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A prospective randomised comparative study of intrathecal nalbuphine versus intrathecal fentanyl as adjuvant to 0.5% hyperbaric bupivacaine for arthroscopic knee surgeries under subarachnoid block

[1]Dr. M Sreya Santhoshi and [2]Dr. Vishwa Saineer

[1,2]Assistant professor, Department of Anaesthesia, Gandhi Medical College, Secunderabad, Telangana, India

Corresponding Author:
Dr. M Sreya Santhoshi

Abstract

Background: Subarachnoid (spinal) block is a safe and effective alternative to general anesthesia for arthroscopic knee surgeries. Hyperbaric bupivacaine, the local anaesthetic most commonly used, don't have the advantage of prolonged analgesia. Due to the early arising post-operative pain the role of various adjuvants has been proposed and evaluated. The present study was aimed to compare the clinical efficiency of intrathecal fentanyl with nalbuphine as adjuvant to 0.5% hyperbaric bupivacaine for arthroscopic knee surgeries.
Patients and Methods: A total of 68 patients were randomly taken for this study and categorized into Group I (nalbuphine) and Group II (fentanyl). Each group received 12.5mg of 0.5% heavy bupivacaine with 1 mg nalbuphine or 25µg fentanyl diluting it to 3 ml total volume. Sensory and motor block characteristics and time to first rescue analgesia were recorded as the primary end points. Drug-related side effects of hypotension, bradycardia, respiratory depression, nausea, vomiting, shivering, urinary retention and pruritus were recorded as the secondary outcomes.
Results: Sensory and motor blockade and time for peak sensory level was earlier in group I as compared to group II. Mean time for 2 segments regression in Group I was prolonged as compared to group II. Duration of motor block in Group I [241.471± 12.464 min]was significantly prolonged compared to Group II [179.265± 6.868 min] with (p=0.000). Sensory level at L4 in Group I was 406.618± 17.953 min and in Group II was 228.235± 8.694 min with (p=0.000). Rescue analgesia time in Group I [401.471±16.946 min] was significantly prolonged as compared to Group II [220.000±11.282 min] with (p=0.000). The adverse events in group I are lesser as compared to group II and was statistically significant.
Conclusion: Nalbuphine is a better adjuvant than fentanyl in spinal anesthesia for prolonging post-operative analgesia.

Keywords: Nalbuphine, fentanyl, postoperative analgesia, subarachnoid block, arthroscopy

Introduction

Arthroscopic knee surgery is one of the most commonly performed orthopedic surgeries. The procedures are performed to treat meniscus injury and to perform anterior cruciate ligament reconstruction. Adequate pain relief was very important to reduce morbidity and promote postoperative recovery [1].

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Subarachnoid block is the most popularly performed procedure in the field of anaesthesiology. It offer many advantages over general anesthesia including reduced stress response to surgery with postoperative analgesia. Hyperbaric bupivacaine, the local anaesthetic most commonly used, don't have the advantage of prolonged analgesia. Due to the early arising post-operative pain the role of various adjuvants has been proposed and evaluated [2].

Adjuvant drugs are pharmacological agents possessing little pharmacological effect by themselves, but enhance or potentiate the action of other drugs when given at the same time. Among various adjuvants, intrathecal opioid has provided an effective prolongation of postoperative analgesia after orthopedic surgical procedures.

Opioid analgesics activate opioid receptors located on the primary afferent neurons, resulting in the activation of pain modulating systems. Their activation may either directly decrease neurotransmission or inhibit the release of excitatory neurotransmitters. Opioid receptors are classified as mu, delta, and kappa receptors. Opioid agonist like fentanyl acts on mu receptors and are principally responsible for supraspinal and spinal analgesia along with sedation, nausea, vomiting, pruritus, and respiratory depression and fentanyl is costlier and needs narcotic licensing. An agonist-antagonist, act principally on kappa receptors. Site of action in the spinal cord is substantia gelatinosa. Analgesia with neuraxial opioids is dose-related and specific for visceral rather than somatic pain [3].

