ORIGINAL RESEARCH

Comparison of Efficacy Of Two Different Doses of Intrathecal Buprenorphine With Isobaric Levobupivacaine In Patients Undergoing Elective Lower Limb Surgeries

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ABSTRACT

Aim: To compare the efficacy of 2 different doses of intrathecal Buprenorphine (45 mcg and 60 mcg) with Levobupivacaine in patients undergoing elective lower limb orthopaedic surgeries. **Materials and Methods:** This randomized double blind controlled study was conducted at IMS and SUM Hospital from March 2020 to April 2021 among 60 patients divided into group I and II of 30 each randomly by computer generated random numbers who were posted for elective lower limb surgeries after obtaining ethical committee approval. Parameters recorded were onset of sensory block and motor blockade, duration of analgesia, haemodynamical changes (HR, SBP, DBP and MAP) and SpO2 was monitored: at baseline, 5 min, 15 min, 30 min, 45 min and 60 min, VAS Score, Sedation score and other side effects (like postoperative nausea and vomiting, pruritis and urinary retention) were monitored at 1st hour, 6th hour, 12th and 24 hours and data were recoded. **Results**: It was found that the duration of effective analgesia was statistically significant on increasing the dose of Buprenorphine from 45 mcg to 60 mcg. Patients in both the groups were hemodynamically stable throughout the procedure except 2 episodes of diastolic hypotension in group II but patients did not require vasopressors at any point of time during the surgery. There was no statistically significant side effects in both the groups. **Conclusion**: Buprenorphine at a dose of 60 mcg in comparison to a dose of 45 mcg when added as adjuvant to isobaric Levobupivacaine for spinal subarachnoid block for lower limb surgeries produces longer duration of postoperative analgesia without much significant adverse effects.

Keywords: Lower Limb, Orthopaedic Surgery, Buprenorphine, Isobaric Levobupivacaine

INTRODUCTION

Spinal subarachnoid block is the most frequently used technique practiced in daily anesthetic practice. The first performed regional anaesthetic technique was spinal anesthesia and the first surgical operation under spinal anesthesia was done in 1898 in Germany by August Bier.The technique has been improvised after that. The main goal of the spinal anaesthesia is to provide comfortable pain free period without much side effects for the patient. Lower limb surgeries being the most performed surgery in today's surgical world, pain after lower limb surgeries is very distressing preventing early ambulation of patient and also emotionally draining [1,2].

Spinal subarachnoid block with Bupivacaine is the most commonly used anesthetic technique in surgeries involving lower limb. Side effects like bradycardia and hypotension are commonly seen with this technique. Marked hypotension in patients with limited cardiac reserve is harmful. Levobupivacaine, an amide local anesthetic agent is the isolated s-enantiomer of racemic Bupivacaine [3]. It is the recently introduced most long acting local anaesthetic in clinical use. Reports of toxicity are scarce with it and to improve the block characteristics of intrathecally administered local anaesthetic, addition of adjuvant is widely in practice.

Buprenorphine was discovered in 1966, at the research labs of a home products company, Reckitt & Colman in Hull, England[1].So Buprenorphine which is an agonist -antagonist opioid, is about 30 times more potent than Morphine with advantage of ceiling effect on respiratory depression [2]. Clinical studies available on efficacy of different doses of intrathecal

Buprenorphine with isobaric Levobupivacaine in patients undergoing elective lower limb surgeries are limited.

The purpose and aim of the present study was to compare the efficacy of 2 different doses of intrathecal Buprenorphine (45 mcg and 60 mcg) with Levobupivacaine in patients undergoing elective lower limb orthopaedic surgeries with regards to:

1. Onset of sensory blockade and motor blockade
2. Duration of analgesia
3. Haemodynamical changes (HR, SBP, DBP and MAP) and SPO2
4. VAS Score, Sedation score and other side effects

MATERIALS AND METHODS

This randomized double blind controlled study was conducted at IMS and SUM Hospital from March 2020 to April 2021 among 60 patients divided into group I and II of 30 each randomly by computer generated random numbers who were posted for elective lower limb surgeries after obtaining ethical committee approval.

