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Original Research Article

Does Bupivacaine Plus Butorphanol Provides Better Anesthesia and Analgesia in Comparison to Bupivacaine Plus Fentanyl?

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Abstract

Background: Neuraxial opioids are widely used as adjuvants to local anaesthetic as they improve quality and duration of block. Neuraxial opioids like butorphanol and fentanyl enable longer surgical analgesia and quicker spinal anesthesia recovery. The current study aimed to assess the efficacy of anesthesia and analgesia between intrathecal bupivacaine plus fentanyl and bupivacaine plus butorphanol for lower limb orthopedic surgeries.

Methods: The n=80 cases were randomly allotted by a computer-generated random number into two groups. Group A cases received 2.5 ml of 0.5% hyperbaric bupivacaine with 0.5 ml of fentanyl (25 µg) a total volume of 3 ml intrathecally. Group B received 2.5 ml of 0.5% hyperbaric bupivacaine with 0.5ml of butorphanol (25 µg), the 0.5 ml of 25 µg butorphanol was obtained by 1ml of 1mg/ml butorphanol with 19ml of sterile distilled water.

Results: In the current study a total of n=80 cases divided equally in two groups (A and B) were included. Our results showed Group A showed a lower sensory level of block in compared to group B and the difference is significant. Both males and female cases in the two groups showed significant differences in the time required to reach the highest level of sensory blockade, which was earlier in group B. Both male and female populations of both the groups had shown similar findings in the time taken for sensory regression to S2.

Conclusion: We conclude that 25µg fentanyl and 25 µg butorphanol with bupivacaine provide good anesthesia and analgesia and fewer side effects. Neuraxial butorphanol plus bupivacaine provide early onset and prolonged duration of sensory and motor block, and prolonged analgesia then fentanyl and bupivacaine.

Keywords: Adjuvants, Bupivacaine, Butorphanol, Fentanyl.

Introduction

A subarachnoid block is one of the most popular anesthetic techniques for lower limb orthopedic surgeries. Spinal anesthesia proves dense motor and sensory block. Spinal anesthesia was invented by Augustus Bier in 1898. [1] Adverse effects are mostly due to sympathetic blockage, which includes hypotension, bradycardia, and reduced cardiac output. These effects are proportional to the level of sympathetic blockade. The most common postoperative complaint is pain after regression of spinal anesthesia in patients undergoing lower limb orthopedic surgeries. Opioids have been added to local anesthetics for the neuraxial blockade, which permits the use of a lesser dose of local anesthetics and also provides sufficient anesthesia and analgesia. [2] Early mobility, the restart of oral nourishment, and a shorter hospital stay are all related to effective postoperative analgesia. [3] It is frequently found that intrathecal bupivacaine is insufficient for lengthier procedures. [4] Adjuvants can lengthen the duration of intraoperative anesthesia, and postoperative analgesia, and amplify the effects of local anesthetics. This effect has shown promising outcomes when local anesthetics are combined with intrathecal opioid delivery. [5,6] Fentanyl interacts with receptors at supra-spinal locations to primarily induce analgesia. Additionally, fentanyl binds to receptors, producing anesthesia, drowsiness, and spinal analgesia. In comparison to other opioids, it has a quicker onset and less frequently causes respiratory depression, making it a favored adjuvant in spinal anesthesia. [5] In addition to competitive antagonist and partial agonist action at the kappa receptors, butorphanol also has partial agonist and antagonist activity at the mu-opioid receptor. [6] There are little data on butorphanol's intrathecal administration, and there is continuous discussion over the selection, dosage, and concentration of medications to be employed as a result of the development of several adjuvants. The antinociceptive synergistic action between opioids and local anesthetics in neuraxial blocks has been demonstrated in animal studies. [7] Neural axial opioids not only produce extended analgesia in the postoperative period but also early regression from spinal anesthesia. [8] Butorphanol is a highly lipid-soluble opioid agonist-antagonist that acts on mu, kappa, and delta opioid receptors in vitro. [9] it has been combined with local anesthetics for spinal anesthesia. Therefore, the current study aimed to determine the efficacy of anesthesia and analgesia between intrathecal bupivacaine plus fentanyl and bupivacaine plus butorphanol for lower limb orthopedic surgeries.

