done using independent test for continuous variables and Chi square test for categorical variables to identify difference between both the groups. Variables with P value <0.05 was considered as statistically significant.

RESULTS

The demographic parameters were comparable (age, gender, weight, height, BMI, ASA grades) were comparable between both the groups-fentanyl and nalbuphine & difference was not significant.

Table 1: Demographic characteristics

Baseline Characteristics		**Group N (N=32) (Mean ± SD)**	**Group F (N=32) (Mean ± SD)**	**P value**
Age		37.22 ±10.34	41.03 ±10.95	0.157
Gender	Males	22(68.75)	23(71.88)	0.784
	Females	10(31.25)	9(28.12)	
Weight		60±9.22	56.06 ±6.36	0.052
Height		163.27 ±7.73	161.02 ±5.38	0.182
BMI		21.92 ±2.04	21.34 ±1.42	0.195
ASA	Grade 1	28(87.5)	25(78.12)	0.509
	Grade 2	4(12.5)	7(21.88)	

Maximum sensory level achieved by both fentanyl and nalbuphine groups was comparable

with a P value of 0.601.

Table 2: Maximum sensory level achieved

Maximum Sensory Level achieved	Group N (N=32)	Group F (N=32)	P value
T6	4 (12.5%)	4 (12.5%)	0.601
T8	27(84.37%)	28(87.5%)	
T10	1 (3.12%)	0(0%)	

Group F has faster onset of sensory and motor blockade with P values of 0.029 and 0.023 respectively as compared to Group N. However, Group N has longer duration of sensory blockade and motor blockade with p values of <0.0001 each as compared to group F.

Table 3: Sensory and motor blockade

Variables	Group N (N=32)	Group F (N=32)	P value
Time of onset Of Sensory blockade (min)	5.87 ±1.24	5.25 ± 0.98	0.029
Time of onset Of motor blockade (min)	5.31 ±1.31	4.56 ± 1.27	0.023
Duration of Sensory blockade (min)	185.31 ± 19.17	143.12 ± 12.03	<0.0001
Duration of Motor blockade (min)	245.62 ± 22.57	195.31± 15.65	<0.0001

Group F had more stable heart rate as compared to Group N and it was statistically significant at 2 min,45 min,60 min,75 min, 90 min,105 min, 120 min, 135 min with a p value of 0.047, 0.025, <0.0001, 0.005, 0.001,<0.0001, 0.004, 0.006 respectively.

Table 4: Comparison of Heart rate

Heart Rate (beats per minute)	Group N(N=32)	Group F(N=32)	P value
Pre-operative	84±6.71	81.94±4.67	0.163
2min	77.5 ±6.92	80.41±4.19	0.047
4min	77.84±6.35	80.56±4.81	0.058
6min	80.09±6.48	80.22±5.09	0.93
8min	79.06±6.57	80.91±5.09	0.215
10 min	80.06±6.61	80.87±4.72	0.574
15 min	79.19±6.79	82.09±5.23	0.06
30 min	79.59±7.8	81.53±4.26	0.222
45 min	79.25±7.33	82.78±3.98	0.025
60 min	77.16±6.53	82.56±4.59	<0.0001
75 min	78.34±5.51	82±4.48	0.005
90 min	78.66±5.56	82.81±3.93	0.001
105 min	78.04±5.14	83.38±4.22	<0.0001
120 min	79.54±5.85	83.43±3.27	0.004
135 min	79.32±6.99	84.28±1.96	0.006
150 min	79.5 ±6.26	83.75±4.35	0.186

Group F had less reduction in SBP as compared to Group N and it was significantly lesser reduction at 4 min,6 min,8 min,10 min,15 min,30 min, 45 min, 60 min, 75 min, 90 min, 105 min with a p value of 0.014, <0.0001, <0.0001, <0.0001, <0.0001, <0.0001, 0.001, 0.027, 0.002, 0.002, 0.031 respectively.

