International Journal of Medical and Health Research
ISSN: 2454-9142
www.medicalsciencejournal.com
Volume 4; Issue 4; April 2018; Page No. 26-31

A prospective randomized double blind comparative study of 0.8 mg nalbuphine hydrochloride and 25 mcg fentanyl as adjuvant to 0.5% hyperbaric bupivacaine in sub arachnoid block in lower limb surgeries

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Abstract
Introduction: Opioids when added to local an aesthetic for sub arachnoid block are known to prolong postoperative an algesiaas the two drugs act at different sites.
Aim: To compare μ opioid agonist fentanyl and partial agonist nalbuphine for post-operative analgesia, hemodynamic parameters and adverse effects as and juvant to hyperbaric bupivacaine
Material and Methods: Sixty patients of either sex, scheduled for elective lower limb surgeries under sub arachnoid block belonging to ASA class I and II were included in this study. Patients received 0.5% hyperbaric bupivacaine 15 mg along with either 25mcg fentanyl or 0.8mg nalbuphine hydrochloride. Onset and duration of sensory and motor block, hemodynamic parameters, adverse effects, effective duration of analgesia and postoperative VAS scores and sedation scores were noted.
Results: Duration of postoperative analgesia was significantly longer with nalbuphine (318±13.88 min)as compared to fentanyl (296.26±13.31min). Side effects like nausea vomiting, hypotension and bradycardia and shivering was more with fentanyl while sedation was minimal with both the drugs.
Conclusion: Nalbuphine hydrochloride is a better alternative as an adjuvant for postoperative analgesia and less side effects than fentanyl for lower limb surgeries.

Keywords: hyperbaric bupivacaine, nalbuphine hydrochloride

Introduction

Spinal anaesthesia is the preferred technique for most of the abdomino-pelvic and lower limb surgeries. Hyperbaric bupivacaine 0.5% is extensively used for spinal anaesthesia. Though the duration of action of bupivacaine is enough for intermediate duration surgery, it will not produce prolonged postoperative analgesia. Opioids are routinely added to local anaesthetics to prolong their duration of action in the postoperative period [1].

Opioid analgesics activate opioid receptors located on the primary afferent neurons, resulting in the activation of pain modulating systems. Local anaesthetic act at the nerve axon and the opioid at the receptor site in the spinal cord. PureOpioid agonist acts on mu receptors and are principally responsible for supraspinal and spinal analgesia along with sedation, nausea, vomiting, pruritus, and respiratory depression. A partial opioid agonist, on the other hand act principally on kappa receptors in thesubstantia gelatinosa [2].

This study was undertaken to compare between pure mu opioid agonist fentanyl and partial agonist nalbuphine as an adjuvant to hyperbaric bupivacaine in lower limb surgeries.

Material and Methods

The calculated sample size was 27 patients per study group determined for a difference in the duration of analgesia of 20 minutes and SD of 25 min. for alpha value 0.05 and power of 80%. However we took sample size of 30 per group for better validation of results, The calculation was based upon previous study results[9] and also keeping in view the lower dose of the study drug i.e nalbuphine hydrochloride and total volume used in our study

Study Groups

Group A (Fentanyl group): patients received intrathecal 0.5% hyperbaric bupivacaine 15 mg (3 ml) + 25 mcg fentanyl (0.5 ml). Total volume 3.5 ml

Group B (Nalbuphine group): patients received intrathecal 0.5 % hyperbaric bupivacaine 15mg (3 ml) + 0.8 mg nalbuphine hydrochloride (in 0.5 ml normal saline). Total volume 3.5 ml

Inclusion Criteria

- ASA physical status I and II patients of both sexes in the

age group of 18-60 y undergoing elective lower limb surgeries under sub arachnoid block.

