Section: Critical Care Medicine

Original Research Article

EFFECT OF DIFFERENT DOSES OF INTRATHECAL BUTORPHANOL AS AN ADJUVANT TO BUPIVACAINE IN ELECTIVE LOWER LIMB ORTHOPEDIC SURGERIES: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND STUDY

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ABSTRACT

Background: The use of intrathecal opioids is a widely accepted technique for providing effective postoperative pain relief. The aim of the present study was to compare the effect of 3 doses of intrathecal Butorphanol (100mcg, 200mcg and 300mcg) with Bupivacaine in patients posted for elective lower limb orthopedic surgeries. **Materials and Methods:** This randomized double blind controlled study was conducted at IMS and SUM Hospital from July 2021 to July 2022 on 135 patients. Patients were randomly allocated into three groups (n=45): Group A: Patients receiving 15mg of 0.5% bupivacaine heavy plus 100 mcg butorphanol., Group B: Patients receiving 15mg of 0.5% bupivacaine heavy plus 200 mcg of butorphanol, Group C: Patients receiving 15mg of 0.5% bupivacaine heavy plus 300 mcg of butorphanol. Parameters, side effects were recorded. A p-value < 0.05 indicated statistical significance, and data analysis was performed using SPSS version 25.0. **Results:** Our study found a statistically significant increase in postoperative analgesia duration with increasing doses of butorphanol, indicating a dose-dependent effect. Patients in all groups remained hemodynamically stable, with no significant episodes of bradycardia or hypotension. Side effects were minimal, with no significant differences between groups, and no respiratory depression or oxygen desaturation was observed. **Conclusion:** Butorphanol at a dose of 300 mcg in comparison to a dose of 100mcg and 200mcg when added as spinal adjuvant to hyperbaric 0.5% Bupivacaine for spinal central neuraxial block for lower limb orthopedic surgeries produces longer duration of postoperative analgesia without much significant adverse effects.

INTRODUCTION

Spinal anaesthesia is the most popular and effective regional anaesthetic technique used for lower limb surgeries. Various local anaesthetics commonly used for spinal anaesthesia are lignocaine, bupivacaine, levobupivacaine and ropivacaine.[1,2] Usage of opioids in conjunction with local anesthetic for spinal anesthesia has been associated with decreased pain scores and reduced analgesic requirement in the post-operative period.[3,4] Opioids have been found to prolong anaesthesia and analgesia, have been seen to improve the quality of analgesia and provide haemodynamic stability. Opioid and local anaesthetic eliminate pain by acting at two different sites. Local anaesthetics act at axon level and opioids act on the receptors present on spine.[3-5] Butorphanol is a lipophilic opioid and has been used safely as an intrathecal agent. Cephalic spread of Butorphanol is slow due to its large molecular weight and lipophilic nature. It acts by opening potassium channels and decreasing influx of calcium which results in inhibition of transmitter release. Butorphanol is a partial agonist and antagonist at μ receptors.[6] It is also a competitive antagonist and partial agonist at κ opioid receptors. Butorphanol has been widely studied in the dose of 250 μg for its intrathecal use and found to be safe and effective.[7] The most popular local anaesthetic for subarachnoid block, bupivacaine, has high potency, delayed onset of action, and a comparatively shorter duration of postoperative analgesic effect with dose ranging from 12 to 15 mg. It acts via binding intracellularly to voltage-gated sodium channels and thus blocking

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sodium influx into neurons and preventing depolarisation and subsequent initiation or propagation of a pain signal. Its systemic absorption is dependent on dosage and route of administration.[8,9] Due to its shorter duration action, various adjuvants have been added to local anaesthetics which helps to decrease the dose of local anaesthetics, improves quality and prolongs the duration of subarachnoid block with decreased toxicity and related complications.[10-12] The aim of the present study was to compare the effect of 3 doses of intrathecal Butorphanol (100mcg, 200mcg and 300mcg) with Bupivacaine in patients posted for elective lower limb orthopedic surgeries.

