Section: Anesthesiology

Original Research Article

EFFECTIVENESS OF INTRATHECAL BUPRENORPHINE VERSUS BUTORPHANOL AS ADJUVANT ON 0.5% LEVOBUPIVACAINE IN LOWER LIMB SURGERIES

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ABSTRACT

Background: Opioid related side effects is more with pure mu receptors agonists than partial mu receptor agonist antagonists. Previously there were studies between pure opioid agonists and partial opioid agonist antagonists. So in this study we compare the efficacy beetween both partial agonist antagonists opioid which was very less studied.

Methods and Results: Patients in group A, group B, group C received 2.8 ml of 0.5% hyperbaric levobupivacaine with 0.2 ml (60 mcg) Buprenorphine in group A, with 0.2 ml (200 mcg) butorphanol in group B, 0.2 ml of preservative free normal saline in group C, each group with total of 3 ml given intrathecally. The time for two-segment regression in sensory block was also significantly prolonged in Group A (2.6±0.5 hours) compared to Group B (0.7±0.3 hours) and Group C (0.4±0.2 hours) ($p < 0.001$). The time to achieve from Bromage grade 3 to 0 was also longer in Group A (8±0.8 hours) compared to Group B (4.1±0.7 hours) and Group C (3±0.6 hours) ($p < 0.001$). The duration before rescue analgesia was needed was significantly prolonged in Group A (8.8±0.8 hours) compared to Group B (4.9±0.9 hours) and Group C (3.6±0.5 hours) ($p < 0.001$).

Conclusion: Buprenorphine provides superior analgesia with extended pain relief and reduced postoperative opioid requirements, whereas butorphanol facilitates faster recovery and earlier ambulation. The choice of adjuvant should be tailored to the patient's surgical needs and recovery goals to optimize perioperative pain management.

Keywords: Buprenorphine, Butorphanol, Levobupivacaine, Spinal Anaesthesia.

INTRODUCTION

Subarachnoid block with hyperbaric local anaesthetics (bupivacaine, levo bupivacaine, Ropivacaine), is the method of choice for lower limb orthopaedic Surgeries. Opioids were used as adjuvants to increase efficacy of local anaesthetics during intra operative and post operative period in spinal anesthesia. Previously there were studies comparing in between pure agonists such as (Morphine, Fentanyl) and partial agonist antagonists (Buprenorphine, Butorphanol). In our study we were comparing efficacy between Buprenorphine and Butorphanol which are both partial agonist antagonist. Gehling and Tryba perform a metaanalysis among twenty-eight studies and found that intrathecal use of lower dose (<0.3 mg) morphine causes nausea, vomiting and lower risk ratio of pruritus and higher dose (>0.3 mg) morphine causes respiratory depression, higher risk ratio of pruritus.[1] Due to these side effects we decided to use only partial agonist antagonists intrathecally and compare the efficacy between buprenorphine and butorphanol as adjuvants with hyperbaric local anesthetics in spinal anaesthesia. Proper intraoperative and postoperative analgesia is the primary goal of spinal anesthesia and if this is fulfilled by partial agonist antagonist opioid with less side effects than it is acceptable. The hypothesis of this study is that intrathecal buprenorphine, when used as an adjuvant to 0.5% heavy levobupivacaine, will provide superior analgesia and a longer duration of pain relief

compared to butorphanol, with a similar or reduced incidence of side effects.

MATERIALS AND METHODS

Study Procedure

This prospective, randomized, double blind study was conducted after approval from the institutional ethics committee (IEC/IMS.SH/SOA/2024/782) and CTRI number CTRI/2024/10/076067). Informed written consent of patients was taken. A study of 105 patients, aged 18-60 years, belonging to ASA physical status 1 or 2 and scheduled for elective lower limb orthopedic surgeries was randomized into three groups using random numbers generated by the computer. Patients in group A (Gp A) received 2.8 ml of 0.5% hyperbaric levobupivacaine with 0.2 ml (containing 60 mcg) buprenorphine, a total volume of 3 ml intrathecally. Similarly, 0.2 ml (200 mcg) of butorphanol was added to 2.8 ml of 0.5% hyperbaric levobupivacaine to make a total volume of 3 ml to be given intrathecally to patients in group B (Gp B) and Group C (Gp C) received 0.5% heavy levobupivacaine with preservative free NS 0.2 ml to make total volume of 3ml.