Exclusion Criteria

- History of drug allergy
- Patients with history of uncontrolled hypertension, diabetes, renal disorder, hepatic disorder and peripheral vascular disease
- Patients with severe cardiac and pulmonary diseases
- Patients with physical dependance on narcotic drugs, psychiatric illness and alcohol abuse
- Patients with history of recent head injury
- Pregnant and lactating women
- Patients having absolute contraindications for spinal anaesthesia (skin infection, coagulopathy, spinal deformity)

Written informed consent was obtained prior to enrolmment of subjects in the study. A detailed pre anaesthetic evaluation was done and routine laboratory investigations were performed prior to study.

They were allowed for a period of absolute fasting of atleast 8 hours starting midnight prior to surgery. All patients were pre medicated with tab diazepam 10 mg at night before and tab ranitidine 150 mg on the morning of surgery.

After arrival to operation theatre, standard monitoring for heart rate (HR), blood pressure, electrocardiogram, and pulse oximetry (SpO2) was recorded Under all aseptic precautions sub arachnoid block was performed in the sitting position at L3-L4 intervertebral space and patient was placed in supine position Sensory and motor block characteristics were assessedin the lower limb at every 2 min interval until no pinprick sensation was achieved. All time intervals were calculated from the time of end of intrathecal injection. Onset of sensory block, defined as time to reach sensory block at L1, maximum cephalic level, and time taken to two dermatome regressions of sensory analgesia were recorded Grading for motor block was done according to modified Bromage scale [3] Grade 0 – no motor block. Grade 1 – inability to raise extended leg, able to move knees and feetGrade 2 – inability to raise extended leg and move knees, able to move feet. Grade 3 – complete motor block, unable to move legs or feet. Onset of motor block was taken as time to achieve Bromage grade 2

For recovery of block, time to two dermatome regressions, regression of sensory block to L1 and time to complete motor recoveries (bromage grade 0) were recorded. The duration of effective analgesia was taken as the time from the completion of spinal injection to the time of administration of the first rescue analgesic reflected by VAS ≥ 4 Patients with VAS ≥ 4 received diclofenac 75 mg intramuscularly for rescue analgesia Postoperatively, sensory and motor block levels were assessed at 30 min intervals until normal sensations returned and patient was able to move his both lower limbs freely.

HR, SBP, and oxygen saturation (SpO2) were recorded just after spinal injection, then every 2 min up to 5 min, then every 5 min up to 30 min and then every 15 min up to 120 min. For the study, hypotension was defined as the fall in mean BP of more than 30 % from baseline or <60 mmHg and treated with increasing the infusion rate of crystalloid solution and by incremental doses of IV me phentermine 6 mg. Bradycardia (HR<50/min) was treated with 0.6 mg atropine intravenously.

Intra operative and postoperative nausea and vomiting was treated with Injection metoclopramide 10 mg slow IV and Pruritus was treated with injection pheniramine maleate 45 mg slow IV

Sedation was assessed using Ramsay sedation scale [4] Grade 1- Anxious or restless or both

Grade 2-Cooperative, oriented and tranquil Grade 3-Responding to commands only

Grade 4 Brisk response to stimulus Grade 5- Sluggish response to stimulus and Grade 6 -No response to stimulus

Any incidence of respiratory depression (respiratory rate <8 breaths/min or SpO_2 <90%) was corrected with supplemental oxygen through facemask.

Postoperatively, the patients were transferred to the recovery room for further monitoring. VAS score was assessed at every 4 hours interval up to 12 hours post operatively

Statistical Analysis

Statistical analysis was done by descriptive statistics as mean and standard deviation (SD)

The distribution of age, height, weight, sensory onset, motor onset, and VAS was checked by the Kolmogorov-Smirnov test.

Chi-square test was applied to find out association between various parameters

Statistical software SPSS 18 for Windows (SPSS Inc., Chicago, Illinois) was used to analyze the data

Results

The present study compared the clinical efficiency of intrathecal fentanyl and nalbuphine as adjuvant to intrathecal 0.5% hyperbaric bupivacaine in 60 adult consented patients, scheduled for elective lower limbsurgery under SAB.