MATERIALS AND METHODS

This randomized double blind controlled study was conducted at IMS and SUM Hospital from July 2021 to July 2022 on 135 patients who were posted for elective lower limb orthopedic surgeries after obtaining ethical committee approval. Patients undergoing elective lower limb orthopedic surgeries, patients who come under ASA PS I and II, patients of BMI <<35 kg/m2, age group between 18-60 years were included in the study. Patients who come under ASA PS III and IV, very long duration lower limb orthopedic surgeries where epidural analgesia was also being utilized, age below 18yrs and age more than 60 years, patients who have a known allergic reaction history towards local anesthetic agents and coagulation disorders, spine deformities and skin infections at the site of block administration, patient with an history of opioid addiction and drug abuse, patient who were not willing to give consent for the study were excluded from the study. A routine and a thorough preanesthesia check-up was done for all patients who were undergoing the procedure, details of procedure was explained to them and written informed consent was obtained from all the patients. Patients were randomly allocated into three groups (n=45) by random generated computerized allotment. Study groups received:

- Group A: Patients receiving 15mg of 0.5% bupivacaine heavy plus 100 mcg butorphanol.
- Group B: Patients receiving 15mg of 0.5% bupivacaine heavy plus 200 mcg of butorphanol.
- Group C: Patients receiving 15mg of 0.5% bupivacaine heavy plus 300 mcg of butorphanol.

Total volume of drug to be administered intrathecally was made up to 3.5 ml using normal saline for injection. The patient and the one who recoded the study parameters were unaware of group allocation and study drugs. Patients were kept nil per oral for atleast 6 hours before the surgery. Patients were on premedication. Intravenous lines access was secured with 18G cannula. Patients were preloaded with 10ml/kg of Ringer lactate IV fluid over 10 min before the patient were given spinal sub arachnoid block. Patients were shifted to the operating room, Non-invasive blood pressure monitor (NIBP), pulse oximeter and ECG were connected and baseline vitals were recorded. Under all available aseptic precautions patient in left lateral position spinal anesthesia was administered with the study drug allocated by the patient using 25G Quincke's needle at the L3-L4 interspace after confirming the free flow of CSF and ensuring negative aspiration of blood. Parameters recorded were as follows: Onset of sensory block and motor blockade, Peak sensory and motor block, effective post op analgesia duration, Intraop patient heart rate, mean arterial blood pressure, Saturation was being monitored at various time intervals of 0min, 5mins, 10mins, 15mins, 30mins, 60mins and 90mins, Patient were monitored for common side effects.

Statistical Analysis: The study used descriptive statistics (mean ± SD) for quantitative variables and frequency percentages for categorical variables. ANOVA tested associations among groups for quantitative variables, while independent sample t-tests compared continuous variables between pairs of groups. Chi-square tests assessed associations for categorical variables. A p-value < 0.05 indicated statistical significance, and data analysis was performed using SPSS version 25.0.

RESULTS

Age, gender and ASA Scoring were found to be comparable as the differences were statistically not significant.

The baseline vitals among the 3 groups were comparable with there being no statistical significance within all the 3 groups in the study population (p>0.05).

The comparison of mean onset times for sensory block among the three groups showed no statistically significant difference (p-value = 0.076).The comparison of mean onset times for motor block among the groups showed no statistically significant difference (p-value = 0.120).

The study found no statistically significant differences among the groups in terms of time to peak sensory block, maximum motor block, and two-segment regression time with p-values indicating insignificant differences (p=0.492, p=0.176, and p=0.154 respectively). These results suggest comparable outcomes across the groups.

Heart rates were compared among the three study groups at various time intervals and found to be comparable, with no statistically significant differences.

Mean arterial blood pressure was analyzed at various time intervals (and found to be statistically insignificant across the three study groups throughout the procedure.

Intra op variations in the Saturation (Spo2) was noted in all the three study groups and was found to be statistically insignificant at all the time intervals.

Group C showed a significantly longer duration of postoperative analgesia (389.18 minutes) compared

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to Group A (278.02 minutes) and Group B (337.09 minutes), indicating a dose-dependent increase in analgesic effect with higher doses of butorphanol ($p<0.001$).

The incidence of side effects was low and comparable across the groups. The majority of patients (80.9-95.6%) did not experience any side effects. Statistical analysis showed that the differences in adverse effects among the groups were not significant.

