



Original Research Article

A comparative study on the effect of intrathecal nalbuphine and buprenorphine as an adjuvant to 0.5% hyperbaric bupivacaine in elective infraumbilical surgeries

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ABSTRACT

Background: Subarachnoid blockade provides excellent operating conditions for lower abdominal, orthopedic, pelvic, urological, gynecological and lower extremity surgery. Most subarachnoid anesthetics are single shot injections and have a definite duration; hence opioids have been used along with local anesthetics in subarachnoid block to prolong its effect, duration, quality of analgesia and minimize the necessity of postoperative analgesics.

Aim and Objectives: The primary objective of the study was to assess the onset and duration of sensory and motor blockade. The secondary objective of the study was to compare the hemodynamics, duration of postoperative analgesia and the complications encountered between the two groups.

Materials and Methods: A prospective randomized double-blinded study was done in 120 patients divided into two groups with 60 in each group as group N and group B by computer generated random numbers. Group N received 0.5% Heavy Bupivacaine (3.2ml) + 0.6mg of Nalbuphine (0.3ml) to a total volume of 3.5 ml and Group B received 0.5% Heavy Bupivacaine (3.2ml) + 90µg of Buprenorphine (0.3 ml) to a total volume of 3.5 ml for spinal anesthesia. The differences between the groups were statistically analyzed with the Independent t test for continuous variables and Pearson's chi-square test for categorical variables. Observations and results: The onset of sensory block (p=0.303) and motor block (p=0.510) was observed to be faster in group N when compared to group B with statistical insignificance, but the duration of both sensory block (p< 0.001) and motor block (p< 0.001) was more pronounced in group B when compared to group N with statistical significance. The duration of effective analgesia was more pronounced in group B (468.35±30.57 minutes) compared to group N (362.70±35.53 minutes).

Conclusion: The duration of the sensory and motor block with effective postoperative analgesia were more pronounced in buprenorphine compared to nalbuphine and hence intrathecal buprenorphine is a better alternative adjuvant to intrathecal nalbuphine in elective infraumbilical surgeries.

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1. Introduction

Subarachnoid blockade is often popular technique of choice for infraumbilical surgeries as it favours many advantages over general anaesthesia. Wang and colleague introduced the intrathecal opioids usage for acute pain management in 1979.¹ Bupivacaine has been combined with a number

of opioids to increase the duration of its effects, enhance the analgesic impact, and reduce the need for postoperative analgesia.² The advantage of local anaesthetic and opioid combination eliminates the pain at the nerve axon and spinal cord respectively.

Bupivacaine is highly lipid-soluble, protein-bound, potent long-acting amide local anesthetic. The distinctive aspect of bupivacaine is that it causes both sensory and motor dissociation.³ Buprenorphine is a derivative of baine

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that acts as an antagonist at the kappa receptor and a longer dissociation partial agonist at the μ receptor. It is roughly 33 times more effective than morphine. As it is also highly fat soluble, it has been used extensively in the management of pain following surgery.⁴

Nalbuphine is an opioid agonist-antagonist that binds to the μ , κ and δ receptors. At the μ -receptor, nalbuphine functions as an antagonist, and at the κ -receptor in the dorsal horn of the spinal cord, it functions as an agonist. Mild analgesia, respiratory depression, and sedation are brought on by the activation of the spinal and supraspinal κ -receptors. Like other agonist-antagonist substances, nalbuphine interferes with the analgesia brought on by pure μ -agonists. The action on kappa receptors produce analgesia with a lower incidence and severity of mu receptor side effects.⁵ It also has a low potential for addiction and little effect on respiratory depression.

Despite the rising popularity of regional anesthesia, adjuvants like buprenorphine and nalbuphine are used far less frequently than fentanyl. In this study, we have examined the onset, duration, need for postoperative analgesia, and side effects of buprenorphine and nalbuphine when added to hyperbaric bupivacaine as an adjuvant in subarachnoid block.