Material and Methods

This prospective randomized controlled study was done in the Department of Anesthesiology, Kasturba Medical College and Hospital, Mangalore, Karnataka State. Institutional Ethical approval was obtained for the study. Written consent was obtained from all the cases included in the study after explaining the nature of the study in the vernacular language.

Inclusion criteria

1. Age from 18 – 60 years.
2. Males and females
3. ASA physical status I and II patients
4. Patients posted for lower limb orthopedic procedures.
5. Voluntarily willing to participate in the study.

Exclusion criteria

1. Patients who refused to undergo surgery under spinal anesthesia.
2. Patients with spinal deformities, local skin infections
3. Patients with mental disorders
4. Morbidly obese patients.

5. Hemodynamically unstable patients or having coagulation disorders.
6. Those not as per inclusion criteria

Sample size calculation: $n=4pq/d^2$

Where n=sample size, p=prevalence taken as p=5, q= 95 d=absolute error

n=4*5*95/25=76

The minimum sample size was 76 we included n=80 cases in the study.

The n=80 cases were randomly allotted by a computer-generated random number into two groups. Group A cases received 2.5 ml of 0.5% hyperbaric bupivacaine with 0.5 ml of fentanyl (25 µg) a total volume of 3 ml intrathecally. Group B received 2.5 ml of 0.5% hyperbaric bupivacaine with 0.5ml of butorphanol (25 µg), the 0.5 ml of 25 µg butorphanol was obtained by 1ml of 1mg/ml butorphanol with 19ml of sterile distilled water.

Anesthetic procedure: All the patients underwent complete general and physical examination. The procedure was explained and the linear visual analog scale scoring system for pain was explained to the patients during the pre-anesthetic check-up. Basic investigations were done which included complete blood count, hemoglobin, bleeding time, clotting time, blood sugar, and if aged above 45 years ECG was done. The patients were kept nil per oral for 6 hours to solids and 2 hours to clear fluids preoperatively and received no premedication. In the operation theatre, an 18G intravenous line was established. Baseline heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, and peripheral arterial oxygen saturation (SPO_2) were recorded for all the subjects. All the patients received 10ml/Kg of lactated ringer solution as preloaded within 20 – 30 minutes. Patients were put in lateral positions. Under aseptic precautions skin and subcutaneous tissue was infiltrated with 1ml of 2% lignocaine. The midline approach was used to perform a subarachnoid block. L3-4 or L4-5 intervertebral space was used to approach subarachnoid space with a 25G Quincke spinal needle. Free flow of cerebrospinal fluid was noted and 3ml of test drug was injected into the subarachnoid space. After the procedure, the patients were put in a supine position. Intraoperative vitals were recorded at 5 minutes intervals for the first 15 minutes from the time of injection of spinal solution and thereafter every 15 minutes for the complete period of surgery. The data was recorded. Hypotension less than 20% of baseline was treated with fluid boluses and 6mg IV boluses of Mephentermine, while bradycardia (HR<50 bpm) was treated with 0.6mg IV atropine.

A 20 G hypodermic needle was used in a pinprick test to determine when the sensory block started. On a four-point scale, the sensory block was graded: normal pin-prick sensation = 1, pin-prick feeling sharp/pointy but weaker in comparison to other areas = 2, pin-prick recognized as touch with blunt object = 3, and no perception of pin-prick = 4. The block in grade four was adequate. The modified Bromage scale (MBS) was used to grade the degree of motor blockade (Grade 0 = no motor block, Grade 1 = inability to raise extended legs but able to flex knees and move feet, Grade 2 = inability to raise extended legs and flex knees but able to move feet, Grade 3 = total motor block). The period between the study medication administration and MBS Grade 3 was used to determine when the motor block started. After the procedure and then every 30 minutes until regression to MBS Grade 0, the motor block was further evaluated. The length of the motor block was measured from the moment it started reaching MBS Grade 0. T10 minimal dermatomal level with Grades 4 and 3 on MBS for the sensory and motor blocks was considered acceptable for surgery to proceed.

