Comparison of Three Different Doses of Nalbuphine as Adjuvant to Intrathecal Hyperbaric Bupivacaine in Knee Joint Surgeries

Amit Pradhan[1], Ranjitha Kusumanchi[2], Pulak Priyadarshi Padhi [3], Saswati Das[4]

[1, 2, 3, 4] Department of Anaesthesia, Kalinga Institute of Medical Sciences (KIMS) Bhubaneswar, Odisha, India.

ABSTRACT

BACKGROUND

Postoperative pain is the most challenging task in patients undergoing knee joint surgeries under spinal anaesthesia. Spinal anaesthesia with bupivacaine provides adequate intraoperative conditions but falls short in providing prolonged postoperative pain relief. Intrathecal opioids are synergistic with local anaesthetics and intensify the sensory block without affecting the sympathetic block. This study intends to compare three different doses of intrathecal nalbuphine as an adjuvant to 0.5 % hyperbaric bupivacaine and determine the optimal dose in knee joint surgeries.

METHODS

A double-blind comparative study was conducted in one hundred and twenty American Society of Anaesthesiologists (ASA) I and II patients undergoing knee joint surgeries in a randomised prospective way. The patients were randomly allocated to A, B, and C groups who received 0.4, 0.8 and 1.2 mg nalbuphine respectively added to 12.5 mg of 0.5 % hyperbaric bupivacaine. The onset, duration of block, duration of effective analgesia, Visual Analogue Scale (VAS) score, and the incidence of adverse effects were studied and compared between the groups.

RESULTS

The mean onset time of sensory and motor block of group B and C was significantly faster as compared to the onset in group A. The duration of sensory, motor blockade and duration of analgesia were highest with 1.2 mg of nalbuphine followed by 0.8 and 0.4 mg ($P < 0.05$). VAS readings were comparable in all the groups. Hemodynamic variability among the three groups was comparable. Incidence of adverse effects was highest in group C when compared with others, although it was statistically insignificant ($P > 0.05$).

CONCLUSIONS

Nalbuphine in a dose of 0.8 mg when added to 0.5 % hyperbaric bupivacaine for subarachnoid block in patients undergoing knee joint surgeries provides excellent analgesia, prolonged duration of sensory block and motor block, with minimal adverse effects.

KEYWORDS

Local Anaesthesia, Opioid, Postoperative Pain, Orthopaedic Surgeries

Corresponding Author:
Dr. Saswati Das,
Department of Anaesthesia,
Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, Odisha, India.
E-mail: saswati.das@kims.ac.in

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BACKGROUND

Analgesia in the post-operative period is one of the most tasking aspects of patients undergoing surgery under spinal anaesthesia. Spinal anaesthesia is a commonly used technique for lower limb surgeries as it is very economical, easy to administer with rapid onset of anaesthesia and good muscle relaxation.[1] Postoperative pain control is a major concern because spinal anaesthesia using only local anaesthetics is associated with relatively shorter duration of action and thus an early analgesic intervention is needed in postoperative period. Intrathecal opioids have proven their usefulness over the years and have become a widely accepted technique for effective postoperative pain relief.[2,3] nalbuphine is a semi-synthetic opioid with mixed κ agonist and μ antagonist properties.[4] Partial agonist-antagonist opioids have a ceiling effect to respiratory depression making them a safe alternative to other opioids.[5,6] nalbuphine when added as an adjuvant to intrathecal bupivacaine has the potential to prolong the duration of postoperative analgesia by acting at two different sites of the pain pathway.[7] Earlier studies have been done using control group and different doses of nalbuphine.[8-11] The efficacy of nalbuphine as an adjuvant to intrathecal bupivacaine has been proven beyond doubt, hence we did not take any control group for our study. To our knowledge no studies have been done using nalbuphine in doses of 0.4 mg, 0.8 mg and 1.2 mg as an adjuvant with intrathecal bupivacaine.

This study intends to compare three different doses of intrathecal nalbuphine as an adjuvant to 0.5 % hyperbaric bupivacaine and determine the optimal dose in knee joint surgeries.