2. Aim and Objectives

The main aim is to differentiate the potency of Nalbuphine and Buprenorphine as adjuvants when amalgamate with 0.5% hyperbaric bupivacaine heavy in patients undergoing elective infraumbilical surgical intervention under subarachnoid blockade. The principal purpose of the study was to determine the onset and duration of sensory and motor hindrance. The additional goal of the study was to examine the hemodynamic, duration of postoperative analgesia, and complications or side effects between the two groups.

2.1. Justification for the study

From literature we found, fentanyl and sufentanil are the most frequently utilized intrathecal opioids since they have been found to enhance neuraxial anesthesia, reduce postoperative pain, and prolong sensory block, whilst morphine extends postoperative analgesia.

Despite the fact that there are numerous adjuvants, only a few studies have been published that compare the benefits and drawbacks of employing buprenorphine and nalbuphine as adjuvants to bupivacaine for lower abdominal surgeries.

3. Methodology

A prospective randomized double-blinded study was undertaken after obtaining Institutional human ethical committee clearance (Project no.21/066 dated March 30, 2021) and approval (PSG/IHEC/2021/Appr/Exp/054).

The study was registered with clinical trials of India (CTRI/2021/05/033520) and conducted during May 2021-May 2022.

Using the duration of sensory and motor blockade parameters in previous Manjula et al⁶ studies, a reference value has been used for sample size calculation. A 95% confidence interval and 80% power of the study were used to calculate the sample size.

$$\text{Formula: } n = \frac{2 \times (Z\alpha + Z\beta)^2 \times SD^2}{(m1 - m2)}$$

$$n = \frac{2(1.96+0.84)^2 \times (5.93)^2}{(141.2-144.40)^2} = 53.84$$

$$10\% \text{ adjustment is } \frac{10}{100} \times 53.84 = 5.38$$

Considering 10% adjustment for non-response (confounder / variable added), the adjusted Sample size = 53.84 + 5.38 = 59.22 and we took 60 as sample size in each group.

The study included 120 patients who were scheduled for subarachnoid blockade in elective infraumbilical surgeries and who were between the ages of 20 and 65, weighed between 50 and 80 years, and height between 150 and 170 cm. All patients belonged to ASA I and II. The following conditions precluded study participation: absolute contraindications to spinal anaesthesia, combined spinal epidural anaesthesia, morbid obesity (BMI>40), known allergies or hypersensitivity to study drugs, pregnancy, and nursing mothers.

To achieve optimal randomization, 120 patients were divided into two groups of 60 each, and then randomly assigned by computer-generated random numbers to one of the two groups listed below: the buprenorphine group (Group B; n=60) or the nalbuphine group (Group N; n=60). A sequentially numbered opaque sealed envelope was used to ensure confidentiality. For spinal anaesthesia, Group N received 0.5% Heavy Bupivacaine (3.2 ml) + 0.6 mg of Nalbuphine (0.3 ml) for a total volume of 3.5 ml, and Group B received the same amount but with 90 μ g of Buprenorphine (0.3 ml) for a total volume of 3.5 ml.

Pre-anaesthetic evaluation which included detailed history, airway and systemic examination was done for the study population a day prior to the surgery. Basic biochemical, pathological investigations were done, and patients were instructed about preoperative starvation orders of 8 hours for solids and clear fluids up to 2 hours prior to surgery. Informed written consent from all the patient who participated in this study was obtained. All the procedures were done as per the guidelines laid down in the Declaration of Helsinki (2013).

Pantoprazole 40 mg and Metoclopramide 10 mg tablets were given to each patient two hours before surgery on the day of the procedure and the night before. Spinal anesthesia procedure was explained to the patient in their vernacular language. Patients were shifted to operating room, a 18G intravenous cannula was inserted intraoperatively and an

infusion of intravenous fluids Plasmalyte started at a rate of 2ml/kg/hr. Pre induction monitors like peripheral oxygen saturation by pulse oximetry (SpO₂), electrocardiogram (ECG) and non-invasive blood pressure (NIBP) were connected, and monitoring of these parameters started after noting the baseline values. Standard noninvasive monitoring were continued perioperatively continuously.