INCLUSION CRITERIA

1. Patients belonging to ASA grade I-II status posted for elective lower limb surgeries
2. Age group:18-60 years

EXCLUSION CRITERIA

1. The patient who did not give consent
2. ASA grade >II
3. H/o Allergy to local anesthetics or opioid
4. Emergency surgery
5. Any contraindication to subarachnoid block

Thorough preanesthetic check-up was done for all patients, details of procedure were explained to them and written informed consent was obtained. Patients were randomly allocated into two groups (n=30) by random computerized allotment. Study groups received:

GROUP I – 60mcg buprenorphine with 0.5% Isobaric Levobupivacaine

GROUP II– 45mcg buprenorphine with 0.5% Isobaric Levobupivacaine

Total volume of drug to be administered intrathecally was made up to 2.6 ml. The anaesthesiologist who was performing the procedure and the one who recoded the study parameters were unaware of group allocation and study drugs.

Patients were kept nil per oral from midnight onwards the day before surgery. They were given a premedication of T. Pantoprazole 40 mg and T. Alprazolam 0.5mg on the night before surgery and on the morning of surgery with sips of water. Intravenous lines was secured using 18G cannula. Patients were preloaded with 10ml/kg of Ringer lactate 15minutes prior to the subarachnoid block.Operating room was prepared and appropriate equipment for airway managements and emergency drugs were kept ready. Patients were shifted to the operating room, Non-invasive blood pressure monitor (NIBP), pulse oximeter and ECG were connected and baseline systolic and diastolic blood pressure, mean arterial pressure, pulse rate, respiratory rate and oxygen saturation were recorded. Under all available aseptic precautions patient in sitting position spinal anesthesia was administered with the study drug using 25G Quincke's needle at the L3-L4 interspace after confirming the free flow of CSF.

PARAMETERS RECORDED WERE AS FOLLOWS

1. Onset of sensory block and motor blockade.
2. Duration of analgesia
3. Haemodynamical changes (HR, SBP, DBP and MAP) and SpO2 was monitored: at baseline, 5 min, 15 min,30 min,45 min and 60 min.
4. VAS Score, Sedation score and other side effects (like postoperative nausea and vomiting, pruritis and urinary retention) were monitored at 1st hour,6th hour,12th and 24 hours and data were recoded.

SENSORY BLOCK

Onset of sensory block was assessed by the loss of sensation to pin prick. This assessment started immediately after turning the patient to supine position and continued every 2 min till loss of sensation to pinprick below at T10 level was noted after spinal anaesthesia.

MOTOR BLOCK

Motor block was assessed using Modified Bromage scale every 2 minutes after spinal anaesthesia.

Assessment of motor block was started immediately after turning the patient to supine position and continued every 2 minutes till a Modified Bromage score of 3 was achieved. The onset of motor block was defined as the time to achieve Modified Bromage score of 3 from the time of intrathecal injection.

DURATION OF ANALGESIA

The duration of effective analgesia was defined as the period from the onset of sensory block to the commencement of pain assessed by a VAS score of 4.

VAS SCORE

Pain was assessed by visual analogue scale (VAS 0= no pain, 10=worst pain imaginable). A VAS score of >4 was taken as the indication to give rescue analgesia of inj. Tramadol 100mg iv

SEDATION SCORE

Sedation score was assessed using a score of 1-6 using Ramsay sedation score. Any score of ≥4 was considered that the patient is sedated.

ADVERSE EVENTS

Side effects like nausea, vomiting, shivering, pruritus were recorded at 1st hour,6th hour,12th and 24 hours

post operatively.Nausea and vomiting was managed with Inj. Ondansetron 4mg intravenously. Pruritus was planned to be managed by inj. Dexamethasone 8 mg IV. Any other side effects like hypotension, bradycardia or fall in SPO2 were managed as done during intraoperative period. On completion of surgery, patients were shifted to recovery room where they were observed for 30 mins and than shifted to post anaesthesia care unit for further observation for 24 hrs.

STATISTICAL ANALYSIS

Quantitative data were analysed by using descriptive statistics Mean ±SD, whereas categorical variables were analysed by frequency percentage. As data were normally distributed parametric hypothesis testing was used. Independent sample t-test was used to find out the association of quantitative variables across the groups. Chi -square test was used to find the association of categorical variables within groups.The p-value <0.05 was considered as statistically significant. Data was analysed using statistical software IBM SPSS version 25.0.

RESULTS

The demographic variables in both our study groups such as age, gender, weight and height were analysed and was found to be comparable as the differences were statistically not significant (table 1).