METHODS

This double-blind comparative study was conducted in Kalinga Institute of Medical Sciences from September 2019 to August 2020. After institutional ethics committee approval (KIMS / KIIT / IEC / 151 / 2018), 120 patients of ASA physical status I and II, aged 18 - 60 years, posted for elective knee joint surgeries were included in the study. Written informed consent was obtained from all patients before enrolment. The study was registered with CTRI / 2019 / 08 / 020916. In this double-blind comparative study patients were randomly allocated to three groups by computer-generated tables (N = 40). The study participants received nalbuphine 0.4 mg (Group A), nalbuphine 0.8 mg (Group B) and nalbuphine 1.2 mg (Group C) made up to 0.5 ml volume with normal saline added to 2.5 ml (12.5 mg) of 0.5 % hyperbaric bupivacaine (total volume 3 ml). Patients belonging to ASA physical status III & IV, pregnant patients, BMI ≥ 30, height less than 155 cm, taking hypnotics, anti-psychotics, tranquilizers or other CNS depressants with contraindications to spinal anaesthesia and history of adverse reactions to opioids were excluded from the study.

The study drug was prepared according to the randomisation list by a resident doctor and administered intrathecally to the patient but did not further participate in the observation or collection of data. Both the patient and the anaesthesiologist were unaware to the patient's group assignment and all observations were recorded by an anaesthesiologist blinded to the randomisation schedule, making it a double-blind study.

Detailed pre-anaesthetic examination was done a day before the surgery and the patients were asked to be kept nil per orally for at least 6 hrs. before the surgery. Preoperative vital parameters were noted. After securing intravenous (18G) access and attaching routine monitors, preloading with Ringer's lactate or normal saline solution with 10 ml / kg over 10 min was done. Under all aseptic precautions, subarachnoid space was located and confirmed with free flow of cerebrospinal fluid. The block was performed with 3 mL of the study drug injected in L3 / 4 or L2 / 3 inter-vertebral space, using a 25-G Quincke spinal needle, in the sitting position slowly at the rate of 0.25 ml / sec with the bevel end cephalad as per our institutional protocol. Then, the patients were allowed to lie down in the supine position for surgery. Equipment and drugs for resuscitation, airway management and ventilation were kept ready, in anticipation of any untoward events.

Sensory blockade was assessed by loss of pinprick sensation to 23G hypodermic needle and cold sensation (cotton swab soaked in spirit) in the mid-axillary line. Time taken for sensory blockade to reach T10 (defined as the time taken for completion of the injection of study drug till the patient does not feel the pin prick at T10 level) was noted.[12] Sensory blockade was checked every 2 min until the highest level was achieved. Time taken for highest sensory blockade (defined as the time taken from the completion of the injection of the study drug to the highest level of sensory blockade attained) was noted. On reaching the T10 level, surgery could start. Duration of sensory blockade (the time of injection of the study drug till the patient feels the sensation at S2 dermatome) was recorded.

The motor block was assessed immediately after sensory block assessment, using a modified Bromage scale.[13] Time taken for maximum motor blockade (time taken from the completion of the injection of the study drug to the maximum motor blockade attained), duration of motor blockade (time required for regression from grade 3 to grade 0 of modified Bromage scale) and duration of effective analgesia (time taken from achievement of highest sensory blockade to requirement of first rescue dose of analgesia) were noted.[14]

The sensory and motor status were checked every 2 minutes after the spinal injection for the first 10 minutes, every 5 minutes for the next 10 minutes, and thereafter every 15 minutes until the regression of sensory level to S2 dermatome and motor block to modified Bromage grade 0. Hemodynamic variables were recorded every 5 minutes intra-operatively and every 15 minutes in post anaesthetic care unit (PACU) after completion of surgery. Continuous monitoring and recording at regular intervals were done until the complete return of sensory and motor function. Postoperatively, the pain score was recorded by using a visual analog pain scale between 0 and 10 (0 = no pain, 10 = most severe pain). Injection paracetamol 15 mg / kg was given as rescue analgesia when VAS was ≥ 3. Adverse

effects like nausea, vomiting, hypotension, bradycardia, pruritus and respiratory depression were recorded and treated according to institutional protocol.

Statistical Analysis

The data on categorical variables were presented as frequency and percentage and the data on continuous variables were presented as mean ± standard deviation (SD) among three study groups. The inter-group statistical comparison of continuous variables was done using analysis of variance (ANOVA) with Tukey's HSD and categorical variables were tested using the chi-square test or Fischer-exact test for multiple group comparisons. The underlying normality assumption was tested before subjecting each variable to ANOVA. The results were shown in tabular as well as graphical format to visualise the statistically significant difference more clearly. In the entire study, the P-value < 0.05 were considered to be statistically significant and were statistically analysed using Statistical Package for Social Sciences (SPSS) version 22.