Patients of both groups were statistically comparable regarding mean age, weight, height, gender and surgical characteristics.

Table 1: Demographic profile of patients

Parameters	Group A	Group B
Age (y)	36.51 yrs. ± 10.21yr	38.70yrs. ± 11.54yr
Weight (kg)	60.83 ± 12.05	61.13 ± 11.68
Height (cm)	163.4±6.03	163.3±5.73
Gender (Male: female)	14:16	17:13
Duration of surgery(min)	109.17±7.06	112.60±11.66

Onset of sensory block at L1 was 104.8±11.47secs for group A and 98.3±11.24secs for group B with no statistical significance (p=0.116). 46% patients in group A and 43% patients in group B achieved T6 cephalic level while T8 level was achieved by 40% and 50% patients respectively in groups A and B. Onset of motor block was faster with fentanyl (354.23±33.36sec) than nalbuphine (374.20±27.62sec) This can be attributed to high lipid solubility of fentanyl

Time to regression of two dermatomes was 109.17±7.06min in group A and 112.60±11.66min in group B with no statistical difference (p=0.647)

Total duration of sensory block at L1 was higher with

nalbuphine (152.9±9.65min) as compared to fentanyl (145.87±6.02min) and this was statistically significant (p=0.001)

Total duration of motor block was significantly prolonged with nalbuphine (197.83±11.29min) as compared to fentanyl (186.80±11.49min) Total duration of effective analgesia was higher with nalbuphine (318.0±13.88min) compared to fentanyl (296.26±13.31min) this was statistically significant (p=0.001)

Table 2: Sensory and motor block profile

Parameters	Group A	Group B	P value
Onset of sensory block at L1 (sec)	104.8±11.47	98.3±11.24	p=0.116
Maximum cephalic level	T8	T8	p=0.595
Two segment regression time(min)	109.17±7.06	112.60±11.66	p=0.647
Duration of sensory block(min)	145.87±6.02	152.9±9.65	p=0.001
Onset of motor block(sec)	354.23±33.36	374.20±27.62	p=0.001
Duration of motor block(min)	186.80±11.49	197.83±11.29	p=0.001
Effective analgesia(min)	296.26±13.31	318.0±13.88	p=0.001

In group A, 6.66% of patients were anxious or restless, 33.334% were cooperative and oriented and 60% were responding to commands only. In group B, 36.67% were cooperative and oriented, 56.66 % were responding to commands only and 6.67% showed brisk response to stimulus (sedated) both drugs showed good sedation

Table 3: Association between Intraoperative sedation (Ramsay sedation scale) in group A and B

Intraoperative sedation (Ramsay sedation scale)	Group A	Group B	Fisher Exact test 'p' value and significance
	No. of cases (%)	No. of cases (%)	
1	2(6.66%)	0	Two tailed p=1.000, not significant 95% Confidence interval =0.6423 to 1.791
2	10(33.34%)	11(36.67%)	
3	18(60%)	17(56.66%)	
4	0	2(6.67%)	
5	0	0	
6	0	0	
Total	30	30	

Patients in both groups experienced side effects. However, more side effects were noted in the fentanyl group.Respiratory depression, pruritus and urinary retention was not seen in either of the study groups