Both fentanyl and nalbuphine are opioid analgesics. Fentanyl is an opioid agonist and acts on mu opioid receptors. Nalbuphine is a synthetic opioid analgesic with agonist-antagonist activity and acts as antagonist at mu receptors and agonist at kappa receptors to provide reasonably potent analgesia. Nalbuphine, when used as adjuvant to hyperbaric bupivacaine, has improved the quality of perioperative analgesia with fewer side effects. Nalbuphine is easily available and devoid of side effects such as nausea, vomiting, pruritus, and respiratory depression [4]. Abuse potential with nalbuphine is very less on comparing with other centrally acting opioid.

Nalbuphine has been used intrathecally by various investigators to enhance the postoperative analgesia and they did not document any reports of neurotoxicity. Limited literature regarding the use of it nalbuphine with hyperbaric bupivacaine is found and thus the aim of our study is to observe the possible prompt onset of sensory/motor block and the duration of action with the use of this drug.

This randomized double-blind study was aimed to compare the clinical efficiency of intrathecal nalbuphine 1mg with fentanyl 25 μg as adjuvant to 0.5% hyperbaric bupivacaine for arthroscopic knee surgeries under subarachnoid block (SAB).

Aim and Objectives of the study

The aim of the study is to compare the effect of intrathecal nalbuphine and intrathecal fentanyl as an adjuvant to 0.5% hyperbaric bupivacaine for arthroscopic knee surgeries under subarachnoid block with respect to duration of analgesia.

Objectives

a) To compare onset and duration of sensory block.
b) To compare onset and duration of motor block.
c) To compare duration of two segments regression.
d) To compare haemodynamic variables intraoperatively.
e) To compare adverse effects.

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Material and Methods

This prospective randomized double-blind study was conducted at Department of Anesthesiology & Critical Care & Pain Medicine, Secunderabad, Hyderabad during the period Nov 2017 to Dec 2018. After getting approval of the Institutional Ethical Committee, complete preanesthetic check-up and investigation and due consent from 68 patients of either sex, aged between 18 and 60 years, American society of Anaesthesiologists physical status grades I and II, we designed a prospective, randomized, double-blinded study. Patients not given consent and with a history of clinically significant cardiovascular, pulmonary, hepatic, renal, neurologic, psychiatric, or metabolic disease were excluded from the study. Patients who were obese (bmi >25 kg/m^2), having coagulation or bleeding abnormalities, infection at the injection site, severe spinal deformity, allergy to local anesthetic or any contraindication to spinal anaesthesia were also excluded from the study.

The selected patients were randomized into two comparable groups of 34 patients each by computer-generated random number table. Group I patients received 12.5mg of 0.5% heavy bupivacaine with 1 mg nalbuphine diluting it to 3 ml total volume. Group II patients received 12.5mg of 0.5% heavy bupivacaine with 25µg fentanyl diluting it to 3ml total volume.

To ensure double blindness of the study preparation of intrathecal drugs was done by an independent anesthesiologist not involved in the study and the drug mixture to be administered by another anesthesiologist who will be blinded and performing spinal anesthesia. None of them were further involved for data collection of the study. Postoperative data were recorded by postoperative resident, who was unaware of the group allocation.

All enrolled patients remained fasting overnight prior to surgery and were premedicated with tablet alprazolam 0.5 mg on the night prior to surgery. Before commencement of anesthesia, patients were explained about the methods of sensory and motor blockade assessments. All patients were explained regarding the visual analog scale (vas) scoring system. The vas consisted of a 10 cm horizontal paper strip with two end points: 0 = no pain and 10 = worst possible pain.

