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Original Article

Comparative study of intrathecal bupivacaine in combination with nalbuphine and bupivacaine for subarachnoid block in a tertiary care hospital

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Abstract

Introduction: Various adjuvant therapies have been developed to prolong intra and postoperative analgesia. A comparative study was conducted to evaluate the onset, maximum level, and duration of motor and sensory block, as well as the duration of analgesia, side effects like hypotension, bradycardia, sedation, and respiratory depression in patients undergoing elective lower segment caesarean section (LSCS).

Methods: The study included 60 patients, divided in to two groups to receive intrathecal hyperbaric bupivacaine (0.5%) in combination with nalbuphine (0.8 mg) (group A) and intrathecal hyperbaric bupivacaine alone (group B). Demographic data, onset of sensory and motor block, regression of motor block, duration of analgesia, hemodynamic changes, and side effects during the procedure were recorded.

Results: A statistically significant difference was observed in time of onset of sensory and motor block, and maximum percentage of sensory block was attained in group B (bupivacaine) with 90% of patients. Mean duration of sensory regression to S1 was attained at 120.16 minutes in group A (bupivacaine + nalbuphine). Mean duration of analgesia was attained at 203.33 minutes in group A, and haemodynamic parameters have remained below the baseline value in both the groups. Side effects during the surgery were statistically insignificant.

Conclusion: Intrathecal nalbuphine (0.8 mg) is an effective adjuvant to 0.5% hyperbaric bupivacaine in subarachnoid block for patients undergoing elective LSCS. It provides prolonged postoperative analgesia without much side effects and may be used as a better alternative over other opioids.

Introduction

Novel techniques in anesthesia treatment are evolving in medical world for betterment in pain management of patients. Central neuraxial blockade is one among the best modern regional anesthesia technique for lower parts of the body especially for spinal, epidural, and combined spinal-epidural (CSE). Compared to general anesthesia, regional anesthesia offers many advantages in reduced costs, decreased post-operative pain, lower incidence pf nausea and vomiting, and less thromboembolism incidents. [1] Additionally, spinal anesthetic lessens blood loss, blunts the surgical stress response, and lowers mortality and morbidity in high-risk procedures. However, this type of anesthesia has several drawbacks, such as a brief anesthetic effect duration and a 75–150 minute duration for spinal analgesia with bupivacaine heavy (H). [2]

Regional anesthetic solutions (hyperbaric) like dextrose-based formulas have shown promise in providing more effective and targeted results with smaller dosages. To extend the duration of anesthesia, various additives like opioids, neostigmine, and epinephrine along with bupivacaine are good supporting agents intrathecally for local anesthesia. In 1979, Wang et al have used intrathecal opioids first time to treat acute pain and later they were widely used for traumatic, chronic, obstetric, postoperative, and intraoperative cancer.[3]

To improve analgesia quality and to decrease postoperative analgesic requirements this method along with regional anesthesia is more advantageous over other methods.[4] This combination treatment of regional anesthesia and opioids allow early ambulation of patients, prolonged analgesia at two different sites in same time,

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lower dosage of drugs, and effective pain management. Local anesthesia will manifest on the spinal nerve axon, while opioids operate on the receptor location in the spinal cord.[5] Among the opioids used to hasten the onset and extend the duration of sensory and motor blockage are nalbuphine, buprenorphine, fentanyl, and morphine. Nalbuphine is a combination of μ antagonist and κ agonist receptors which stimulates κ receptors prepared synthetically to avoid adverse effects on patients. Nalbuphine hydrochloride does not contain any side effects as other opioids have, furthermore it contains slight respiratory depressant effect. As an additive, lower doses of nalbuphine will reach to ceiling level at nominal intrathecal dosage that is a safer margin for surgical treatments. In the present study, we compared the effect of nalbuphine hydrochloride as an adjuvant to hyperbaric bupivacaine in subarachnoid block with hyperbaric bupivacaine alone.

The main aim of this study is to evaluate the combination of nalbuphine and bupivacaine compared to intrathecal bupivacaine for subarachnoid block in elective lower segment caesarean section (LSCS). The objectives of the study include assessing onset, maximum level, and duration of motor and sensory block, as well as evaluating the duration of analgesia and any adverse effects, such as respiratory depression, bradycardia, hypotension, and respiratory depression.