RESULTS

The effects of intrathecal 0.5 % hyperbaric bupivacaine with nalbuphine hydrochloride at three different doses (0.4, 0.8, and 1.2 mg) was studied and compared with 0.5 % hyperbaric bupivacaine alone in 120 patients belonging to ASA grade I and II who underwent knee joint surgeries. The three groups of patients A, B and C included in the study did not differ significantly with respect to age, sex, body weight, height, ASA-PS status, type of surgery as shown in [Table – 1, 2].

Variables	Group A	Group B	Group C	P-Value
Age (yrs.)	43.50 ± 14.38	40.03 ± 16.23	39.35 ± 15.20	0.43
Sex (M:F)	25 : 15	26 : 14	26 : 14	0.56
Height (cm)	163.05 ± 5.82	163.33 ± 5.99	163.48 ± 4.77	0.94
Weight (kg)	67.38 ± 7.81	70.63 ± 6.04	67.88 ± 8.88	0.57
ASA (I:II)	26 : 14	27 : 13	27 : 13	0.98

Table 1. Demographic Data

Type of Surgery	Group A (N = 40)	Group B (N = 40)	Group C (N = 40)
Total knee replacement	14 (35 %)	6 (15 %)	10 (25 %)
Arthroscopic ACL reconstruction and repair	16 (40 %)	18 (45 %)	18 (45 %)
Patella TBW	5 (12.5 %)	6 (15 %)	5 (12.5 %)
Arthroscopic meniscal repair	5 (12.5 %)	10 (25 %)	7 (17.5 %)

Table 2. Type of Surgery

Spinal Block Characteristics	A	B	C	P-Value
Time taken for sensory blockade to reach T10 segment level (min)	4.45 ± 2.08	3.75 ± 1.44	3.25 ± 0.80	0.002*
Time taken to reach highest sensory level (min)	6.8 ± 2.51	6.825 ± 1.61	6.875 ± 1.86	0.982
Time taken to reach maximum motor blockade (min)	5.375 ± 1.25	4.45 ± 2.0	3.72 ± 1.86	0.002*
Time taken for sensory block regression to S2 dermatome (min)	252.75 ± 27.57	290.12 ± 45.87	328.87 ± 41.47	0.006*
Time taken for motor block regression to modified Bromage 0 (min)	175.225 ± 24.32	211.375 ± 33.55	242.25 ± 33.51	0.000*
Time taken to first rescue dose of analgesia (min)	223.62 ± 25.67	300.65 ± 45.53	342.65 ± 33.09	0.000*

Table 3. Spinal Block Characteristics

*indicates statistically significant difference

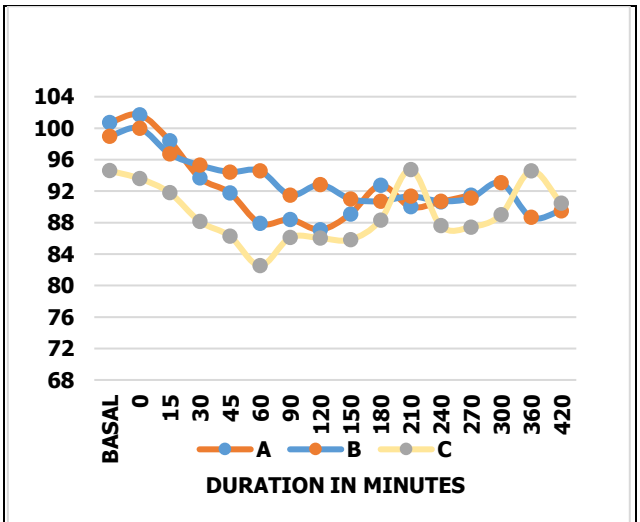
Following are the observation comparing the effect of spinal block with three different doses of nalbuphine as an adjuvant [Table 3].