The patient was sent to the recovery room after the procedure. Postoperative pain was measured using a VAS (0–10-point scale)

right away, at 15–30–1–hour–and 2-hour intervals. following 2 hours, patients were moved to the ward, and their VAS scores were checked at 4, 8, 16, and 24 hours following surgery. The period of analgesia was calculated as the delivery of intrathecal medication and the interval between the rescue analgesic.

Statistical analysis: The SPSS version 19.0, was used to analyze the data after they were put into an Excel spreadsheet in Windows format. Continuous variables were represented as mean standard deviation, whereas categorical variables were represented as numbers and percentages. Quantitative factors were studied using the t-test, while qualitative variables were evaluated using the Chi-square test/Fisher's exact test. Statistics were deemed significant at $P < 0.05$.

Results

The demographic profile and distribution of cases in the groups have been depicted in Table 1. Based on the patient characteristics we found both groups were comparable for the distribution of cases based on the age, sex, weight, duration of surgery, and ASA I and II categories. All the p values were insignificant hence the distribution was considered uniform in both groups.

Table 1: Patient characteristics in the two groups of the study.

	Group A	Group B	p-value
Age	42.1 ± 12.02	40.25 ± 14.36	0.53
Sex (M: F)	26.:14	30:10	0.33
Weight	61.4 ± 1.874	56.98 ± 1.722	0.60
Duration of surgery	71.625 ± 18.130	64.875 ± 15.338	0.076
ASA I and II	28/12	32/8	0.30

Each group had n=40 patients and they were similar in demographic characteristics like age, sex, weight, ASA physical status, and duration of surgery given in Table 2. Group A showed a lower sensory level of block in compared to group B and the difference is significant. Both males and female cases in the two groups showed significant differences in the time required to reach the highest level of sensory blockade, which was earlier in group B. Both male and female populations of both the groups had shown similar findings in the time taken for sensory regression to S2.

Table 2: Sensory blockage characteristics in both groups of the study

Sensory block characteristics	Group A	Group B	P value
Level of sensory blockade (T10:T12)	12: 8	32: 8	0.001*
Time from injection to the highest level of sensory blockade in (min)	8.90 ± 1.355	5.45 ± 1.431	0.001*
Time for sensory regression to S2 from the highest level of sensory blockade in (min)	125.98 ± 20.716	154.80 ± 26.678	0.001*
Time from injection to the highest level of sensory blockade in (min) Male	8.692 ± 1.379	5.548 ± 1.524	0.001*
Time from injection to the highest level of sensory blockade in (min) Female	9.286 ±1.266	5.111 ± 1.054	0.001*
Time for sensory regression to S2 from the highest level of sensory blockade in (min) [Male]	124.38 ± 22.98	156.71 ± 26.795	0.001*
Time for sensory regression to S2 from the highest level of sensory blockade in (min) [Female]	128.93 ± 16.021	148.22 ± 26.79	0.001*

Motor block analysis in both groups showed significantly earlier onset and prolonged duration in group B the statistical comparison of motor block characteristics was found to be significantly earlier onset and duration in male cases the details have been depicted in Table 3.

Table 3: Motor blockage characteristics in both groups of the study

Motor block Characteristics	Group A	Group B	P value
The onset of motor blockade (min)	9.40 ±1.29	5.95 ± 1.46	0.0001*
Duration of motor blockade (min)	126.42 ±24.16	155.30 ± 26.40	0.0001*
The onset of the motor blockade in males (min)	9.31 ± 1.37	6.129 ± 1.54	0.0001*
The onset of the motor blockade in females (min)	9.57 ± 1.158	5.33 ± 1.00	0.0001*
Duration of the motor blockade in males (min)	123.7 ± 27.12	157.4 ± 26.33	0.0001*
Duration of the motor blockade in females (min)	131.50 ± 17.12	148.0 ± 26.85	0.085

* Significant

The comparison of intraoperative SBP showed that group A had a decrease in SBP at 15 minutes and end of 2 hours. While group B showed a greater degree of decrease in SBP at 105 minutes and SBP in group B remained lower compared to group A at the end of 2 hours. The variations of SBP were found to be greater for group B given in Figure 1.