Materials and Methods

A comparative study was conducted after obtaining ethical approval from the institutional ethical committee, on 60 patients undergoing elective LSCS surgeries at a tertiary care hospital. All the patients were randomly divided into two groups under ASA I/II involving 30 in each group and the study was conducted from January 2017 to December 2019. Group A received bupivacaine along with nalbuphine and group B received bupivacaine alone. Study inclusion criteria were ASA grade I and II, 20 to 40 years of age, patients who gave informed written consent, and patients who were scheduled to undergo elective LSCS surgeries. Exclusion criteria followed were ASA grade III or greater, age above 40 years and less than 18years, baseline heart rate less than 60 bpm, baseline blood pressure less than 100/60 mm Hg, and individuals with a history of severe renal or hepatic disease, ischemic heart disease, cardiac block, left ventricular failure, or hypertension.

Before surgery, each patient received a thorough examination, and the pre-operative assessment form was double checked. Every patient's height, weight, and body mass index were measured and documented. The patient's dietary state, airway assessment, and spine examination were assessed. Preoperative investigations like Complete blood picture (CBP), random blood sugar (RBS), blood grouping and typing, electrocardiography (ECG), chest X-ray (CXR), renal and liver function tests, Total Leukocyte Count (TLC), serum creatinine, HIV, hepatitis B surface antigen (HbsAg) and prothrombin time (PT), international normalized ratio (INR), Activated Partial Thromboplastin Time (APTT) depending on the history and medical condition of the patient were evaluated. The purpose of the study was described to each patient, and written informed consent was acquired. Every patient was pre-medicated with a tablet and fasted for six hours during the night. omeprazole 20mg and tab. metoclopramide 10mg orally. Standard monitors with noninvasive blood pressure, ECG, and pulse oximetry were connected when the patient arrived in the operating room, and baseline readings were taken. Patients were preloaded with an IV fluid of Ringer Lactate (RL) solution after an 18G cannula was used to establish an intravenous line. Using the slips-in-the-box technique, patients were randomly assigned to either group A or group B. The right lateral decubitus position was used for the patients. The median approach was used to perform a lumbar puncture using a 25G Quincke Babcock needle at the L3-L4 intervertebral area while adhering to stringent aseptic measures. The medicine was given at a rate of 0.2 mL/s once the free flow of clear cerebrospinal fluid (CSF) was verified. Nalbuphine 0.8 mg (0.5 mL) and 10 mg (2 mL) of 0.5% bupivacaine (H) were administered to group A (study group) for a total volume of 2.5 mL. Group B (control group) was given 2 mL of 0.5% bupivacaine (H) at a dose of 10 mg. A face mask was used to provide oxygen at a rate of 4 L/min. Up to 12 hours after surgery, hemodynamic measures such as pulse rate, non-invasive blood pressure, and peripheral arterial oxygen saturation were monitored at regular intervals.

Systolic blood pressure below 90 mm Hg or less than 20% of baseline is known as hypotension. IV fluid and injectable mephentermine 6 mg boluses were administered if the hypotension persisted. Bradycardia is defined as a heart rate below 50 beats per minute. Atropine 0.6 mg was administered as treatment. The sensory block was evaluated every minute until it reached the T6 dermatome, the sensory block was evaluated using the pinprick technique in the midclavicular line with a 27G needle. The level was then assessed every two minutes until the maximum sensory block was achieved. This protocol procedure was submitted and approved by institutional review committee.

Sensory block was graded as Grade 0, 1 and 2 based on a Sharp, dull and nil sensation respectively on pin prick. Onset of sensory blockade was defined as the time interval between the end of anesthetic injection to loss of sensation to pinprick at T10 level. The modified Bromage scale was used to evaluate the quality of the motor block. GRADE 0: the leg can be raised at the hip with no motor blockage. In grade 1, the ankle and knee can be flexed, but the leg cannot be raised at the hip (hip blocked); in grade 2, the foot can be moved only (hip and knee blocked); and in grade 3, the foot cannot be moved at all (hip, knee,

and ankle blocked). The period between finishing the study medication injection and Bromage 3 registration was considered the onset of total motor blockage. Once full anesthesia was achieved, surgery began. Following surgery, the patient's motor and sensory levels were recorded. Regression time to level L1 and regression time from the maximal level were also recorded in two segments.