Patients in whom spinal anaesthesia or the study drugs are contraindicated were excluded from the study that was those with ASA Physical status >2 or a history of opioid dependence, coagulation disorder, any Neurological condition and patient refusal are excluded from the study.

Patients with adequate nil per oral status, an intravenous line was established and 500 ml ringer lactate as preload was given. The intrathecal drugs were prepared by a trained pharmacist beforehand to maintain the blinding process. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR) and peripheral arterial oxygen saturation (SpO2) were recorded for all subjects. The primary investigator was blinded to the patient allocation. All spinal blocks were given by the same anaesthesiologist. Subarachnoid block was performed under strict aseptic conditions in the sitting position at the level of L 3-4 inter vertebral space using 25 G Quincke's spinal needles. The test drug was injected over 15 seconds. Following the subarachnoid block, the patient was put in supine position.

Intraoperatively, HR, SBP, DBP, RR and SpO2 were recorded at 3 minutes intervals for the first 30 min from the time of injection of spinal solution and there after every 15 min for the complete period of surgery. This data was recorded by the attending anaesthesiologist and the primary investigator, who were unaware of the patient allocation. Hypotension (MAP <60 mmHg) was treated with fluid boluses and 6 mg intravenous (IV) boluses of ephedrine, while bradycardia (HR <50bpm) was treated with 0.6 mg IV atropine. All patients were given supplemental O2 via face mask at 6 l/min if the SpO2 decreased below 95%.

The highest level (T10) of sensory block and the time taken to attain it from the time of the intrathecal injection was recorded. Further sensory testing was performed during inra and post operative period at 20-min intervals till the recovery of S2 dermatome. Motor block was assessed using the modified Bromage scale (grade 0 = no motor block; grade 1 = inability to raise extended legs, able to move knees and feet; grade 2 = inability to raise extended leg and move knee, able to move feet and grade 3 = complete motor block of the lower limbs) till achievement of the highest sensory level; at the end of the surgery and then at 30 min intervals till the patient had no motor blockade.

Side effects such as hypotension, bradycardia, nausea, vomiting, sedation, pruritis, shivering and respiratory depression were recorded. The time to voiding was also be recorded. The quality of postoperative analgesia was assessed using LVAS (linear visual analogue scale) at 15 min, 30 min and thereafter every 30 min, till 2 hours postoperatively; and then every hour, till 4 hours postoperative duration. the linear visual analogue scale (LVAS) scoring system for pain during the pre-anaesthetic check-up. The LVAS used is a 11-cm line where 0 denote “no pain” while 10 denote “worst pain imaginable”.

The time of first request of rescue analgesia was recorded. Patients reporting an LVAS score of ≥4 were treated with inj TRAMADOL 100mg IV, as rescue analgesic and Inj PARACETAMOL 1gm IV TDS was administered irrespective of LVAS.

Statistical Analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean ±standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square ($\chi 2$) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript “c” are the degrees of freedom. “O” is observed value and E is expected value. C= (number of rows-1)*(number of columns-1)

The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

The t statistic to test whether the means are different can be calculated as follows:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{{s_1}^2}{n_1} + \frac{{s_2}^2}{n_2}}}$$

where $\bar{x}_1$ = mean of sample 1

$\bar{x}_2$ = mean of sample 2

n_1 = number of subjects in sample 1

n_2 = number of subjects in sample 2

s_1^2 = variance of sample 1 = $\frac{\Sigma(x_1 - \bar{x}_1)^2}{n_1}$

s_2^2 = variance of sample 2 = $\frac{\Sigma(x_2 - \bar{x}_2)^2}{n_2}$

The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance.