In the operating room, routine monitors like noninvasive blood pressure, pulse oximetry, Electrocardiogram were connected. Before administration of subarachnoid block, vital parameters were recorded. Patients received intravenous pre hydration with 10 mL/kg Ringer lactate. Under aseptic precaution, lumbar puncture performed in the L3-4 interspace with 25 G Quincke's spinal needle in the sitting position. Patients were moved to the supine position immediately after administering the spinal block. They were supplemented with oxygen at a rate of 6 l/min via face mask.

Sensory and motor block characteristics were assessed in the normal 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 T10, maximum cephalic level, time taken to achieve maximum sensory block and time taken to two dermatome regressions of sensory analgesia were recorded.

Grading for motor block was done according to bromage scale:

1. Free movements of legs and feet (no motor block-0%).
2. Able to move knee with free movement of feet (prtial motor block-33%).
3. Unable to flex knee with free movement of feet (near complete motor block-66%).
4. Unable to move any part of lower limb (complete motor block-100%) [8].

Onset of motor block was defined as the time taken to achieve bromage scale 3. Time taken to achieve complete motor blockade was also noted.

The surgical anesthesia was considered to be achieved when the levels of sensory block were reached to T10 thoracic dermatome level or above with attainment of complete motor block (bromage-3).

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Patients with vas score ≥3 received diclofenac 75 mg intramuscularly for rescue analgesia. The vas score of >3 constituted the end point of the study. Postoperatively, the sensory and motor block levels were assessed at 15 min intervals until normal sensations returned.
Respiratory depression (RR<8 or SpO_2 <95%) could be treated with oxygen supplementation or respiratory support if required. Hypotension defined as a decrease of systolic blood pressure by > 20% from baseline or a fall below 100 mmHg, was treated with incremental Intravenous (IV) doses of 6 mg of injection mephentermine and IV fluid as required. Bradycardia i.e., Heart Rate (HR) below 50 bpm, or >20% decrease from the baseline value was treated with 0.3-0.6 mg of IV atropine. HR, Mean Arterial blood Pressure (MAP) and oxygen saturation (SpO_2) were monitored and recorded. Intraoperative nausea was treated with ondansetron (4 mg) and any incidence of pruritus was treated with injection pheniramine maleate 2 ml (45 mg) intravenously.
Sedation was assessed by a categorical scale as used by mostafa *et al*. And graded as:

1. Awake and alert.
2. Awake but drowsy, responding to verbal stimulus.
3. Drowsy but arousable, responding to physical stimulus.
4. Unarousable, not responding to physical stimulus [9].

Sensory and motor blockade profile recorded

Onset time of sensory block at t10 level (min).
Median cephalic sensory level at t6 level (min).
Time taken to achieve sensory blockade at most cephalic level (min).
Time taken to achieve complete motor block (min).
Time taken for two regressions of sensory block (min).
Duration of motor block (min).
Time to administer first rescue analgesia (min).

Statistical analysis

Data was entered in MS EXCEL and analysed in SPSS software. Descriptive statistics like mean and standard deviation were used to summarise numerical data when normally distributed and median and interquartile range when non-normally distributed. Categorical data was summarized as count and percentage. Chi-square test and Z-test were applied to identify difference in success or failure rate of two methods. Unpaired t-test was used to test the difference in secondary objectives. Value of P <0.05 was considered statistically significant.

Results

The groups were comparable with respect to age, sex, height, weight and ASA grade. [Table 1]
Mean duration of surgery in group I was 149.706±14.031 and group II was 143.235±10.932 and P value was 0.038, thus duration of surgery is prolonged in group I. [Table 2]
Patients in group I had earlier onset of sensory and motor block compared to group II. [Table 3]
Mean time of onset of sensory block at T10 in Group I was 1.551±0.627 min and with Group II was 4.232±0.834 min with a (p= 0.000).
Mean time of onset of motor block in Group I was 1.412±0.511 min and in Group II was 3.647±0.901 min with (p=0.000).
Mean time for sensory block to reach T6 in Group I was 5.912±1.897 min and with Group II