Statistical methods

Mean ± SD (Min-Max) is used to display results for continuous measures, while Number (%) is used to display findings for categorical measurements. Five percent is considered significant. The following data-related assumptions are made: Samples taken from the population should be random, the dependent variables should be regularly distributed, and the sample cases should be independent. The significance of research parameters on a continuous scale between two groups (intergroup analysis) on metric parameters has been determined using the two-tailed, independent student *t* test. The significance of study parameters on a categorical scale between two or more groups has been determined using the chi-square/Fisher exact test. The *P* value was determined as follows: $P > 0.05$ was not significant, $P < 0.05$ was significant, and $P < 0.001$ was highly significant.

Results

Demographic data with respect to age, weight, ASA physical status was tabulated in Table 1. Age, ASA grading of the patients was comparable and it is statistically insignificant whereas the weights of the patients were significant.

The mean time of onset of sensory blockade in group A (bupivacaine + nalbuphine) is 3.86 minutes, and in group B (bupivacaine) is 5.03 minutes (Table 2). There is an observed statistically significant difference between group A and group B ($P < 0.005$).

In Table 3, 10 patients of group A and 10 patients of group B had T4 level of sensory blockade. 20 patients of group A and 20 patients of group B has T6 level of sensory blockade. There is no statistically significant difference between two groups.

Group A (bupivacaine + nalbuphine) experienced sensory regression to S1 on average for 3.86 minutes, while group B (bupivacaine) experienced it on average for 5.03 minutes. Table 4 shows that there is a highly statistically significant difference between the two groups ($P < 0.0001$).

In group A (bupivacaine + nalbuphine), the average time for the onset of motor blockade was 5.8 minutes, while in group B (bupivacaine), it was 7.1 minutes. The two groups differ statistically significantly ($P < 0.0015$ in Table 5). Every group has comparable motor blockage quality (Bromage grade 3).

According to the results in Table 6, the average length of motor blockade was 159.8 minutes for group A (bupivacaine + nalbuphine) and 137.23 minutes for group B (bupivacaine). The difference between the two groups is statistically significant ($P = 0.0001$).

In group A (bupivacaine + nalbuphine), the average duration of analgesia is 203.33 minutes, while in group

Table 1. Patient demographic data

Demographics	Group A (Mean ± SD)	Group B (Mean ± SD)	*P* value
Age (y)	27.6 ± 2.0	28.7 ± 2.0	0.45
Weight (kg)	63.7 ± 2.5	69.5 ± 2.5	0.001
ASA grade (I/II)	23/7	17/13	0.17

ASA, American Society of Anesthesiologists; SD, Standard Deviation

Table 2. Time of onset of sensory block (min)

Groups	Mean	SD
Group A	3.86	1.13
Group B	5.03	1.9
t-value	2.8	
P value	0.005	

Table 3. Maximum level of sensory block attained.

Time points	Group A (n = 30)		Group B (n = 30)	
	Number of Patients	Percent	Number of Patients	Percent
T4	20	66.6	3	10
T6	10	33.3	27	90

Table 4. Duration of sensory block

Groups	Duration (min)	
	Mean	SD
Group A	3.86	1.13
Group B	5.03	1.9
t-value	13.23	
P value	0.0001	

Table 5. Time of onset of motor block

Groups	Duration (min)	
	Mean	SD
Group A	5.8	1.21
Group B	7.1	1.76
t-value	3.33	
P value	0.001	

Table 6. Duration of motor block

Groups	Duration (min)	
	Mean	SD
Group A	159.8	5.75
Group B	137.23	9.32
t-value	11.28	
P value	0.0001	

B (bupivacaine), it is 120.4 minutes. The two groups' differences are statistically significant ($P=0.0001$) (Table 7).

Both groups' pulse rates stayed below the baseline value for the duration of the trial. Throughout the study period, there were no discernible differences between the two groups at any point ($P>0.05$) (Table 8).