Table 1: Demographic details among the study subjects

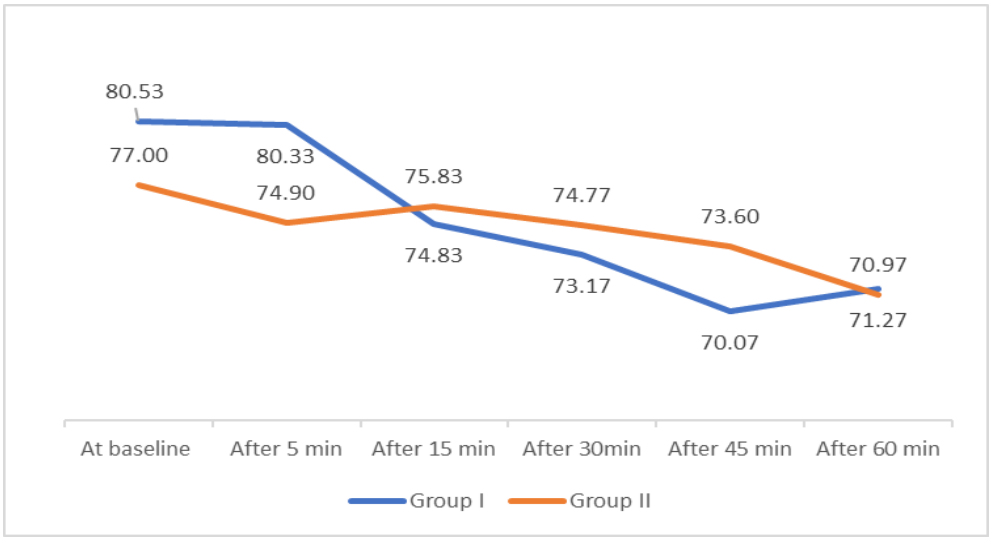
		Group I	Group II	P-Value
Age in completed years		47.67 ± 8.24	42.67 ± 11.17	0.053
Gender	Male	16 (53.33%)	17 (56.66 %)	1.000
	Female	14(46.66%)	13(43.33%)	
Weight		58.70 ±4.95	59.56 ±3.86	0.454
Height		164 .27 ±6.75	165.83±4.677	0.303
ASA GRADING				
ASA I		28(62.2%)	17(37.8%)	0.001
ASA II		2 (13.3%)	13(86.7%)	
Duration of surgery (in min)		112.50±33.03	133.67±35.86	0.021

In our study the mean time to onset of maximum sensory blockade in group I was 2.83±0.95 min and group II was 3.33±1.06 min. The p-value is 0.059. On analysis the mean time to onset of sensory block was not significant. Mean time to maximum motor blockade in group I was 4.03±1.83 min and group II was 4.23±0.43 min. The analysis showed it was statistically not significant (P value 0.569). Mean duration of analgesia for group I is 519±43.42 minutes and group II was 592.00 ± 67.13. The P-value is 0.000. This difference is statistically significant denoting that increasing the dose of Buprenorphine significantly increased the duration of analgesia (table 2).

Table 2: Onset of sensory and motor blockade, duration of analgesia (in min)

	GROUP I	GROUP II	p-value
Time to onset of maximum sensory blockade (in min)	2.83±0.95	3.33±1.06	0.059
Time to onset of maximum motor blockade (in min)	4.03±1.87	4.23±0.43	0.569
Duration of analgesia (in min)	519.00±43.42	592.00±67.13	0.000

Baseline heart rate and heart rate at 5 min, 15min, 30 min, 45 min and 60 mins (graph 1) were analyzed and compared within two groups. The variations in heart rate were found to be statistically insignificant in any time interval in our study except at 5 min though that was clinically insignificant.



Graph 1: Variation in heart rate (intraoperative)

In table 3; systolic blood pressure of two groups were studied and analyzed at time intervals of baseline, 5 min, 15 mins, 30 mins,45 mins and 60 mins. It was not significant throughout the study period. Similar results were revealed by diastolic blood pressure.

Table 3: Comparison of blood pressure between the groups

Systolic Blood Pressure	Group I	Group II	P-value
At baseline	69.46 ±5.99	69.30 ±6.76	0.782
After 5 min	76.73±14.49	72.667±4.70	0.157
After 15 min	71.33±7.61	72.47 ±4.972	0.500
After 30 min	71.00±5.97	66.80±7.01	0.015
After 45 min	71.63±4.53	64.77±11.10	0.003
After 60 min	68.53±6.62	66.80±6.57	0.313
Diastolic Blood Pressure			
At baseline	69.46 ±5.99	69.30 ±6.76	0.782
After 5 min	76.73±14.49	72.667±4.70	0.157
After 15 min	71.33±7.61	72.47 ±4.972	0.500
After 30 min	71.00±5.97	66.80±7.01	0.015
After 45 min	71.63±4.53	64.77±11.10	0.003
After 60 min	68.53±6.62	66.80±6.57	0.313

Variation in SPO_2 was analysed and it was found to be statistically insignificant at all time intervals (graph 2).