was 8.588± 1.500 min with a (p=0.000) thus showing that time taken for sensory block to reach T6 is earlier in group I compared to group II.
Mean time for 2 segments regression in Group I was134.706±10.797 min and in Group II was 86.471±6.340 min with (p=0.000) thus showing 2 segments regression is prolonged in group I.
Duration of motor, sensory block and time for rescue analgesia were also significantly prolonged in group I compared to group II.
Duration of motor block in Group I was 241.471± 12.464 min and in Group II was 179.265± 6.868 min with (p=0.000).
Sensory level at L4 in Group I was 406.618± 17.953 min and in Group II was 228.235± 8.694 min with (p=0.000).
Rescue analgesia time in Group I was 401.471±16.946 min and in Group II was 220.000±11.282 min with (p=0.000). [Table 4 & Figure 1]
Adverse events in Group I was 0.000±0.000 and in Group II was 0.294±0.462 with (p=0.000). [Table 5 & Figure 2]
This shows that the adverse events in group I are lesser as compared to group II and was statistically significant
Fall in pulse rate, SBP, DBP, MAP was observed in both the groups following institution of spinal anaesthesia.
After spinal till 30 minutes there was a fall in the pulse rate of 9% in group I and 10% in group II, fall in the SBP of 6% in group I and 15% in group II, fall in the DBP of 9% in group I and of 11% in group II, fall in the MAP of 8% in group I and of 13% in group II. This fall is non-significant as the cut off is taken as 20% fall.

Table 1: Demographic data

Variable	Statistics	Group I	Group II	P Value
	N	34	34	
Age in years	Mean ± SD	37.559±9.586	34.147±11.576	0.190
Weight in kgs	Mean ± SD	62.294±9.587	66.265±7.417	0.060
Height in cms	Mean ± SD	163.147±8.023	165.500±8.918	0.257
Gender	No. of cases (% of cases)	Male=21 (61.7%) Female=13(38.3%)	Male=22 (64.7%) Female=12(35.3%)	0.805
ASA Grade	No. of cases (% of cases)	ASA I 18(52.9%) ASA II16(47.1%)	ASA I 21(61.7%) ASA II13(38.3%)	0.469

Table 2: Duration of surgery

Variable	Statistics	Group I	Group II	P Value
Surgery duration in min	MEAN±SD	149.706±14.031	143.235±10.932	0.038

Table 3: Sensory and motor blockade characteristics

Variable	Statistics	Group I	Group II	P Value
Onset of sensory block at T10 in min	Mean ± SD	1.551±0.627	4.232±0.834	0.000
Onset of sensory block at T6 in min	Mean ± SD	5.912±1.897	8.588±1.500	0.000
Onset of motor block (bromage scale 3) in min	Mean ± SD	1.412±0.511	3.647±0.901	0.000
Time for 2 segments regression in min	Mean ± SD	134.706±10.797	86.471±6.340	0.000
Duration of motor block in min	Mean ± SD	241.471± 12.464	179.265± 6.868	0.000

Table 4: Rescue analgesia

Variable	Statistics	Group I	Group II	P Value
Sensory level at L4 in min	Mean ± SD	406.618± 17.953	228.235± 8.694	0.000
Rescue analgesia time in min	Mean ± SD	401.471±16.946	220.000±11.282	0.000

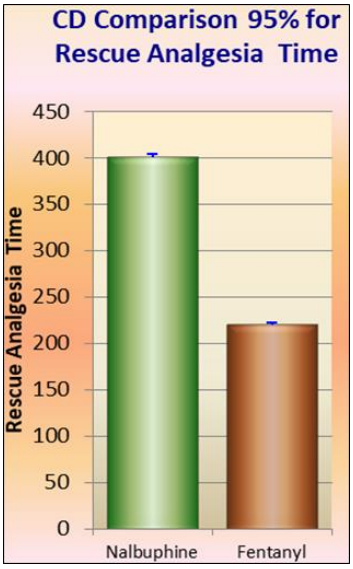

Fig 1: Time for rescue analgesia

Table 5: Adverse effects

Variable	Statistics	Group I	Group II	P Value
Adverse events	Mean ± SD	0.000±0.000	0.294±0.462	0.000