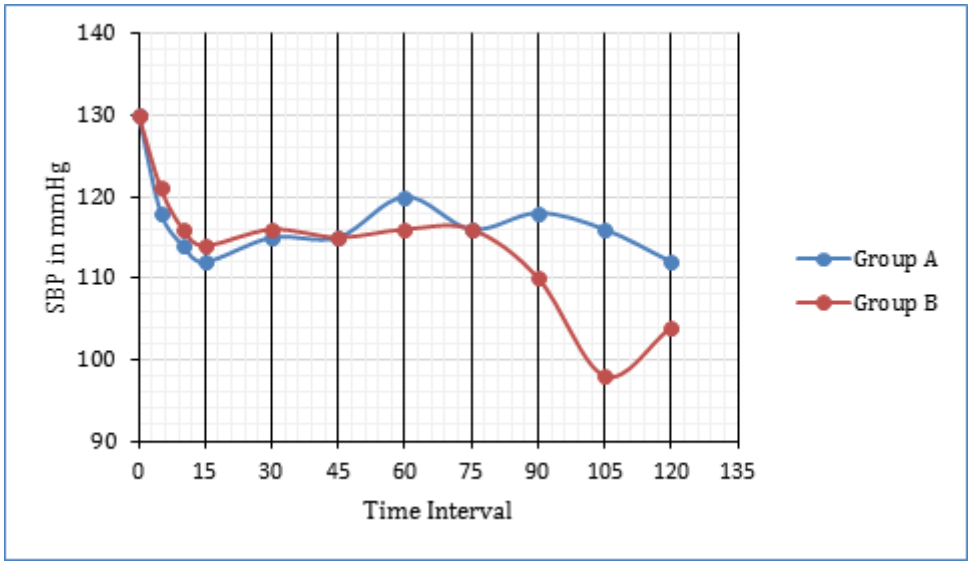

Figure 1: Comparison of intraoperative SBP between two groups

The DBP in both groups tends to fluctuate in both groups in the initial 15 minutes followed by stabilization of DBP from 15 – 75 minutes and again fluctuating at the beginning of 90 minutes and ending at the lower level at 120 minutes in group B. In group A the initial decrease of DBP was followed by lower DBP levels than in group B and increased at the 75 minutes interval and decreased at the end of 120 minutes depicted in figure 2.

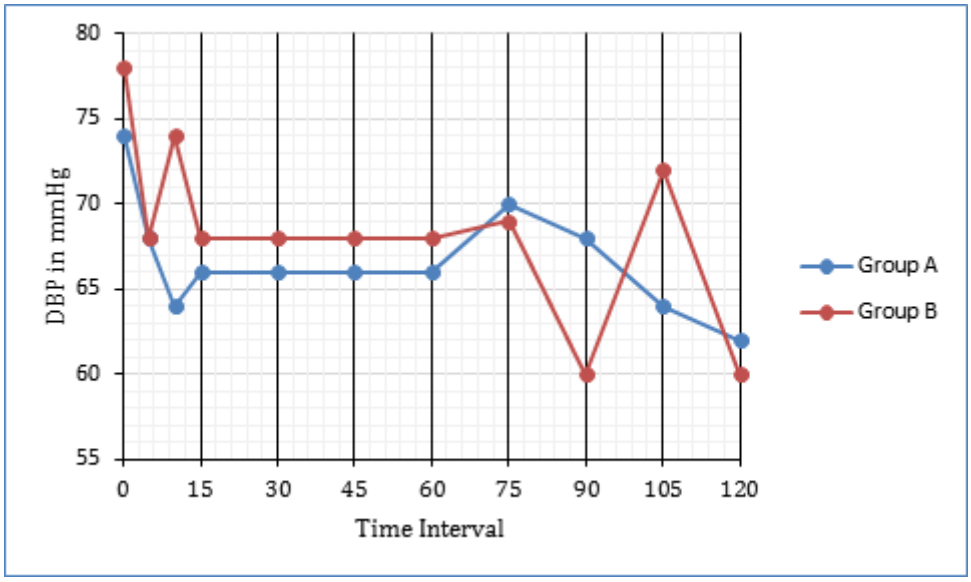

Figure 2: Comparison of intraoperative DBP between two groups

The Heart rate comparison in the intraoperative period showed the heart rate tend to decrease in both groups and the decrease in group A is more than in group B and remained lower at the end of 60 minutes in group A slight increase at the end of 90 minutes and decrease at the end of 120 minutes. However, in group B it was found that after 60 minutes the heart rate tend to increase and reach a maximum at the end of 120 minutes depicted in Figure 3.