Both groups' diastolic and systolic blood pressures stayed below the baseline during the research (Table 9). Throughout the study period, there were no discernible differences between the two groups at any point ($P>0.05$).

According to the data in Table 10, there was no statistically significant difference in the side effects reported by the two groups. Therefore, intrathecal administration of nalbuphine is safe.

Discussion

Extensive research is going on to improve the quality of spinal anesthesia in addition to various adjuvant combinations. A study by Yaksh and Rudy in 1976 was a pioneering work in administration of opioids and from there growth was logarithmic.[5] However, opioid-associated side effects were widely increased, leading to the development of numerous adjuvants for spinal anesthesia. Over the past two decades usage of 0.5% Hyperbaric bupivacaine became commonly used drug for spinal and epidural anesthesia. By adding adjuvant drugs, 0.5% Hyperbaric bupivacaine prolongs the anesthetic effects and produces antinociceptive effect. When intrathecal opioids are used as adjuvants, sensory blockade, motor blockade, and extended postoperative analgesia are all initiated early. Nalbuphine is a partial agonist-antagonist opioid with antagonism at μ-receptor and agonism at κ-receptor which activates spinal and supraspinal κ-receptors to produce analgesic effect without any unwanted side effects of μ-agonist. The antagonistic potency of nalbuphine hydrochloride was ten times of pentazocine and just one-fourth of nalorphine. There is an abundant supportive literature available on nalbuphine as a useful analgesia in humans when given as a sole opioid or in combination with μ-agonist.[6]

The results of the current trial, which combined 0.8 mg of nalbuphine with hyperbaric bupivacaine, indicated an extended duration of analgesia and an earlier onset of sensory and motor blockage.

Demographic factors such as age, weight, and ASA grading showed similar outcomes in the study and control groups. Patients in the bupivacaine + nalbuphine group (A) were 27.6 ± 2.0 years old on average. Patients in the bupivacaine group (B) had an average age of 28.7 ± 2.0 years. Patients in the bupivacaine + nalbuphine group (A) weighed an average of 63.7 ± 2.5 kg. Patients in the bupivacaine group (B) weighed 69.5 ± 2.5 kg on average. Patients in the bupivacaine + nalbuphine group (A) received an ASA grading of 23/7, whereas those in the bupivacaine group (B) received an ASA grading of 17/13. Levene's test for equality of variances and independent sample testing were used to compare the variables, and the *P* value was determined to be non-significant.

At the end of one hour, the mean pulse rate of the patients in the bupivacaine + nalbuphine group (A) was

Table 7. Duration of Analgesia

Groups	Duration (min)	
	Mean	SD
Group A	203.33	16.06
Group B	120.4	16.37
t-value	19.8	
P value	0.0001	

Table 8. Mean pulse rate

Time interval	Group A	Group B	*P* value
Preoperative	79.43 ± 13.64	84.52 ± 11.61	0.125
2 min	73.96 ± 16.24	80.93 ± 12.30	0.066
10 min	71.6 ± 14.48	78.1 ± 12.46	0.0674
30 min	69.33 ± 10.21	74.4 ± 10.28	0.0602
1 h	69 ± 12.2	73.93 ± 10.11	0.0937
2 h	69.63 ± 10.09	74.4 ± 10.78	0.082

Table 10. Side effects during the procedure

Type of effect	Group A		Group B	
	No. of Patients	%	No. of Patients	%
Nil	18	60	20	66.6
Hypotension (H)	6	20	6	20
Nausea (N)	0	0	2	6.6
Shivering (S)	6	20	2	6.6
P value	4.11			

Table 9. Mean systolic blood pressure and diastolic blood pressure

Time interval	Group A (SBP)	Group B (SBP)	*P* value	Group A (DBP)	Group B (SBP)	*P* value
Preoperative	130.4 ± 10.45	131.9 ± 9.9	0.57	85.7 ± 5.33	85.6 ± 5.22	0.714
2 min	126.47 ± 9.71	129.07 ± 10.97	0.337	83.76 ± 6.19	84.16 ± 5.57	0.793
10 min	118.1 ± 13.1	123.47 ± 15.9	0.158	75.5 ± 11.31	79.7 ± 8.85	0.114
30 min	115.47 ± 14.1	119.07 ± 12.37	0.297	74.23 ± 10.97	77.3 ± 6.09	0.185
1 h	112.3 ± 14.06	118.57 ± 11.67	0.065	74.7 ± 10.09	73.9 ± 6.75	0.719
2 h	115.8 ± 13.51	120.67 ± 10	0.118	74.8 ± 8.8	76.33 ± 6.55	0.448