Graph 2: Variation in SPO_2

16% patients in group I had rigors. Hypotensive episode was seen in 6 % patient in group II but not in group I. 10% of patients in group I and 13% of patients in group II were sedated. But when the incidences of these adverse effects were analysed, the differences were not statistically significant (table 4).

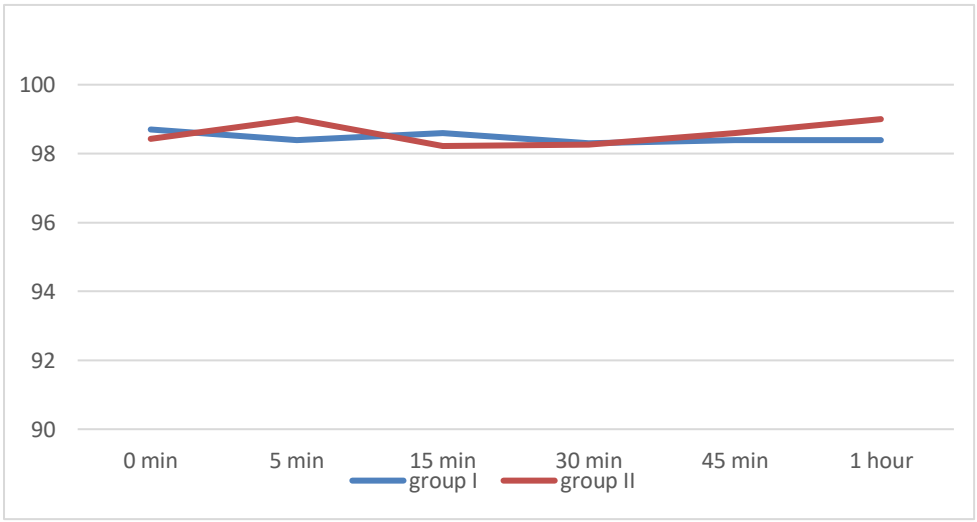


Table 4: Complications among the study subjects

Complications	Group I	Group II	P-VALUE
Hypotension	0	2(6.7%)	0.601
Sedation	3 (10%)	4(13.3%)	0.237
Rigor	5(16.7%)	0	1.00

DISCUSSION

This double blinded, prospective, randomized study of Intrathecal hyperbaric Bupivacaine with varying doses of Buprenorphine for postoperative analgesia after lower limb surgeries was conducted in IMS and SUM hospital with an aim to compare the effects of two doses of Buprenorphine GROUP I (45 mcg), GROUP II(60mcg) as an adjuvant to 0.5% isobaric Levobupivacaine for postoperative analgesia.

In our study, time to onset of sensory block in group I was 2.83±0.95 mins and group II was 3.33 ± 1.06 mins. The time difference in onset of sensory block between group I and II was 10%. With increased dosage, there was increased time to onset of sensory blockade. Our study correlated with Kamal Sonya et al [4] where sensory onset with 75 mcg Buprenorphine was 4.56+1.21mins. Similar study by Rasmi Pal et al [5], found sensory onset was achieved at 7.96+1.08 mins.

In patients of GROUP I onset time of motor block was 4.03 + 1.87 mins, GROUP II had 4.23 ± 0.43 mins where difference was statistically insignificant. On analysis it was seen that increase in dose of Buprenorphine was associated with prolonged time to onset of motor blockade. A satisfactory explanation could not be suggested for this phenomenon, however physiochemical properties like pKa of Buprenorphine and its interaction with pH of local anesthetic could be one of the reasons. So further studies and clinical trials are required. Our study was found to be similar with that of study done by Jagadish Chandra Mishra et al [6] where the time to onset of motor block was 9.12+3.908 mins with 150mcg dose of Buprenorphine. Hence the increase in dose of Buprenorphine was associated with prolonged time to onset of motor blockade. The time to onset of motor block achieved with 75 mcg of Buprenorphine was 4.56±0.93 mins in Rasmi pal et al [5] study which was similar to our study.Similarly study conducted by Ture et al[7] showed no significant difference in the onset of the sensory and motor blockade between the two groups.