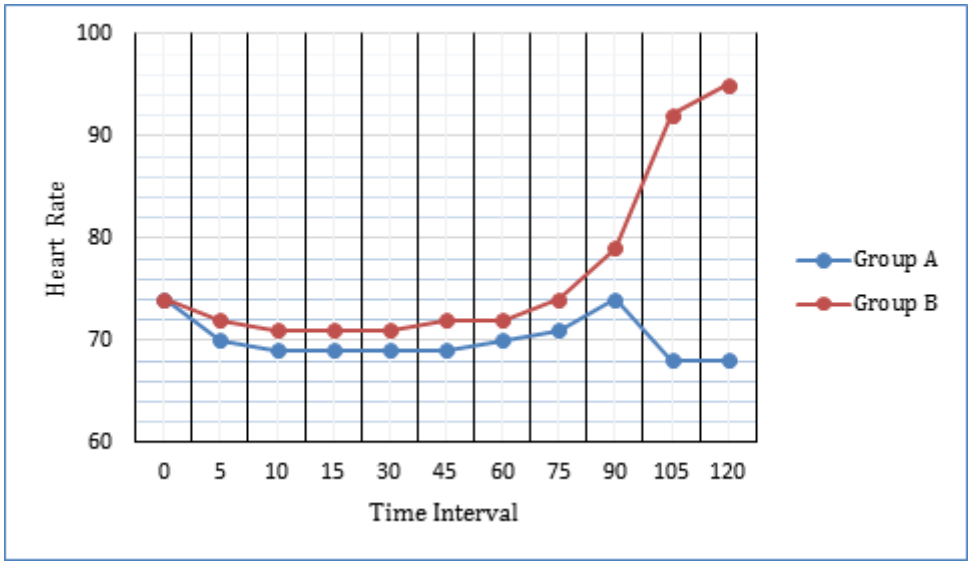

Figure 3: Comparison of intraoperative Hear Rate between two groups

Time for rescue analgesic request was specifically higher in group B as compared to group A and both male and female populations showed significantly higher rescue analgesic demand in group B depicted in Table 4.

Table 4: Time of the first request for rescue analgesia in the cases of study

Parameter	Group A	Group B	p-value
Time of the first request for analgesia (min)	210.28 ± 31.331	282.10 ± 32.976	0.0001*
Time for the first request for analgesia in males (min)	212.15 ± 32.264	286.74 ± 33.061	0.0001*
Time for the first request for analgesia in females (min)	206.79 ± 30.380	266.11 ± 28.838	0.0001*

* Significant

In this study for group A the commonest side effect was hypotension in 12.5% of cases followed by itching, bradycardia, and vomiting in 10.0%, and 7.5% respectively (table 4). Similarly, for group B the major side effect was hypotension in 15% of cases followed by Bradycardia and itching in 5% and nausea and vomiting in 2.5% of cases. The common follow-up side effect reported was a headache in both groups (Table 4).

Table 5: Perioperative and Follow-up complications recorded in the cases of study.