Table 1: Demographic Variables

		Group A	Group B	Group C	Group A vs B	Group A vs C	Group B vs C	Group A vs B vs C
AGE		43.35±11.58	42.89±10.60	42.73±12.70	0.844	0.810	0.951	0.966
SEX	Male	27 (60.0%)	28 (62.2%)	31 (68.9%)	0.631	0.312	0.600	0.600
	Female	18 (40.0%)	17 (37.8%)	14 (31.1%)				
ASA	I	31 (68.9%)	32 (71.1%)	31 (68.9%)	0.581	0.878	0.691	0.852
	II	14 (31.1%)	13 (28.9%)	14 (31.1%)				

Table 2: Baseline Vitals

	Group A	Group B	Group C	Group A vs B vs C
MAP (Baseline)	93.30±7.24	92.30±8.04	94.49±8.52	0.430
HR (Baseline)	81.52±11.52	86.61±11.63	81.73±13.17	0.085
SpO2 (Baseline)	99.50±1.01	99.55±0.85	99.27±1.07	0.356

Table 3: Onset of Sensory and Motor Blockade

	Group A	Group B	Group C	Group A vs B vs C
Time to Sensory onset (in sec)	34.56±7.14	32.07±6.85	31.07±7.16	0.076
Time to Motor onset (in sec)	68.82±10.58	64.84±8.86	65.27±10.43	0.120

Table 4: Variation in Heart Rate (Intraoperative)

	Group A	Group B	Group C	Group A Vs B Vs C
At 0 min	81.24±11.35	86.96±11.60	81.73±13.17	0.079
At 5 min	81.16±11.16	86.62±11.13	81.58±12.48	0.091
At 10 min	81.87±10.65	86.44±10.96	81.76±12.14	0.083
At 15 min	81.56±10.33	86.16±9.83	81.91±12.18	0.085
At 30 min	80.11±10.12	84.49±9.27	80.76±11.62	0.101
At 60 min	79.27±9.93	83.58±9.40	79.58±11.47	0.090
At 90 min	79.53±9.91	83.36±9.32	79.73±11.06	0.135

Table 5: Variation in Mean Arterial Blood Pressure (In mmhg)

	Group A	Group B	Group C	Group A vs B vs C
At 0 min	91.91±6.17	92.47±8.67	93.91±7.21	0.421
At 5 min	89.71±6.38	90.76±8.41	92.27±7.35	0.263
At 10 min	88.60±6.83	89.22±8.55	90.58±7.22	0.450
At 15 min	87.71±6.97	88.13±8.11	89.09±6.97	0.663
At 30 min	87.07±6.09	86.96±7.54	87.76±7.15	0.840
At 60 min	86.44±5.63	87.02±7.46	86.18±14.04	0.915
At 90 min	87.62±5.59	88.27±6.81	89.38±7.09	0.437

Table 6: Variation in Spo2

	Group A	Group B	Group C	Group A vs B vs C
At 0 min	98.49±1.1	97.50±0.82	97.21±1.0	0.246
At 5 min	98.69±1.0	98.51±0.81	98.22±1.0	0.326
At 10 min	98.59±1.0	98.52±0.86	97.26±1.0	0.226
At 15 min	97.79±1.0	97.53±0.85	98.30±1.0	0.236
At 30 min	98.59±1.0	96.54±0.86	99.29±1.0	0.244
At 60 min	97.69±1.0	97.53±0.87	98.31±1.0	0.221
At 90 min	98.19±1.0	98.52±0.87	99.32±1.0	0.231

Table 7: Effective Post Op Analgesia

	Group A	Group B	Group C	Group A vs B vs C
Time to Rescue Analgesia (in min)	278.02±7.75	337.09±7.31	389.18±6.80	<0.001

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Table 8: Adverse Effects

	Group A	Group B	Group C	Group A vs B vs C
Nausea	5 (11.1%)	1 (2.2%)	5 (11.1%)	0.144
Vomiting	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Itching	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Constipation	0 (0.0%)	1 (2.2%)	3 (6.7%)	
RS Depression	0 (0.0%)	0 (0.0%)	0 (0.0%)	
No side effects	40 (80.9%)	43 (95.6%)	37 (82.2%)	

DISCUSSION

The study found similar onset and peak times for sensory block across the three groups, with no statistically significant differences. Onset times ranged from 32.07 to 34.56 seconds, and peak sensory blockade times were around 3 minutes for all groups, indicating comparable effects despite varying dosages. Our study's peak sensory onset time was comparable to Sandip Roy et al,[13] who reported 3.15±0.25 minutes with 250 mcg of butorphanol. In contrast, Vinita Singh et al14. reported a longer peak sensory onset time of 7.2±1.8 minutes with 25 mcg of butorphanol.