Under strict aseptic precautions, skin infiltration was done with 2ml 2% Lignocaine and dural puncture given preferably at L3-L4 inter vertebral space using 25G Quincke spinal needle with patient in after allowing the cerebrospinal fluid (CSF) to flow freely, in a left lateral position. To guarantee the anaesthesiologist's blinding, one of the study groups' medications (group N or group B) was prepared by a non-participating individual. Following the intrathecal injection of the study drug, the patient was placed in a supine position. During and after subarachnoid blockade, the hemodynamic parameters were noted at interval of 1, 3, 5, 10,15,30, 60, 90, 120, 180 minutes, and the two study groups were compared using the parameters like the duration of the motor block (measured by the Modified Bromage scale), duration of sensory block (measured by the pin prick method), duration of study drug administration in the spinal space, and duration of post-operative analgesia (Effective analgesia: time from the start of sensory block to the first request for rescue analgesics using VAS score)

Modified Bromage Scale as used by Breen et al:⁷

Grade	Description
1	Complete block (Unable to move feet or knees)
2	Almost complete block (able to move feet only)
3	Partial block (just able to move knees)
4	Detectable weakness of hip flexion (between scores 3 and 5)
5	No detectable weakness of hip flexion while supine (Full flexion of knees)
6	Able to perform partial knee bend

The sensory block's onset was evaluated by changes in pin prick sensation using modified Gormley and Hill scale⁸ (normal sensation – 0; blunted sensation – 1 and no sensation – 2). The time to reach T₁₀ dermatome sensory block, peak sensory level, modified bromage motor block was recorded before the start of the surgery. The duration of the motor block was measured from the time intrathecal drug was administered until modified bromage 3 was achieved. From the time of the intrathecal medication injection until the first rescue analgesic supplementation when the patient complained of pain, the length of time that effective analgesia lasted was measured. Time to two dermatome regression of sensory block and time to full recovery from motor block were recorded for block recovery.

Post-operative pain, sensory level and motor level of blockade were evaluated every 60 minutes for the next 4

hours in the recovery unit during the observation period. Respiratory depression was defined as SpO₂ < 90% on room air.

The patient was given a scale with numbers ranging from 0 to 10 and instructed to mark the scale in accordance with their level of pain. The patient was then taught how to use the visual analogue scale (VAS). When VAS score was more than 4, rescue analgesia was given with Injection Tramadol 25mg intravenously. Side effects such as respiratory depression, pruritis, and urinary retention, postoperative nausea and vomiting were recorded. Injection Ondansetron 0.1mg/kg supplemented for anti-emetic action and pruritis was treated with antihistamines.

3.1. Statistical analysis

All the data were entered in Excel 2019 and statistical analysis was performed using the statistical software, SPSS 25.0.0.0. Data were expressed in percentages and mean values (with standard deviation). Differences between the groups were analyzed using Pearson's chi-square test is used for categorical variables and the independent t-test for continuous variables. In cases where the p-value was less than 0.05, the results were deemed statistically significant.

4. Observation and Results

This randomized study was conducted on 120 patients with 60 participants in each group, where one group received hyperbaric bupivacaine with nalbuphine and other group received hyperbaric bupivacaine with buprenorphine. Majority of the study participants were in the age group between 33 and 57 years with mean age of 47.54 in group N and 46.28 in group B. Other demographic parameters like sex distribution of the individual, height, weight, and ASA grades were comparable among both the groups (Table 1).