Table 5: Comparison of SBP

SBP (mm Hg)	Group N (N=32)	Group F (N=32)	P value
Pre-operative	116.25±6.83	118.87 ± 6.85	0.13
2 min	117.19±7.65	117.62 ± 5.43	0.793
4 min	114.12 ± 10.25	119.44 ± 6.06	0.014
6 min	108.12 ± 5.97	118.94 ± 5.3	<0.0001
8 min	102.44 ± 6.46	118.87 ± 5.47	<0.0001
10 min	104.5 ± 9.31	120.56 ± 5.88	<0.0001
15 min	110.44 ± 10.29	120.19 ± 5.38	<0.0001
30 min	113.81 ± 7.69	120.19 ± 5.99	<0.0001
45 min	115.5 ± 9.34	122.25 ± 6.07	0.001
60 min	117.25 ± 9.2	121.56 ± 5.53	0.027
75 min	115.87 ± 9.28	122.31± 5.9	0.002
90 min	115.94 ± 8.18	121.5 ± 5.59	0.002
105 min	118.57 ± 8.48	122.55 ± 4.59	0.031
120 min	118.23 ± 8.41	120.86 ± 6.24	0.334
135 min	122.36 ± 6.4	122.11± 5.33	0.892
150 min	118.4 ± 8.15	121.5 ± 4.43	0.383

Group F had less reduction in DBP as compared to Group N and it was significantly lesser reduction at 6 min, 8 min, 10 min, 15 min, 30 min, 45 min, 60 min, 75 min with a p value of <0.0001, <0.0001, < 0.0001, 0.004, <0.0001, 0.038, 0.004, 0.032 respectively.

Table 6: Comparison of DBP

DBP (mm hg)	Group N(N=32)	Group F(N=32)	P value
Pre-operative	80.75±7.5	77.69±4.74	0.055
2min	76.5 ±7.74	75.62±4.83	0.589
4min	73.12±7.88	76.12±4.34	0.064
6min	71.06±6.57	77.31±3.79	<0.0001
8min	66.37±7.44	76.19±4.5	<0.0001
10 min	67.22±7.72	77.19±4.48	<0.0001
15 min	71.81±7.05	76.12±4.09	0.004
30 min	73.87±5	78.75±2.82	<0.0001
45 min	76±4.77	78.06±2.76	0.038
60 min	74.15±5.39	77.56±3.58	0.004
75 min	75.5 ±7.34	78.56±2.92	0.032
90 min	76.31±6.12	78.25±3.86	0.135
105 min	77.93±5.87	78.89±3.53	0.452
120 min	77.57±6.93	79.14±1.48	0.246
135 min	78±6.62	78.78±2.29	0.638
150 min	77.6 ±4.79	75±3.46	0.292

Group F had less reduction in MAP as compared to Group N and it was significantly lesser reduction at 4 min, 6 min, 8 min,10 min, 15 min, 30 min, 45 min, 60 min, 75 min, 90 min with a p value of 0.042,<0.0001,<0.0001, <0.0001, <0.0001, <0.0001, 0.004, 0.001, 0.002, 0.011 respectively.

Table 7: Comparison of MAP

`MAP(mm Hg)	Group N (N=32)	Group F (N=32)	P value
Pre-operative	92.19±5.69	90.81±4.42	0.285
2min	90.03±6.77	89.62±3.46	0.764
4min	87.41±7.91	90.53±3.11	0.042
6min	83.47±5.04	91.09±2.9	<0.0001
8min	78.22±6.59	90.34±3.44	<0.0001
10 min	79.62±6.6	91.69±3.1	<0.0001
15 min	85.12±7.51	90.81±2.91	<0.0001
30 min	86.97±4.8	92.5 ±2.66	<0.0001
45 min	89.62±5.66	92.81±2.17	0.004
60 min	88.34±5.78	92.22±2.16	0.001
75 min	88.91±6.77	93.22±2.83	0.002
90 min	89.56±8.72	92.54±2.94	0.011
105 min	91.82±6.11	93.38±6.17	0.221
120 min	91.32±6.34	93±2.19	0.191
135 min	92.77±5.46	93.11±1.6	0.801
150 min	91.2 ±5.51	90.25±2.06	0.748

Ramsay sedation score in Group F was 1.25 and in Group N was 1.18. Both the groups were comparable in Ramsay sedation score. P value was not statistically significant. The duration of post operative analgesia in group N (200.7min) was significantly prolonged (P< 0.0001) than in group F (154.69min).