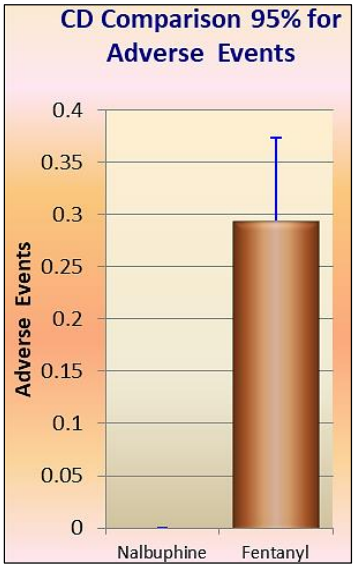

Fig 2: Adverse events

Discussion

Arthroscopic knee surgery is the one of the most common minimally invasive surgical procedure in modern orthopedic setup. It is commonly performed as an outpatient procedure and is associated with variable amount of post-operative pain, which is caused by irritation of free nerve endings of synovial tissue, anterior fat pad and joint capsule during surgical excision and resection[5]. Undoubtedly, post-operative pain has a negative impact on patient's early mobilization and discharge as well as it causes unanticipated hospital admission particularly in a day care setting[6]. Thus Pain frequently hampers implementation of ambulatory surgery in spite of so many analgesic drugs and regimens.

Adequate pain relief reduces surgical stress response, so reduces patient's morbidity and improve post-operative recovery. Several analgesic strategies such as systemic medication

(narcotic, non-steroidal anti-inflammatory drugs), central or peripheral nerve block and intra-articular drug administration such as ketorolac, α_2 -agonists, opioids, local anesthetics have been used to interrupt the pain pathway, which is called multimodal approach. However, none is free from limitations such as needs for special equipments, monitoring and risks of complications. Optimal post-operative pain control for day-care surgery should be effective and safe, producing minimal side-effects, facilitating recovery and be easily managed by patients at home [7].

The post-arthroscopy pain was found to be more pronounced during the first 8 post-operative hours. These findings should be expected since postoperative pain is at its peak immediately after surgery and becomes less severe with time. Supplementary analgesia was required only in patients that underwent operative arthroscopy and more often in patients with tourniquet time of more than 40 minutes [8].

By adding adjuvants, the dose of local anesthetics like bupivacaine can be reduced, thereby reducing its side effects like myocardial depression, hypotension, bradycardia, heart block, and ventricular arrhythmias and Adjuvants are often used with local anaesthetics for its synergistic effect by prolonging the duration of sensory-motor block and thus post-operative analgesia and limiting the cumulative dose requirement of local anaesthetics [9].

The use of neuraxial opioid agonists is associated with quite a few side effects, so various options including opiod agonist-antagonists like nalbuphine are being extensively evaluated as an alternative with emphasis on opioid-related side effects such as hypotension, bradycardia, respiratory depression, nausea, urinary retention and pruritus.

Hence we have undertaken a study to evaluate the efficacy of intrathecal nalbuphine versus intrathecal fentanyl as adjuvant to 0.5% hyperbaric bupivacaine for arthroscopic knee surgeries under subarachnoid block. The following results were found:

The demographic profile of our patients was comparable with respect to mean age, body weight, height, gender distribution, and ASA grading.

The onset of sensory and motor characteristics were earlier in group I compared to group II.

Intraoperative hemodynamics, quality of subarachnoid block, and oxygen saturation were comparable between both the groups.

Sensory level at L4 in Group I was 406.618± 17.953 min and in Group II was 228.235± 8.694 min with (p=0.000).

Rescue analgesia time in Group I was 401.471±16.946 min and in Group II was 220.000±11.282 min with (p=0.000).

This shows that the mean time for sensory level at L4 and rescue analgesia time, in group I is prolonged as compared to group II and was statistically significant.