Table 1: Demographic details between Group N and Group B

Parameters	Group N	Group B	p Value	
Age	Mean in yrs. ± S. D	47.54±10.23	46.28±12.43	0.569
Sex	Male	26 (49.1%)	29 (54.7%)	0.560
	Female	27 (50.9%)	22 (45.3%)	
Weight	Mean in kg ± S. D	71.96±10.30	72.07±13.12	0.961
Height	Mean in cm ± S. D	162.73±6.96	162.22±7.11	0.760
ASA	I	30 (56.6%)	25 (47.2%)	0.331
	II	23 (43.4%)	28 (52.8%)	

When comparing group N to group B, the onset of sensory block (p=0.303) and motor block (p=0.510) was

seen to occur more quickly in group N with statistical insignificance; however, group B showed a more marked duration of both sensory block ($p < 0.001$) and motor block ($p < 0.001$) when compared to group N with statistical significance (Table 2). Group B experienced an effective analgesic for a longer duration (468.35 ± 30.57 minutes) than group N (362.70 ± 35.53 minutes).

Table 2: Association of onset, duration of sensory and motor blockade with study participants

Parameters	Group N	Group B	p value
1. Onset of sensory block (mins)	2.26±0.78	3.30±7.28	0.303
2. Duration of sensory block (mins)	186.30±4.34	269.01±9.77	<0.001
3. Onset of motor block (mins)	2.60±0.65	2.69±0.64	0.510
4. Duration of motor blockade (mins)	184.0.8±4.14	194.03±6.29	<0.001
5. Duration of surgery (hours)	1.23±0.89	1.34±0.64	0.461
6. Duration of effective analgesia (mins)	362.70±35.53	468.35±30.57	<0.001

When comparing the degree of motor blockade, which was measured using the Bromage scale, there was no discernible difference between the two groups for any grade between 1 and 4. The p-value was 1.000 (>0.05).

The statistical insignificance of complications such as arrhythmia, bradycardia, hypotension, bradycardia, nausea, and vomiting were observed in both groups. (Table 3)

Table 3: Complications encountered between two groups

Complications	Group N	Group B	p value
1. Hypotension			
Yes	1 (1.9%)	1 (1.9%)	1.000
No	52 (98.1%)	52 (98.1%)	
2. Bradycardia			
Yes	1 (1.9%)	2 (3.8%)	0.558
No	52 (98.1%)	51 (96.2%)	
3. Arrhythmia			
Yes	0	0	-
No	53 (100%)	53 (100%)	
4. Nausea / Vomiting			
Yes	0	0	-
No	53 (100%)	53 (100%)	

5. Discussion

Subarachnoid blockade provides excellent operating conditions for lower abdominal, orthopedic, pelvic, urological, gynecological and lower extremity surgery.