Table 8: Ramsay Sedation Score

	Group N (N=32)	Group F (N=32)	P value
Ramsay Sedation Score	1.18 ±0.39	1.25 ±0.44	0.553
Duration of post-operative Analgesia (min)	200.7 ± 45.29	154.69 ± 11.91	<0.0001

Postoperative VAS score was comparable at different time (6,12,18 & 24 hrs.) intervals between group N and group F. P value was not statistically significant.

Table 15: Post-operative VAS score

Post-operative VAS score	Group N (N=32)	Group F (N=32)	P value
6 hrs.	4.4 ± 0.61	4.34 ± 0.6	0.682
12 hrs.	3.84 ± 0.68	3.62 ± 0.55	0.162
18 hrs.	3.53 ± 0.57	3.34 ± 0.54	0.183
24 hrs.	3.12 ± 0.42	3.09 ± 0.39	0.759

The complications such as nausea, vomiting, bradycardia, pruritus and respiratory depression was not seen in any of the patients Hypotension was seen in 3 patients of nalbuphine group but it was not significant statistically (P=0.071).

6 patients in nalbuphine group and 1 patient in fentanyl group experience urinary retention this difference was statistically significant (P= 0.047).

Table 9: Side effects between nalbuphine and fentanyl.

Complications	Group N	Group F	P value

	(N=32)	(N=32)	
Hypotension	3 (9.37)	0	0.078
Urinary Retention	6 (18.75)	1 (3.12)	0.047

DISCUSSION

Satisfactory pain relief has always been a difficult problem in clinical practice.[7] It is found that operative pain is more severe after surgery and thereafter gradually diminishes over the next 24 hours. Existence of pain has been a constant stimulus to the discovery of both drugs and procedures for relief of pain.[8]

Neuraxial block techniques are often used for lower extremity orthopedic surgery. One of the most important benefits of neuraxial block is the ability to provide extended postoperative pain control that is superior to that provided by systemic opioids alone.[9] Lower limb orthopedic surgeries have shown increased acceptance of subarachnoid block. Since the immediate postoperative analgesia of subarachnoid block is limited, adjuvants especially narcotics have been used with local anesthetics.

Spinal anesthesia using local anesthetics is a rapid onset and effective sensory and motor blockade technique for orthopedic lower limb surgeries and spinal anesthesia remains a preferred technique for such surgeries. In lower limb orthopedic surgeries postoperative pain management is a major issue because spinal anesthesia with only local anesthetics provides analgesia of short duration.[10]

Bupivacaine is an amide type of local anesthetic drug acting mainly by inhibiting voltage-gated sodium channels in the spinal cord by interfering with afferent and efferent sensory and motor impulses while intrathecal opioids activate opioid receptors in the dorsal gray matter of the spinal cord (substantia gelatinosa) to modulate the function of afferent pain fibers.

In present study, results obtained for maximum sensory level achieved were comparable between nalbuphine and fentanyl and are similar to the observations done by Gupta K et al.,[2] ,Naaz S et al.,[11] Bengali R et al.,[12] Kumaresan S et al.,[13] and Mukherjee A et al.,[14].