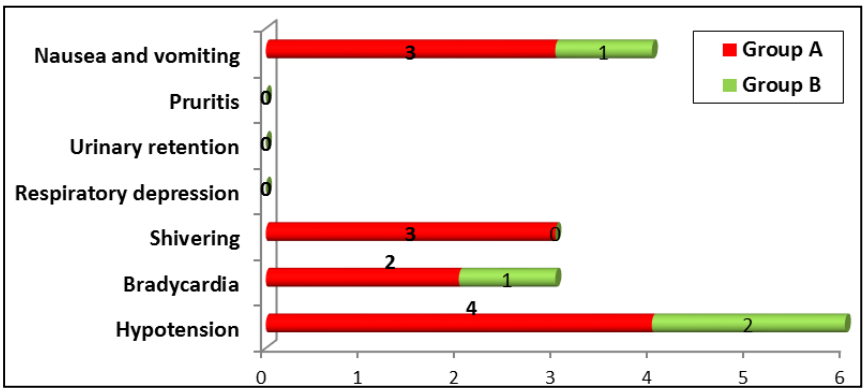

Fig 1: Comparison of Adverse effects in group A and B

The VAS pain scores at measured times 1st hour, 4th hour, 8th hour and 12th hour postoperatively were lower in nalbuphine group as compared to fentanyl group. However this difference was statistically and clinically not significant

Table 4: Comparison of Postoperative Visual analogue score in Group A and Group B

Postoperative period	Group A	Group B	Student Unpaired 't' test value	'p' value and significance
	Mean ± SD	Mean ± SD		
1st hour	0.63±0.61	0.47±0.51	1.10	p=0.101, not significant
4th hour	3.53±1.41	3.27±1.04	0.81	p=0.119, not significant
8th hour	4.30±0.83	4.0±0.90	1.34	p=0.982, not significant
12th hour	4.50±1.13	4.27±0.91	0.87	p=0.114, not significant

After applying General Linear Model for repeated measures, there was no significant variations in systolic BP, diastolic BP and heart rate between both groups.

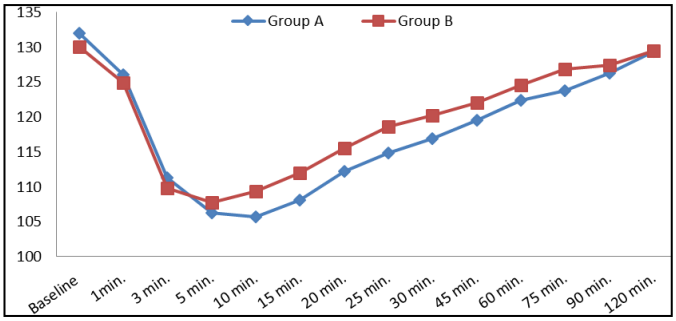

Fig 2: Comparison of Systolic BP between group A and B

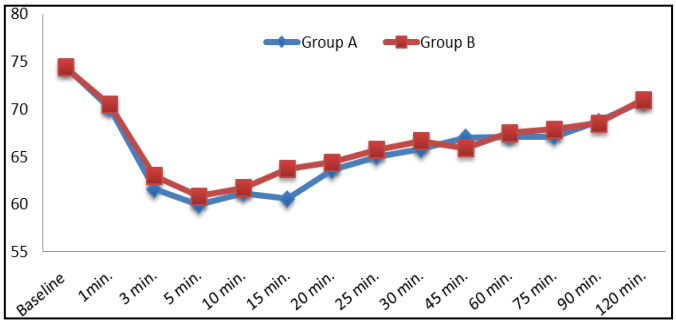

Fig 3: Comparison of Diastolic BP between Group A and B

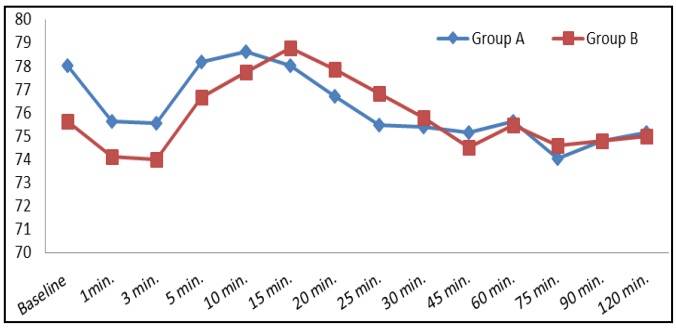

Fig 4: Comparison of Heart Rate between Group A and B

Discussion

Spinal anesthesia consists of the temporary interruption of nerve transmission within the subarachnoid space produced by the injection of a local anesthetic solution into the cerebrospinal fluid. Local anesthetics work 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. The combination of adjuvants to local anesthetic is synergistic for producing the analgesia of prolonged duration without measurably increasing sympathetic or motor blockade, thus allows early ambulation of patients and reduction in dosages of local anesthetics, hence the decline of their systemic side effects.