The study found that the onset and peak times of motor block were comparable across the three groups. The onset times were approximately 65-69 seconds, while peak motor block times were around 4.25-4.29 minutes. Statistical analysis revealed no significant differences between the groups, indicating that increasing the dose of butorphanol did not significantly impact the onset or peak time of motor block. The results suggest that the effects of the different dosages on motor block timing were similar across the groups. Our study's findings on motor block onset time are comparable to those of Sandip Roy et al,[13] who reported 5.27±0.32 minutes with 250 mcg of butorphanol as an adjuvant to hyperbaric bupivacaine.

The study found a significant increase in the duration of effective analgesia with increasing doses of butorphanol. Group A (100mcg) had approximately 5 hours of analgesia, Group B (200mcg) had around 6 hours, and Group C (300mcg) had about 7 hours. The differences between groups were statistically significant ($p<0.001$), with a 12% increase in duration of analgesia between each group, indicating a dose-dependent effect. Our findings align with study by Sandip Roy et al,[13] which demonstrated a significant increase in postoperative analgesia duration with higher doses of butorphanol (250 mcg vs 25 mcg) as an adjuvant to spinal blockade, suggesting a dose-dependent effect.

The study found no statistically significant changes in heart rate among the three groups at various time intervals. Additionally, no cases of bradycardia (heart rate <50/min) were reported, and thus no atropine administration was required. This finding is consistent with study by Sandip Roy et al,[13] that also observed good cardiac stability with intrathecal butorphanol and hyperbaric bupivacaine, with no significant reduction in heart rate during surgery. Our study's findings on heart rate variation are consistent with Gupta et al,[15] who also reported insignificant changes in heart rate during the intraoperative period when intrathecal butorphanol was used as an adjuvant for lower limb orthopedic surgeries.

The study found no statistically significant differences in mean arterial blood pressure (MAP) among the three groups at various time intervals. Hypotension was defined as a 15% decrease from baseline or MAP <65 mmHg, which would be treated with ephedrine 6mg IV. However, the study does not report the occurrence of hypotension requiring ephedrine administration. The stable MAP suggests that the drug had a minimal impact on hemodynamic variables, aside from potential effects of sympathetic blockade. Our findings are consistent with Gupta et al,[15] who reported a drop in systolic, diastolic, and mean arterial blood pressure in the initial 10 minutes with 25mcg of butorphanol and hyperbaric bupivacaine, although the changes were statistically insignificant.

The study found no statistically significant differences in oxygen saturation among the three groups at various time intervals. Oxygen saturation remained high, ranging from 97-99%, and no patients experienced respiratory depression (SpO2 <90%) or required supplemental oxygen. This suggests that the different doses of butorphanol did not impact oxygen saturation, maintaining stable respiratory function intraoperatively and postoperatively. Studies by Sandip Roy et al,[13] and Gupta et al,[15] using higher doses of butorphanol (250 mcg and 200 mcg), reported no significant drop-in respiratory rate or oxygen saturation, and no instances of respiratory depression were noted.

The study found that nausea occurred in a few patients across the groups, but the differences were statistically insignificant. No other adverse effects like vomiting, pruritis, or respiratory depression were noted. The affected patients with nausea were treated with ondansetron, and the overall incidence of side effects was low. The study suggests that butorphanol is well-tolerated, with no significant differences in adverse effects among the groups.

The study has limitations, including a short 90-minute monitoring period that may not capture full hemodynamic changes, limited postoperative analgesia assessment, and catheterization of patients which prevents evaluation of urinary retention as a potential side effect.

CONCLUSION

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Butorphanol at a dose of 300 mcg in comparison to a dose of 100mcg and 200mcg when added as spinal adjuvant to hyperbaric 0.5% Bupivacaine for spinal central neuraxial block for lower limb orthopedic surgeries produces longer duration of postoperative analgesia without much significant adverse effects.

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