In our study emphasis was made on opioid-related side effects such as hypotension, bradycardia, respiratory depression, nausea, vomiting, shivering, urinary retention and pruritus and found that adverse events in Group I was 0.000±0.000 and in Group II was 0.294±0.462 with (p=0.000).

10 patients had adverse effects in group II (3 had nausea, 3 had vomiting, 4 had shivering).This shows that the adverse events in group I are lesser as compared to group II and was statistically significant.

There are only few studies available of central neuraxial administration of nalbuphine as intrathecal adjuvant, which concluded that nalbuphine significantly enhanced the sensory analgesia with minimal pruritus and respiratory depression.

Culebras *et al*. studied the advantages of nalbuphine at doses of 0.2, 0.8 and 1.6 mg over intrathecal morphine in ninety obstetric patients undergoing cesarean section and concluded that intrathecal nalbuphine was more effective over morphine to provide better postoperative analgesia without any side effects. We have also observed that nalbuphine provided enhanced sensory analgesia as compared to fentanyl [10].

Gupta *et al*. conducted a randomized double-blind study to compare the clinical efficiency of

intrathecal fentanyl (25 μg) with nalbuphine (2 mg) as adjuvant to 17.5 mg of 0.5% hyperbaric bupivacaine during orthopedic surgery of lower limbs under subarachnoid block (SAB)and the study revealed no statistically significant difference in the onset and cephalic extension of sensory blockade of hyperbaric bupivacaine when intrathecal fentanyl or nalbuphine was used as adjuvant. The duration of sensory block and motor block was significantly enhanced by the addition of intrathecal nalbuphine as compared to intrathecal fentanyl in the present study showed that time for sensory level regression and rescue analgesia time is prolonged in nalbuphine group [7]. In our study 1 mg nalbuphine is used with less adverse effects and there was significant difference in the onset and cephalic extension of sensory blockade [11].

Naaz S *et al*. compared nalbuphine hydrochloride (0.8 mg) and (1.6 mg) and fentanyl group. A randomised, double blinded, prospective study on 90 patients of ASA I and II undergoing lower limb orthopaedic surgery under subarachnoid block was done. The duration of analgesia was prolonged in nalbuphine group and the adverse effects were least in nalbuphine group which was in accordance with our study [12].

Sapate *et al*. observed the effects of intrathecal nalbuphine (0.5 mg) with 0.5% spinal bupivacaine (3 mL) for lower abdominal surgeries in elderly patients in a randomized control study. They concluded that nalbuphine provided better quality of SAB as compared to bupivacaine alone and also enhanced the postoperative analgesia. No patients in their study developed any side effects. Which is in accordance to our study [13].

Babu V *et al*. compared the efficacy of intrathecal fentanyl versus intrathecal nalbuphine as adjuvants to 0.75% ropivacaine for post-operative pain relief in cesarean section. Two-segment regression time was prolonged in nalbuphine group. Duration of sensory blockade was also significantly prolonged in nalbuphine group. The duration of motor blockade was significantly higher in nalbuphine group. The time to first request of analgesia was significantly prolonged in nalbuphine group [14].

Ahmed *et al*. evaluated the potentiating effect of intrathecal nalbuphine with bupivacaine for postoperative analgesia in three different doses (0.8, 1.6, and 2.4 mg) in a randomized control study. They concluded that the combination of intrathecal bupivacaine with nalbuphine significantly prolonged postoperative analgesia as compared to control group and a 1.6 mg dose showed the best results [15].

Conclusion

Nalbuphine (1 mg) as intrathecal adjuvant to 0.5% hyperbaric bupivacaine (12.5 mg) for subarachnoid blockade was clinically more efficient than fentanyl. We conclude that nalbuphine is a better adjuvant than fentanyl in spinal anesthesia as far as prolonged post-operative analgesia, stable cardio-respiratory parameters, quality of intra-operative block and patient comfort is concerned.

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