Parameter	Group A	Group B
Perioperative		
Hypotension	5	6
Bradycardia	3	2
Respiratory Depression	0	0
Sedation	0	0
Shivering	0	0
Itching	4	2
Nausea/Vomiting	3	1
Follow-up		
Headache	3	2
Dysesthesia	0	0

Discussion

The present study found that the addition of butorphanol to bupivacaine is associated with early onset, prolonged duration of sensory block, motor block, and analgesia than fentanyl and bupivacaine combination. Previous studies have found that adding opioids to sub-therapeutic doses of local anesthetics produced prolonged pain relief without affecting the duration of recovery. [11] Wang et al., [7] showed synergism exists between fentanyl and bupivacaine. Local anesthetics and opioids have different mechanisms of action on the spinal cord for their pain relief. Fentanyl and butorphanol act on mu receptors responsible for K+ channels and reducing Ca^{2+} influx results in inhibition of neurotransmitter release. The mu receptor agonistic action also is responsible for post-synaptic hyperpolarization and lower activity of neurons. [11,12] Bupivacaine, a local anesthetic that acts on voltage-gated Na^{+} channels, is responsible for the additional inhibition of presynaptic Ca^{2+} channels. [13] this phenomenon explains the synergistic action of fentanyl/butorphanol with bupivacaine in our study. Other studies have shown the prolongation of a sensory block with the addition of fentanyl to lidocaine and bupivacaine. [14-16] Present study showed a significant difference in the onset and duration of sensory and motor block in the butorphanol group than the fentanyl group, which is different from previous studies. [16] The addition of opioids to local anesthetics lowers the LA dose and incidence of side effects. [17] In this study n=5 (12.5%) in the fentanyl group experienced side effects whereas, in

the butorphanol group, n=6(15%) experienced the same they were treated with a bolus of crystalloids and i.v mephenteramine. Previous studies found the incidence of hypotension in the fentanyl and bupivacaine group is 20% and in butorphanol with bupivacaine group was 17%. [18] Adding fentanyl to bupivacaine had not been associated with potentiating sympathetic blockade in animal studies. [7] Bupivacaine 4mg with fentanyl (20-25µg) for a neuraxial block in elderly patients showed greater spinal block and low cardiovascular side effects. [19]

The incidence of pruritus in the fentanyl and bupivacaine group was 10% and in the butorphanol and bupivacaine group was 5% which was mild in severity and did not receive any medication. Previous studies have shown the incidence of pruritus was 48% to 75% in fentanyl with bupivacaine compared to bupivacaine alone for knee arthroscopy and only 1.4% of patients who received epidural butorphanol experienced itching. [20] Epidural Kappa receptor-stimulating opioids showed lowered pruritus than sole mu-receptor stimulating opioids as shown by Ackerman et al., [21] Activation of itch center (medullary dorsal horn) and inhibition of inhibitory neurotransmitters may be the possible mechanism of action. [22] None of the patients in the fentanyl and butorphanol group experienced sedation and respiratory depression. Previous studies showed the incidence of sedation after neuraxial opioids were dose-dependent. [23] In this study we used a very low dose of butorphanol therefore no incidence of sedation was seen in this study. The dose of 25mcg of fentanyl with 15mg of bupivacaine is not associated with respiratory depression in the elderly, as reported by Varassi et al., Mixed agonist may lessen the respiratory depression caused by intrathecal sufentanil as shown by Atkinson et al., [24] Butorphanol also an agonist-antagonist used in the present study might have a similar effect on respiratory depression. The incidence of nausea and vomiting in our study was three patients 975%) in the fentanyl group and one (2.5%) in the butorphanol group, which is consistent with the previous study. Dahlgren et al., [25] reported that lower incidence of nausea and vomiting with the addition of opioids to the LA for cesarean delivery. Duration of analgesia was significantly greater in the butorphanol group compared to the fentanyl group in our study. Similar findings have been reported by Singh V et al., [18] where intrathecal butorphanol patients required lower rescue analgesic than fentanyl. The synergistic action of fentanyl/butorphanol with bupivacaine in inhibiting A-delta and C fibers explains the better perioperative analgesia. [7] The limitation of the present study was the lack of a control group (bupivacaine + saline), the presence of which might have supported our findings. The wider range of patients included in our study may be a confounding factor, as the perception of pain may vary with age. Lack of blinding is also a limitation of the present study.

Conclusion

We conclude that 25µg fentanyl and 25 µg butorphanol with bupivacaine provide good anesthesia and analgesia and fewer side effects. Neuraxial butorphanol plus bupivacaine provide early onset and prolonged duration of sensory and motor block, and prolonged analgesia then fentanyl and bupivacaine.

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