Spinal Block Characteristics	Intergroup Comparisons Group A vs. Group B	Group B vs. Group C	Group C vs. Group A
Time taken for sensory blockade to reach T10 segment level	0.108	0.317	0.002***
Time taken to reach highest sensory level	0.998	0.993	0.985
Time taken to reach maximum motor blockade	0.050	0.155	0.000***
Time taken for sensory block regression to S2 dermatome	0.000***	0.000***	0.000***
Time taken for motor block regression to modified Bromage 0	0.000***	0.000***	0.000***
Time taken to first rescue dose of analgesia	0.000***	0.000***	0.000***

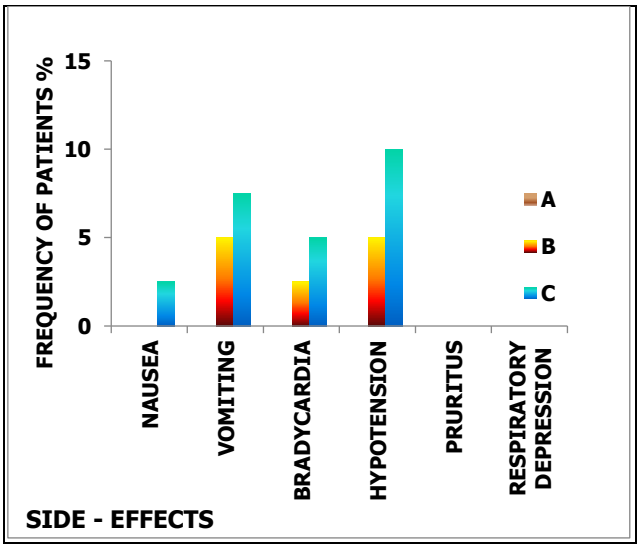
Table 4. Intergroup Comparison of Spinal Block Characteristics

P-Value < 0.05 was considered to be statistically significant. ***P-value < 0.001

All the three groups did not vary significantly in terms of haemodynamic parameters. The following figure shows distribution of mean arterial pressure among three groups [Graph 1].



Graph 1. Distribution of Mean Arterial Pressure



Graph 2. Frequency of Adverse Effects in Each Group (P > 0.05)

There was no statistically significant difference in the incidence of adverse effects among the three groups although group C had more incidences of nausea, vomiting, hypotension and bradycardia than others [Graph 2].

DISCUSSION

Regional anaesthesia offers many advantages over general anaesthesia including better attenuation of stress response to surgery with good postoperative analgesia. Spinal opioids can provide profound analgesia with fewer central and systemic adverse effects than with opioids administered systematically.[3]

Nalbuphine is a mixed agonist–antagonist opioid. The agonistic quality at the kappa receptors supports it to provide good intraoperative and postoperative analgesia. The antagonistic activity at the mu receptors, exert their effects by exhibiting less mu-mediated side effects.[15,16] The synergistic action between bupivacaine and nalbuphine in our study was characterised by enhanced somatic analgesia without an effect on the degree of the amide local anaesthetic induced sympathetic or motor blockade.[14] There have been a few studies that supported the utility of intrathecally administered nalbuphine in managing postoperative pain with minimal pruritis and respiratory depression and better haemodynamic stability.[17-20]

In our study, the onset of sensory block was 4.45 ± 2.08, 3.75 ± 1.44, and 3.25 ± 0.80 mins and motor block was 5.375 ± 1.25, 4.45 ± 2.0, and 3.72 ± 1.86 mins in group A, B, and C respectively. The onset time of both sensory and motor blocks reduced incrementally in groups A, B and C with 0.8 mg and 1.2 mg having fastest onset time but was not statistically significant. (P > 0.05). However, intergroup comparison between groups A and C show a statistical significance. Mukherjee et al. compared 100 patients undergoing orthopaedic lower limb surgeries under spinal anaesthesia. They used nalbuphine 0.2 mg, 0.4 mg and 0.8 mg added to 0.5 % hyperbaric bupivacaine and reported 0.8 mg having faster onset time compared to 0.2 mg and 0.4 mg but was not statistically significant.[21] S Kumaresan et al. had compared 120 patients undergoing lower limb orthopaedic surgery using nalbuphine 0.4 mg, 0.6 mg, 0.8 mg added to 0.5 % hyperbaric bupivacaine and found that there was no statistical significance in the onset of sensory and motor blockade among the groups.[22] Tridipjyoti et al. compared 120 patients undergoing lower limb orthopaedic surgery using nalbuphine 0.4 mg, 0.8 mg, and 1.6 mg added to 0.75 % isobaric ropivacaine and found that there was no statistical significance in the onset of sensory and motor blockade.[23]