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

67.36 ± 12.09 bpm, while the bupivacaine group (B) had a mean pulse rate of 73.96 ± 10.17 bpm. At the end of one hour, the patients in the bupivacaine + nalbuphine group (A) had systolic and diastolic blood pressures of 112.3 ± 14.06 mm Hg and 74.7 ± 10.09 mm Hg, respectively, while those in the bupivacaine group (B) had systolic and diastolic blood pressures of 118.57 ± 11.63 mmHg and 73.9 ± 6.5 mm Hg (data not provided in the results section for pulse and systolic and diastolic blood pressure). The mean blood pressure and mean pulse rate were statistically analyzed, and the study's *P* value was found to be statistically insignificant. Following subarachnoid block, the sensory and motor blocks were assessed using a modified Bromage scale and a pinprick, respectively. In the bupivacaine + nalbuphine group (A), the mean start time of sensory block (T10) was 3.86 ± 1.13 minutes, while in the bupivacaine group (B), it was 5.03 ± 1.90 minutes. The bupivacaine + nalbuphine group (A) experienced a mean onset time of 5.8 ± 1.21 minutes for motor block, while the bupivacaine group (B) experienced a mean onset time of 7.1 ± 1.76 minutes. The bupivacaine + nalbuphine group (A) had a substantially faster onset time for sensory and motor block, with a *P* value of less than 0.05, according to statistical analysis using the independent sample test and the t test for equality of means. Compared to the bupivacaine (B) group, a greater proportion of patients in the bupivacaine + nalbuphine group (A) attained a higher sensory level (T4). The bupivacaine + nalbuphine group (A) experienced sensory blockade for an average of 120.16 ± 6.02 minutes, while the bupivacaine group (B) experienced it for 90.16 ± 10.86 minutes. The bupivacaine + nalbuphine group (A) experienced motor blockade for an average of 159.8 ± 5.75 minutes, while the bupivacaine group (B) experienced it for 137.23 ± 9.32 minutes. After statistical analysis, a significant *P* value (< 0.05) was determined.

The mean duration of analgesia in the bupivacaine + nalbuphine group (A) was found to be 203 ± 16.06 minutes and in the bupivacaine group (B) it was found to be 120.4 ± 16.37 minutes. A statistical study of the two groups showed a significant *P* value (< 0.05).

In 2018 Bindra et al, performed randomized comparative study on postoperative analgesia with intrathecal nalbuphine versus intrathecal fentanyl in cesarean section and concluded that both intrathecal nalbuphine 0.8 mg and intrathecal fentanyl 20 μg are effective adjuvants to 0.5% hyperbaric bupivacaine.[7] They increase the duration of sensory block as well as post-operative analgesia without any side effects. Intrathecal nalbuphine prolongs post-operative analgesia and may be used as an alternative to intrathecal fentanyl during surgeries.

In 2018 Ahmed et al,[8] performed a randomized double-blind study comparing intrathecal nalbuphine versus fentanyl as an adjuvant to bupivacaine in spinal anesthesia for elective cesarean section and concluded that fentanyl was superior to nalbuphine in enhancing the onset of both sensory and motor block. Nalbuphine is superior to fentanyl in increasing duration of postoperative complete and effective analgesia and decreasing incidences of pruritis and shivering and both drugs have similar effects on neonatal APGAR score and neurological, adaptive capacity score.

In 2014 Gomaa et al,[9] compared post-operative analgesia after intrathecal nalbuphine with bupivacaine and intrathecal fentanyl with bupivacaine after cesarean section and concluded that either intrathecal nalbuphine (0.8 mg) combined with (10 mg) bupivacaine or intrathecal fentanyl (25 μg) combined with (10 mg) bupivacaine improves intra-operative analgesia and prolonged early post-operative analgesia in cesarean section.