In present study, the mean time of onset of sensory blockade in nalbuphine group was 5.87 ± 1.24 min and in fentanyl group was 5.25± 0.98 min. Fentanyl had statistically significant faster onset of sensory blockade compared to nalbuphine($P < 0.029$). Similar observations were noted by Ahmed FI et al.,[15], Bengali R et al.,[12] Pawar AB et al.,[16] and Bisht S, Rashmi D et al.,[17]

However, the studies conducted by Gupta K et al.,[2] Singh N et al.,[3],Gommaa HM, et al.,[5] Bindra TK, Kumar P, et al.,[18] Naaz S et al.,[11] Prabhakaraiah UN et al.,[19] and Sharma DN, .,[10] on the meantime of onset of sensory blockade had faster results in fentanyl group as compared to nalbuphine group. But the difference was not statistically significant. This may be because of different volume of the drug used or different types of study population like Elective cesarean section in Gommaa HM.,[6] and lower abdominal surgeries in Prabhakaraiah UN et al.,[19]

In present study, the mean time of onset of motor blockade in nalbuphine group was 5.31 ± 1.31 min and in fentanyl group was 4.56 ± 1.27 min. Fentanyl had statistically significant faster onset of motor blockade than nalbuphine ($P < 0.023$). Similar results were observed by Gommaa HM et al.,[5] Ahmed FI.[15], Bengali R et al.,[12] and Bisht S et al.,[17]

However, the observations done by Gupta K et al.,[2] Singh N et al.,[3], Bindra TK et al[18], Naaz S et al.,[11] Prabhakaraiah UN et al.,[19] Sharma DN et al,[10] and Pawar AB et al[16] on mean time of onset of motor blockade had comparable results between fentanyl and nalbuphine groups.

In our study, the mean duration of sensory blockade was prolonged in nalbuphine group

(185.31 ± 19.17 min) compared to fentanyl group (143.12 ± 12.03 min). Nalbuphine had a highly significant prolongation of duration of sensory blockade with a P value less than 0.0001.

In the observations done by Singh N, Kumar S, et al.,[3] Gommaa HM et al.,[5], Prabhakaraiah UN et al.,[19] on mean duration of sensory blockade between nalbuphine and fentanyl had comparable results and the difference was not statistically significant.

In our study, the mean duration of motor blockade was more prolonged in group N (245.62 ± 22.57 min) compared to group F (195.31 ± 15.65 min). Nalbuphine had highly significant prolongation of mean duration of motor blockade with a P value of less than 0.0001.

In our study, the mean duration of postoperative analgesia in nalbuphine (200.7 min) was more prolonged than in fentanyl (154.69 min), difference was highly significant. Since nalbuphine has a half-life of 5 hours as compared to fentanyl (3-4 hours). This could explain longer duration of sensory blockade, motor blockade and postoperative analgesia of nalbuphine compared to fentanyl.[20]

There was no incidence of side effects like, nausea and vomiting, pruritus, respiratory depression with either nalbuphine or fentanyl. In our study, hypotension was seen with 3 patients only in nalbuphine group and was treated with a single dose of Inj. Mephentermine 3mg. Observation by Singh N et al.,[3] Gommaa HM et al.,[5] Prabhakaraiah UN, et al.,[19] and Bisht S et al.,[17] on side effects were minimal, similar to our study and comparable between nalbuphine and fentanyl groups.

In our study, nalbuphine had 6 patients with urinary retention while fentanyl had only 1 patient and this difference was statistically significant. The mechanism by which opioids cause urinary retention is not completely clear. The micturition reflex could be affected by the opioids on both spinal and supraspinal.

The urodynamic evaluation done by Kuipers PW et al.,[21] found that there was reduction in urinary flow rate with increased voiding time and residual volume, decreased urge to void and reduced detrusor contractility. The reduced detrusor contractility strength is the main effect of intrathecal opioids.

The combination of opioids as adjuvant to local anesthetic is synergetic for producing the analgesia for prolonged duration without measurably increasing sympathetic or motor blockade, thus allows early ambulation of patients and reduction in dosages of local anesthetics, thus leading to the decline of their systemic side effects.[2]

CONCLUSION

20 mcg Intrathecal Fentanyl hastens the onset of sensory and motor blockade with 3 ml of 0.5% Hyperbaric Bupivacaine as compared to 0.8 mg Intrathecal Nalbuphine with more stable hemodynamics clinically. However, 0.8 mg Intrathecal Nalbuphine prolongs the duration of sensory and motor blockade and also has more prolonged postoperative analgesia as compared to 20 mcg Intrathecal Fentanyl

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