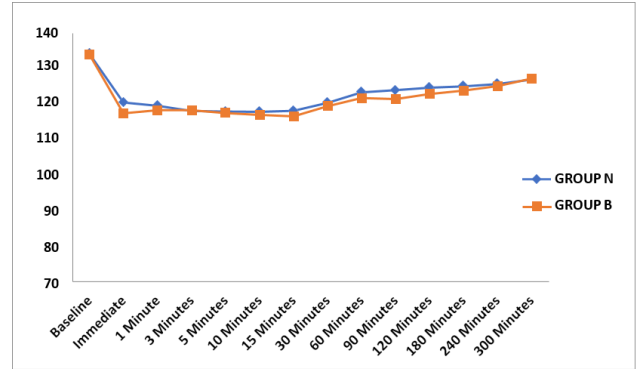


Figure 1: Systolic blood pressure variations between groups

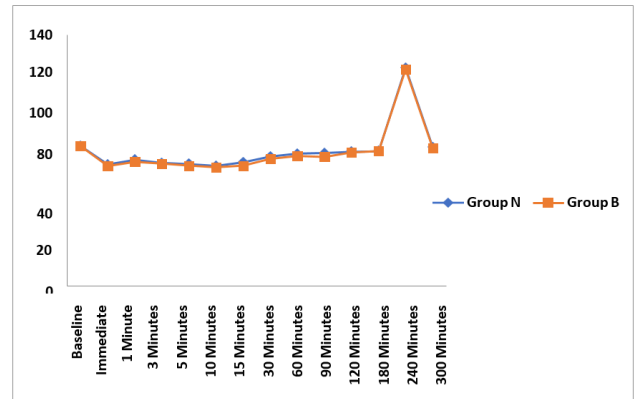


Figure 2: Diastolic blood pressure variations between groups

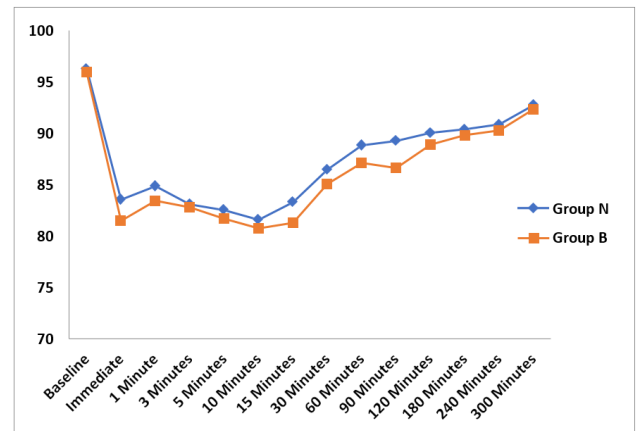


Figure 3: Mean arterial pressure calculated in two group

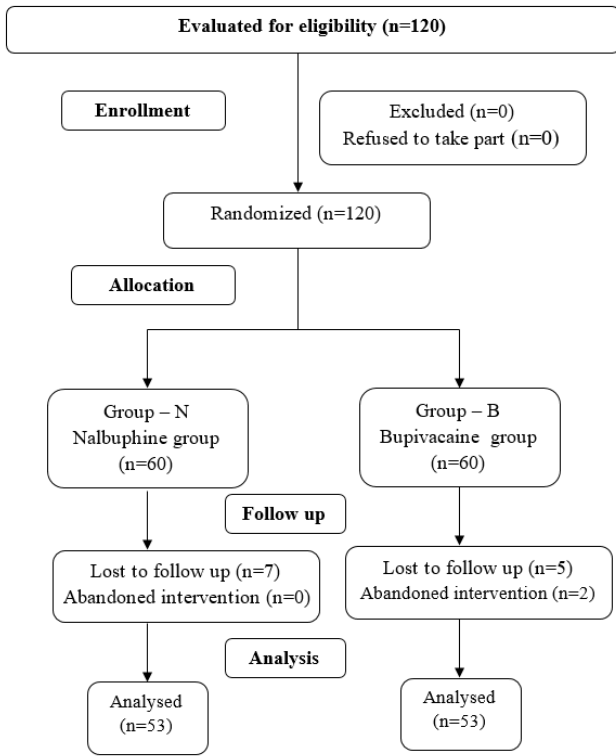


Diagram 1: Consort flow diagram

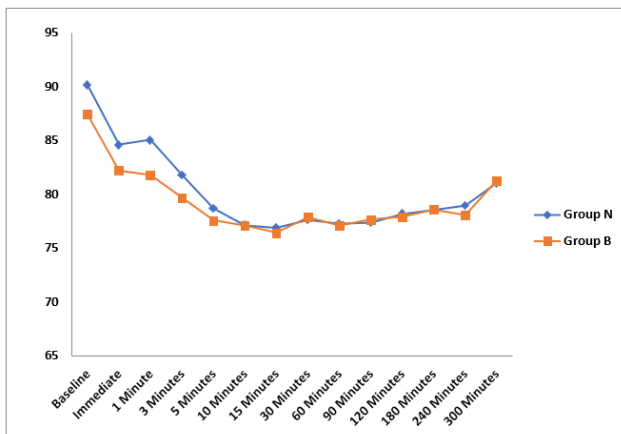


Figure 4: Heart rate recorded between Group N and Group B

Victor Whizar and M Goma⁹ observed that major limitations of spinal anesthesia are its shorter duration of action and inadequate postoperative analgesia when used only with local anesthetics, hence paved the pathway for adding adjuvants to local anesthetics. Most subarachnoid anesthetics are single shot injections and have a definite duration; hence in order to increase the effectiveness, duration, and quality of analgesia from subarachnoid block and reduce the need for postoperative analgesics, opioids have been used in conjunction with local anaesthetics.¹⁰