In 2019 Sharma et al,[10] performed randomized comparative study to assess the effect of intrathecal nalbuphine versus intrathecal fentanyl as adjuvant to bupivacaine for lower limb orthopaedic surgery and concluded that nalbuphine (1 mg) as intrathecal adjuvants to 0.5% hyperbaric bupivacaine increases the duration of sensory block, motor block and the effective analgesia time more efficiently than fentanyl in patients scheduled for elective lower limb orthopedic surgery under subarachnoid block.

When comparing intrathecal nalbuphine and clonidine as adjuvants to hyperbaric bupivacaine in infraumbilical surgeries, Kumar et al[11] in 2018 came to the conclusion that bupivacaine gave sufficient subarachnoid block for infraumbilical procedures when paired with either nalbuphine or clonidine. In terms of (i) a longer period of sensory blocking and postoperative analgesia (ii) fewer doses of rescue analgesia needed, the nalbuphine group outperformed the clonidine group in providing appropriate surgical anesthetic with hemodynamic stability. Except for pruritus, which was observed in the nalbuphine group, the adverse effects of bradycardia, hypotension, and nausea/vomiting were similar in the two groups.

The effectiveness of intrathecal nalbuphine at varying doses as an adjuvant to L-bupivacaine in subarachnoid block was compared by Das et al[12] in 2017. They found that intrathecal nalbuphine (0.75 mg and 1 mg) was linked to a longer duration of motor and sensory block than 0.5 mg nalbuphine and L-bupivacaine alone.

In 2016 Gupta et al,[13] compared intrathecal nalbuphine with intrathecal fentanyl as adjuvant to 0.5% hyperbaric bupivacaine for orthopedic surgery of lower limbs under subarachnoid block and conclude that nalbuphine (2 mg) as intrathecal adjuvant to 0.5% hyperbaric bupivacaine (17.5 mg) for subarachnoid blockade was clinically more efficient than fentanyl for extending the duration of sensory motor block and enhancing the postoperative analgesia following orthopedic surgery of lower limb, with negligible adverse effects.

An investigation into the optimal dosage of intrathecal nalbuphine as an adjuvant to subarachnoid block was

Study Highlights

What is current knowledge?

- Intrathecal nalbuphine prolongs the duration of postoperative analgesia when used as an adjunct 0.8 mg is the most effective dose that prolongs early postoperative analgesia without increasing the risk of side-effects.

What is new here?

- Nalbuphine is an useful adjuvant in SAB and lower doses prolongs postoperative analgesia without increased side-effects.

conducted in 2011 by Mukherjee et al.[14] For patients undergoing lower limb orthopedic procedures, they advise using 0.4 mg of nalbuphine intrathecally in conjunction with 12.5 mg of 0.5% hyperbaric bupivacaine for subarachnoid block (SAB). Though his study recommended 0.4 mg as the optimal dose, our study with 0.8mg provided excellent analgesia.

In 2013, Verma et al,[15] compared post-operative analgesic efficacy of intrathecal tramadol versus nalbuphine (2 mg) added to bupivacaine in spinal anesthesia for lower limb orthopedic surgery.

Conclusion

From the present study, we could conclude that comparison of intrathecal bupivacaine + nalbuphine (0.8 mg) with bupivacaine alone in the patients undergoing elective LSCS surgery decreased onset time for sensory and motor blockade, produced higher level of sensory blockade, prolonged sensory and motor blockade, and prolonged duration of analgesia. Further evaluation is needed to provide assured usage of combinatorial treatment with more research and increased number of patients on intrathecal nalbuphine.

Authors' Contribution

Data curation: Nallolla Rahul Dev, Sunil Kumar Cherukuri.
Formal analysis: Nallolla Rahul Dev.
Investigation: Lavanya Bachula, P.V. Shiva.
Methodology: Nallolla Rahul Dev, Lavanya Bachula.
Project Administration: P.V. Shiva, Sunil Kumar Cherukuri.
Resources: Nallolla Rahul Dev.
Supervision: P.V. Shiva.
Validation: P.V. Shiva,Lavanya Bachula.

Competing Interests

There are no conflicts of interest.

Ethical Approval

The current study was approved by research ethics committee of Osmania medical college (ECR/300/Inst/AP/2013/RR-16).

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