In our study, duration of effective analgesia was increased in group II and was found to be statistically significant(p=0.00). On intergroup comparison of total duration of analgesia, between group I and II it was 14%. This suggests that a dose increase from 45mcgs to 60 mcgs increased the duration of analgesia significantly. Our study findings were substantiated by a study done by Capnoga et al[8] where 30 mcg had duration of analgesia for 8hrs, while patients who received 45 mcg had duration of analgesia of 7-12 hrs. In Naresh Bhukya et al [9] study, the duration of analgesia with 60mcg Buprenorphine along with 10 mg Bupivacaine was 6-10hrs (mean of 7.8hrs). The present study also coincides with studies of Usha Bafna et al [10], where 60mcg Buprenorphine with 0.75% ropivacaine, showed analgesic effect up to 8hrs 30 min.

Jagadish Chandra Mishra et al [6] used Intrathecal Buprenorphine 150mcg as an adjuvant to 0.5% Bupivacaine in vaginal hysterectomy and found an average duration of analgesia of 1027 minutes (17hrs). This difference may be due to difference in type of cases taken in both the studies. Our study included orthopaedic surgeries where as in, Jagadish Chandra Mishra et al, they included patients undergoing vaginal hysterectomy, with lesser surgical pain compared to orthopaedic procedures.

In this study, heart rates of baseline, 5 min,15min, 30 min,45 min and 60 mins were analysed and compared within two groups. The change in heart rates was statistically insignificant in any time interval in our study except at 5 min. But Bradycardia was not seen in any of the patients in both the group I and group II denoting the good hemodynamic stability and less cardiotoxic nature of Levobupivacaine.Our study was further supported by study done by Ture et al[7] where there was no report of bradycardia in buprenorphine and Levobupivacaine group. They concluded that the addition of buprenorphine to intrathecal Levobupivacaine produced similar onset of sensory block compared to racemic bupivacaine with buprenorphine but with better preserved haemodynamics in the former group.Our present study findings coincided with the findings of Naresh Bhukya et al [9] where variation of heart rates was insignificant.

It was seen that systolic change in blood pressure was not statistically significant in baseline, 5 min, 15 min, 30 mins,45mins and 60 min. And diastolic change in blood pressure was statistically insignificant in baseline, 5min, 15 min and 60 mins of surgery, clinically the blood pressure was adequate and bolus dose of vasopressors was required only for 2 episode of hypotension during the time of surgery in group II. This analysis on systolic and diastolic blood pressure shows the effect of the drug on hemodynamic variables. Decrease in blood pressure may also be due to sympathetic blockade in initial few mins. Similarly, in study of Kamal Sonya et al [4] with 75mcg of Buprenorphine along with Bupivacaine significant changes occurred in systolic and diastolic blood pressure and cases of hypotension was noted in first 10 mins, but was statistically insignificant.Our study is consistent with research conducted by Gulen G et al (2012) which compared the clinical effectiveness of Levobupivacaine and hyperbaric

Bupivacaine for spinal anesthesia (both administered Fentanyl 15mcg adjuvant) in the caesarian section. The results of that study showed that the incidence of hypotension, bradycardia, and nausea were less common in the isobaric Levobupivacaine group, and the need for ephedrine supplementation was higher in the hyperbaric Bupivacaine group. D'souza et al also reported that side effects such as nausea, bradycardia, and hypotension were more common in the hyperbaric Bupivacaine group than isobaric Levobupivacaine and isobaric Levobupivacaine + Fentanyl. From a review article by A Macleod in 2001, it is known that the toxicity of Levobupivacaine is lower than the toxicity of bupivacaine.

Although previous studies with Buprenorphine and Bupivacaine showed significant changes in hemodynamics our study with Levobupivacaine and Buprenorphine has proved to be hemodynamically stable.

LIMITATIONS

1. Vital parameters of each of the study group was taken up to 60 mins irrespective of the duration of surgery as hemodynamics of intra and post-operative was depended on the factors like amount of blood loss during the surgery which is likely to have effect on the outcome and cause bias.
2. The time of total analgesia was calculated for period of 24 hours only.
3. Cases taken for the study was lower limb orthopedics surgeries, so prior to time of surgical incision all patients were catheterized. As a result, side effect of urinary retention could not be ascertained in this study.
4. Level of sensory analgesia achieved and regression of motor block, were not studied as our main area study of interest was on post -operative analgesic requirement.

CONCLUSION

Buprenorphine at a dose of 60 mcg in comparison to a dose of 45 mcg when added as adjuvant to isobaric Levobupivacaine for spinal subarachnoid block for lower limb surgeries produces longer duration of postoperative analgesia without much significant adverse effects.

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