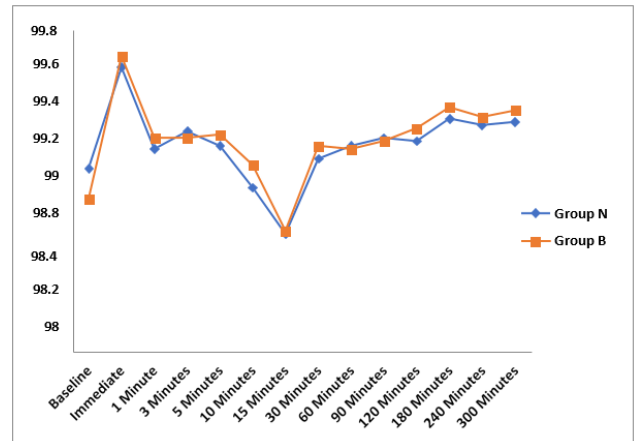


Figure 5: SpO₂ levels noted between two groups

Buprenorphine may have a quicker and longer-lasting effect because of its high lipid solubility, which allows it to penetrate lipid membranes more quickly and bind to receptors quickly and persistently, hastening the block. Pal et al¹¹ further analyzed the three different doses of nalbuphine (0.2, 0.4, and 0.8 mg) to ascertain the optimal dose that would be effective without causing major side effects, and they found that it was 0.4 mg. As a result, we chose to administer hyperbaric bupivacaine along with 0.6 mg of nalbuphine in our study.

However, there are several factors which can influence the outcome of the study that includes the dose and concentration of the adjuvants used in the study, individual variations in drug metabolism and receptor sensitivity, type of infraumbilical surgery can impact the response to intrathecal adjuvants, age, gender and coexisting illness may influence the drug effects, and spinal anatomy with individual variations in cerebrospinal fluid dynamics can affect drug distribution.

The demographic parameters between two groups included in our study was quite similar to the study conducted by Naaz et al,¹² who examined the use of buprenorphine and nalbuphine as an adjuvant to hyperbaric bupivacaine in lower limb orthopaedic procedures to alleviate pain.

While T4, T6, and T8 were the most common dermatomal levels attained for different elective lower limb surgeries in the buprenorphine group, the dermatomal levels attained for Nalbuphine group were comparable but not statistically significant (0.696>0.05). (Table 4)

The onset of sensory blockade in the nalbuphine group was significantly quicker than in the buprenorphine group, which cannot be explained without statistical significance between the two groups. However, the values for the onset of motor and sensory blockade in our study are identical to those of Kaushal et al¹³ who compared buprenorphine with intrathecal nalbuphine as adjuvants

Table 4: Association of dermatomal levels with Group B and Group N

Groups	Segmental Level							p value
	T-4	T-5	T-6	T-7	T-8	T-9	T-10	
Group N	14 (26.4%)	1 (1.9%)	22 (41.5%)	1 (1.9%)	8 (15.1%)	3 (5.7%)	4 (7.5%)	0.696
Group B	11 (20.8%)	1 (1.9%)	21 (39.6%)	0 (0.0%)	15 (28.3%)	2 (3.8%)	3 (5.7%)	

in lower limb orthopedic procedures and discovered that neither group experienced many adverse effects. For lower limb orthopedic procedures, intrathecal buprenorphine is a better adjuvant to 0.5% bupivacaine because it prolongs the sensory block and delays the delivery of the first dose of rescue analgesia.