Opioids selectively decrease nociceptive input from a delta and C fibers without affecting dorsal root axons or somatosensory evoked potentials. Various μ agonists opioids such as morphine, tramadol, and fentanyl are used as adjuvant to hyperbaric bupivacaine to prolong its clinical efficacy and minimize the requirement of postoperative analgesics, but they are associated with side effects of pruritus, nausea, vomiting, respiratory depression, constipation, and urinary retention [5].

Nalbuphine hydrochloride, an agonist–antagonist, is a synthetic lipid soluble opioid analgesic and possess an agonist action at the κ-opioid receptor and antagonist action at the μ-opioid receptor to provide reasonably potent analgesia of visceral nociception. The greatest concentrations of kappa-receptors in nociceptive regions are in lamina I and II of Rex in the spinal cord dorsal horn as well as in the spinal nucleus of the trigeminal nerve (substantiagelatinosa). Taken together, these data suggest that nalbuphine acts primarily at the level of the first synapse in the nociceptive system in producing analgesia

Jyothi *et al*. [6] conducted a study on 100 patients undergoing lower abdominal and lower limb orthopedic surgeries to compare 3 different doses of nalbuphine with bupivacaine. They found that nalbuphine 0.8 mg showed better postoperative analgesia and increasing the dose beyond 0.8 mg did not increase the analgesic effect of the drug.

Gomaa *et al*. [7] compared these two drugsin patients undergoing elective caesarean section and found that sensory onset of fentanyl was 1.64 ±0.09 mins and that of nalbuphine was 1.60 ± 0.10 mins with no statistical difference (p=0.116). However, onset of motor block was faster in fentanyl group (5.57±23 min) as compared tonalbuphine group (5.72±0.17min) and this was statistically significant (p=0.008) in their study. This was explained by more lipid solubility and rapid tissue uptake of fentanyl more than nalbuphine. Our study results are in accordance with this study.

Singh J *et al*. [8] This group did a similar study in 60 patients undergoing elective lower limb surgeries and found no statistical difference in onset of sensory block among both the groups, fentanyl (1.64 min) and nalbuphine (1.60 min) As regards to motor block, onset was more rapid with fentanyl (5.57 min) than nalbuphine (5.72 min) ($p < 0.05$) and their results are comparable with our study

In another study by Gupta K *et al*. [9] the median cephalic sensory level achieved in both groups was T6– fentanyl (T4-T8) and nalbuphine (T4-T7). In our study the maximum cephalic level achieved was T6 in both groups.

Singh N *et al*. [10] Used fentanyl 30 mcgs and nalbuphine 0.5 mg in lower abdominal surgeries. Duration of two segment regression from highest sensory level was fentanyl (96.75± 3.35mins) and nalbuphine (96.5 ±4.0 mins) and plain bupivacaine group (90.75± 4.78 mins). This duration was found to be statistically insignificant between the study groups ($p > 0.05$) but it was statistically significant between study and control group ($p < 0.001$)

In our study, this duration was found to be statistically insignificant between both groups.

Another study by Thote *et al*. [11] found no statistical difference in 2 segment depression time between the study groups - fentanyl (95.9± 8.6 min) and nalbuphine (97.5± 10.9 min) sensory block was more prolonged in nalbuphine group (166.5 ±11.5min) as compared to fentanyl group (158.9 ±11.3

min) and control group (137.4± 9.6 min.) The results were statistically highly significant (p<0.001)

Gupta K *et al*. [9] In their study total duration of motor blockade was significant in nalbuphine group (183.26 ±29.63 min) compared to fentanyl group (141.63 ±11.06 min).Mild pruritus was observed in 5 (14.7%) patients of fentanyl group. The incidence of respiratory depression was minimal and comparable ($P > 0.05$). Postoperatively, the SpO2 was well maintained above 97% on air in all patients. No patient suffered from postspinal shivering, nausea, vomiting, or respiratory depression.