The mean duration for sensory regression to S2 was 252.75 ± 27.57, 290.12 ± 45.87, and 328.87 ± 41.47 mins in group A, B, and C respectively. The mean duration for sensory regression to S2 dermatome was incrementally higher and was significantly prolonged among the groups (P < 0.05). We have taken the time to S2 regression for calculation of sensory blockade however, other studies had taken time to two-segment regression. Mukherjee et al. noted a mean duration of two-segment regression as 134 ± 6.95, 141.5 ± 5.83, and 153.3 ± 6.05 mins (P-value < 0.05).[21] S Kumaresan et al. recorded a mean duration of two-segment regression as 152.4 ± 5.83, 180.2 ± 6.02 and 190.4 ± 6.78 mins (P-value < 0.05).[22] Tridipjyoti et al. used Nalbuphine 0.4 mg, 0.8 mg, 1.6 mg, and recorded a mean duration of two-segment regression as 152.6 ± 18.65, 155 ± 19.09, and 156.2 ± 18.38 mins respectively which was significantly prolonged (P-value < 0.05).[23]

The time taken for regression of motor blockade to modified Bromage 0 was 175.225 ± 24.32, 211.375 ± 33.55, and 242.25 ± 33.51 mins in group A, B, and C respectively which was significantly prolonged with incremental doses (P < 0.05), which was also reported by previous studies.[21, 20]

The mean duration of effective analgesia was 223.62 ± 25.67, 300.65 ± 45.53 and 342.65 ± 33.09 mins in group A, B and C respectively which was significantly prolonged (P < 0.0.5). Our study results are in accordance with previous studies like Culebras et al.[14] Tridipjyoti et al.[23] who concluded that duration of effective analgesia prolonged significantly with incremental doses of Nalbuphine. Culebras et al.[14] stated that analgesic ceiling effect was seen at doses higher than 1.6 mg of nalbuphine when used as an adjuvant. So, we have not compared doses more than 1.2 mg.

The post-operative pain score was assessed by Visual Analogue Scale. When the VAS score was ≥ 3, rescue analgesia was given. The patients required rescue analgesia at 240 min, 300 min and 330 min in group A, B and C respectively. Our results are in accordance with Tiwari et al. Mostaffa et al. who reported that nalbuphine prolonged duration of analgesia with reduced VAS pain score.[24,25]

Nausea was noted in 1 (2.5 %) patient of group C, vomiting in 2 (5.0 %) patients of group B and 3 (7.5 %) patients of group C. Bradycardia was seen in 1 (2.5 %) patient of group B and 2 (5.0 %) patients of group C. Hypotension was recorded in 2 (5.0 %) patients of group B, 4 (10 %) patients of group C respectively. Other effects like pruritus and respiratory depression were not noted in any of the groups. There was no statistical significance in the incidence of side effects among the groups (P-value > 0.05). Our results correlate with previous studies like Culebras et al. Tridipjyoti et al. who recorded higher incidence of side effects with increasing doses of nalbuphine but were not statistically significant.[14,23]

In the present study the efficacy of intrathecal nalbuphine in different doses were compared and we noted that nalbuphine in a dose of 0.8 mg was better than 0.4 mg with regard to the duration of both sensory and motor blockade as well as the duration of analgesia. Nalbuphine when given in a dose of 1.2 mg had a greater incidence of nausea, vomiting, bradycardia, and hypotension though it provided a longer duration of analgesia. Hence, nalbuphine in a dose of 0.8 mg is the optimum dose as it provides excellent operative conditions, prolonged postoperative analgesia, stable haemodynamics with minimal side-effects.

CONCLUSIONS

Nalbuphine when added as an adjuvant to intrathecal bupivacaine has the potential to prolong the duration of

postoperative analgesia. Our study was aimed to find out the optimum dose of nalbuphine as adjuvant in a subarachnoid block. We conclude that nalbuphine 0.8 mg added to 0.5 % hyperbaric bupivacaine for a subarachnoid block in patients undergoing knee joint surgeries provides excellent analgesia, prolonged duration of sensory block and motor block, with minimal adverse effects.

Limitations

1. Our study might not be applicable to ASA III and IV patients.
2. Measuring nalbuphine with 1 ml syringe should be meticulous as a slight error would alter the dosage.
3. We have studied only three of many plausible doses of intrathecal nalbuphine.
4. We have not studied the sedative effect of nalbuphine.
5. We could have been more specific regarding our choice of patients by choosing anyone specific surgery involving knee joint instead of choosing all surgeries of knee joint.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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