A statistically significant difference ($p=0.001$) was observed in the mean duration of the sensory block between the buprenorphine group (269.01 ± 9.77 minutes) and the nalbuphine group (186.30 ± 4.34 minutes). Likewise, there was a statistically significant difference in the mean duration of the motor block between the buprenorphine (194.03 ± 6.29) and nalbuphine (184.08 ± 4.14) groups ($p=0.001$). According to Chetty et al,¹⁴ intrathecal nalbuphine at a dose of 2 mg induced a faster onset of sensory and motor blockade, whereas intrathecal clonidine extended the duration of the blockade. Fournier et al¹⁵ discovered that when 400 mg of nalbuphine or 160 mg of morphine were injected intrathecally and dissolved in 4 ml of normal saline, nalbuphine exhibited a significantly quicker onset of sensory blockade and a shorter duration of analgesia compared to morphine.

Kaushal et al¹³ showed that analgesia lasted for 371.56 ± 33.70 minutes in nalbuphine group, compared to 362.70 ± 35.53 minutes in our study and the results were comparable. In Naaz et al¹² study, The NL Group and the NH Group experienced analgesia for 441 ± 119.69 and 450 ± 103.38 minutes, respectively, after using 0.8 and 1.6 mg of nalbuphine as adjuvants to hyperbaric bupivacaine. Naaz et al demonstrated that the dose-related significant difference in the lengthening of analgesia was present. Jyothi B et al. found that increasing the dose of nalbuphine from 0.8 to 1.6 mg and 2.4 mg did not improve the analgesic efficacy. This suggests that there is a ceiling effect of nalbuphine on analgesia.

The mean duration of effective analgesia was observed to be shorter in the nalbuphine group with statistical significance ($p=0.01$). Since higher doses of nalbuphine have been linked to more side effects and have been exhibiting a ceiling effect, they were excluded from our study. According to research by Ravindran et al¹⁶ for postoperative analgesia following caesarean section, increasing the dose of buprenorphine from 45 mcg to 60 mcg caused a noticeably longer duration of analgesia without increasing the incidence of adverse effects.

Using hyperbaric bupivacaine as an adjuvant for postoperative analgesia in caesarean deliveries, Shrinivas et al¹⁷ compared the efficacy of two doses of buprenorphine

(60 mcg and 90 mcg). They found that the duration of postoperative analgesia was significantly longer and that increasing the dose of buprenorphine from 60 mcg to 90 mcg provided longer duration of analgesia without experiencing any notable side effects. Therefore, in our study, we determined that the dosage of intrathecal buprenorphine to be used as a supplement to hyperbaric bupivacaine would be 90 mcg.

In the buprenorphine group, the analgesia lasted 468 ± 30.75 minutes, whereas in the trial by Kaushal et al., it lasted for 471.20 ± 76.29 minutes. The difference in buprenorphine dosage in our study (90 mcg versus 60 mcg) may have contributed to the prolongation of duration. Tiwari et al¹⁸ study found Nalbuphine hydrochloride (400 mcg) significantly increases the duration of sensory blockade and postoperative analgesia when administered intrathecally along with hyperbaric bupivacaine.

However, our study's mean duration of analgesia was quite similar to that of the studies by Shaikh and Kiran et al,¹⁹ Capogna et al,²⁰ Shailaja et al,²¹ and Dixit S,²² which were 475 minutes, 430 minutes, 300 minutes, and 491 minutes, respectively. This explains the duration of age-related and dose-dependent effective analgesia. As per the findings of Lin ML et al,²³ the Nalbuphine study group experienced reduced side effects and better intraoperative and postoperative pain control when 0.4 mg of either morphine or nalbuphine was added to hyperbaric tetracaine for subarachnoid block.

By comparing three different intrathecal nalbuphine doses and determining the adjuvant's efficacy, Pal et al¹¹ aimed to determine the ideal dose of intrathecal nalbuphine with a long-lasting analgesic effect and minimal side effects.