Singh N *et al*. [10] found more prolonged sensory block (time to regression of sensory block to S2 dermatome) in nalbuphine group (156.5± 12.7min) as compared to fentanyl group (142.0± 9.09 min) and control group (130.0± 6.48 min) and this difference was statistically significant.

Results of our study are in accordance with these studies.

Effective analgesia was found to be more prolonged in nalbuphine group (318.0 ±13.88 min) compared to fentanyl (296.26 ±13.31min) and this was statistically significant in our study (p<0.001)

Studies that support our findings

Naaz *et al*. [12] performed a comparative study of two doses of nalbuphine (0.8 mg and 1.6 mg) and fentanyl 25 mcg combined with bupivacaine. They found that all the three groups showed increased post-operative analgesia, but nalbuphine 0.8 mg showed maximum duration of analgesia followed by nalbuphine 1.6 mg and fentanyl. They also studied CACS (cumulative analgesic consumption score) and VRS (verbal rating scale) to check postoperative analgesic requirements in 24 hours duration. The mean of highest VRS score during 24 hour time were NL (0.8 mg) (3±1.4), NH (1.6mg) (3.9±1.7) and Fentanyl (5.5±1.8) groups. The 24 hour analgesic consumption was significantly higher in fentanyl group compared to nalbuphine group indicating higher VAS scores in fentanyl treated group.Adverse effects like shivering, pruritus, hypotension, urinary retention were higher in fentanyl group. Respiratory depression was observed in 3 patients in fentanyl group and none in nalbuphine group Gupta et. al. [9] showed similar results. Total duration of analgesia was more prolonged in nalbuphine group (318.64±21.92min) compared to fentanyl (278.74±29.67min) and this was statistically significant.

Culebras *et al*. [13] in 2000, performed a comparative study to evaluate post-operative analgesia and adverse effects after using three doses i.e. 0.2mg, 0.8mg, 1.6mg of intrathecalnalbuphine or morphine 0.2mg given for caesarean section along with bupivacaine. The longest durations of complete and effective analgesia among the nalbuphine-treated groups were provided by 0.8 mg added to bupivacaine.

Gupta KL *et al*. [14] performed a study comparing nalbuphine 1mg added to 0.5%bupivacaine and bupivacaine alone in 60 patients of ASA PS I and II undergoing lower limb orthopedic surgery. They found the duration of postoperative analgesia was 6-8 hours in nalbuphine added group versus 3-4 hours in bupivacaine only group. This difference was statistically significant (p<0.0001)

Fournier *et al*. [15] compared between intrathecalnalbuphine 400µg and intrathecal morphine 160 mcg in old patients undergoing total hip replacement using continuous spinal anesthesia. They concluded that intrathecalnalbuphine produces faster onset of pain relief but the duration of analgesia is shorter than intrathecal morphine.

Alaaeldin *et al*. [16] 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. They found that 20 % patients in nalbuphine treated group had sedation and none in fentanyl group.Our results are comparable to this study.

Sapate *et al*. [17] in a randomized control study, they observed the effects of intrathecalnalbuphine (0.5 mg) with 0.5% spinal bupivacaine (3 mL) for lower abdominal surgeries in elderly patients. They concluded that nalbuphine provided better quality of spinal anaesthesia as compared to bupivacaine alone and also enhanced the postoperative analgesia. No patients in their study developed any side effects.

Conclusion

Nalbuphine hydrochloride is a better alternative as an adjuvant for postoperative analgesia, potentiating sensory and motor block of bupivacaine with hemodynamic stability and less side effects than fentanyl for lower limb surgeries.

However, more clinical trials are required before it's superiority can be established over fentanyl as a stand alone analgesic.

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