In order to provide postoperative analgesia, Shah et al²⁴ used intrathecal nalbuphine as an adjuvant to 0.5% hyperbaric bupivacaine in two different doses. They discovered that intrathecal nalbuphine at a dose of 1.6 mg was a helpful addition to 0.5% hyperbaric bupivacaine for subarachnoid blockade (SAB) without causing any respiratory side effects that would have prolonged analgesia. The group of patients receiving 0.8 mg of nalbuphine with bupivacaine provides excellent analgesia with a longer duration of action and no side effects, according to Jyothi B et al²⁵ analysis.

In their study, Borah et al²⁶ determined that 0.4 and 0.8 mg of nalbuphine are equally effective as adjuvants to isobaric 0.75% ropivacaine in elective lower limb surgeries. They also concluded that nalbuphine can be a good option to other opioids as an adjuvant intrathecally to prolong

postoperative analgesia with a low side effect profile. Along with early motor recovery, this combination offers the added benefit of significant analgesia.

Patients in the buprenorphine group reached a VAS > 4 later than those in the nalbuphine group, and the buprenorphine group had a delayed time for the first dose of rescue analgesic when compared to the nalbuphine group, according to the extended postoperative period mean VAS score monitoring in the various groups. In our study, 4 patients required rescue analgesic in nalbuphine group compared to 2 in buprenorphine group but since it turned out to be comparable; it was statistically insignificant. (Table 5)

Table 5: Mean VAS score and rescue analgesia between Group N and Group B

Parameter	Group N	Group B	p value
1. Mean VAS score	4.02 ± 0.84	4.17 ± 0.61	0.294
2. Rescue analgesia			0.401
Yes	4 (7.5%)	2 (3.8%)	
No	49 (92.5%)	51 (91.6%)	

Following SAB, an intragroup comparison revealed no appreciable and statistically significant differences in the groups' perioperative mean PR, SBP, DBP, MAP, and SpO₂.

Nalbuphine also provided haemodynamic stability and similar findings were seen in the study by Culebras,²⁷ Tiwari¹⁸ and Bindra et al²⁸ where there were no gross hemodynamic changes throughout their study. In our study, there were two cases of bradycardia in the buprenorphine group and one in the nalbuphine group, and there was one case of hypotension in both groups, which was treated with injections of mephentermine at incremental doses of 6 mg. The study by Sonali et al²⁹ showed similar results. This might be as a result of nalbuphine's strong affinity for k-opioid receptors, which also causes cardiovascular stability, sedation, minimal respiratory depression, and analgesia.

Neither group displayed any desaturation, euphoria, respiratory depression, ECG changes or pruritus. Kaushal et al¹³ study showed more incidence of vomiting, nausea in buprenorphine group when compared to nalbuphine group which could be attributed to the higher dose of buprenorphine. Kaushal et al. compared buprenorphine with intrathecal nalbuphine as adjuvants in lower limb orthopedic procedures and discovered that neither group experienced adverse effects. Rabiee et al³⁰ described the benefits of using intrathecal buprenorphine in regards with hemodynamic status and adverse effects since there is a paucity in literature for the use of buprenorphine intrathecally when compared to intrathecal fentanyl. It is one of the study drugs since its use has been widely established in lower limb surgeries.

The limitations in our study includes

1. This was an Institutional and a single trial.
2. Larger sample size enhances statistical power and generalizability
3. Longer duration surgeries may require prolonged analgesia, affecting the choice of the adjuvant.
4. As an adjuvant in the intrathecal route, we have utilized lower doses of nalbuphine and buprenorphine, which differs from what is used in other institutions.
5. Lower or higher doses of adjuvants may alter sensory and motor block characteristics including postoperative analgesia.

6. Conclusion

Our study leads us to the conclusion that the beginning of the motor and sensory blockade, the intraoperative hemodynamic, and the side effects were statistically not significant. Intrathecal buprenorphine is a superior adjuvant to intrathecal nalbuphine in elective infraumbilical surgeries because it more strongly exhibited the duration of the sensory and motor block with effective postoperative analgesia.

7. Source of Funding

None.

8. Conflict of Interest

None.


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