ANOVA

Source	d.f.	SS	MS	F
Treatment	$a-1$	SS_{treat}	$\frac{SS_{treat}}{a-1}$	$\frac{MS_{treat}}{MS_{error(a)}}$
Error (a)	$N-a$	$SS_{error(a)}$	$\frac{SS_{error(a)}}{N-a}$	
Time	$t-1$	SS_{time}	$\frac{SS_{time}}{t-1}$	$\frac{MS_{time}}{MS_{error(b)}}$
Treat x Time	$(a-1)(t-1)$	$SS_{treat\ x\ time}$	$\frac{SS_{treat\ x\ time}}{(a-1)(t-1)}$	$\frac{MS_{treat\ x\ time}}{MS_{error(b)}}$
Error (b)	$(N-a)(t-1)$	$SS_{error(b)}$	$\frac{SS_{error(b)}}{(N-a)(t-1)}$	
Total	$Nt-1$	SS_{total}		

The sources of the variation include treatment; Error (a); the effect of Time; the interaction between time and treatment; and Error (b). Error (a) is the effect of subjects within treatments and Error (b) is the individual error in the model. All these add up to the total.

If the p-value was < 0.05, then the results were statistically significant otherwise it was considered as not statistically significant. Data were analysed using SPSS software v.23(IBM Statistics, Chicago, USA) and Microsoft office 365.

RESULTS

There was no statistically significant difference among the three groups in terms of age (p = 0.399) and weight (p = 0.176) both of which are continuous variables expressed as mean ± standard deviation (SD). The sex distribution was also comparable across groups (p = 0.315) which is a categorical variable, with statistical measures used are frequency and percentage. ASA grade distribution showed a non-significant difference (p = 0.137), indicating a homogenous population, it is a continuous variable with percentage and frequency used as statistical measures. Throughout the intraoperative period, all groups maintained stable heart rate, blood pressure, and oxygen saturation, indicating that the addition of buprenorphine or butorphanol did not lead to significant hemodynamic compromise.

However, intraoperative SBP, DBP, and MAP showed statistically significant differences at later intervals, with Group C exhibiting slightly higher fluctuations. This suggests that opioid adjuvants may provide additional cardiovascular stability by reducing sympathetic responses to surgical stimuli.

Sensory and Motor Blockade

Onset and Duration of Sensory Blockade: Group A had the longest time to achieve the highest sensory blockade (8.3±1.5 min), followed by Group B (4.1±1 min) and Group C (3.6±0.8 min), with a statistically significant difference (p < 0.001). The time for two-segment regression was also significantly prolonged in Group A (2.6±0.5 hours) compared to Group B (0.7±0.3 hours) and Group C (0.4±0.2 hours) (p < 0.001).

Motor Blockade: The time to achieve Bromage grade 3 was significantly prolonged in Group A (7.7±1.2 min) compared to Group B (5.4±1.4 min) and Group C (4.2±0.8 min) (p < 0.001). The duration until recovery to Bromage grade 0 was also longer in Group A (8±0.8 hours) compared to Group B (4.1±0.7 hours) and Group C (3±0.6 hours) (p < 0.001).

Motor and sensory blockade between the groups is continuous variable with mean ± SD, pairwise intergroup comparison (p-values) used as statistical measures.

Analgesia Duration and Rescue Analgesic Requirement

The duration before rescue analgesia was needed was significantly prolonged in Group A (8.8±0.8 hours) compared to Group B (4.9±0.9 hours) and Group C (3.6±0.5 hours) (p < 0.001).

The requirement for additional tramadol doses was significantly lower in Group A, where 60% of patients required only one dose compared to 80% in Group B and 100% in Group C requiring multiple doses (p < 0.001).

Total analgesia dose required between study group are categorical variables with frequency and percentage used as statistical measures.

Pain Assessment (VAS Score)

VAS scores were significantly lower in Group A during the postoperative period, particularly at 60 minutes (p < 0.001), 120 minutes (p < 0.001), 4 hours (p < 0.001), and 8 hours (p = 0.001). Group B also had lower VAS scores compared to Group C, but Group A showed the most prolonged analgesic effect. Distribution of VAS (visual analogue scale for pain) is continuous variable with mean ± SD, pairwise Intergroup Comparison (p-values) used as statistical measures.

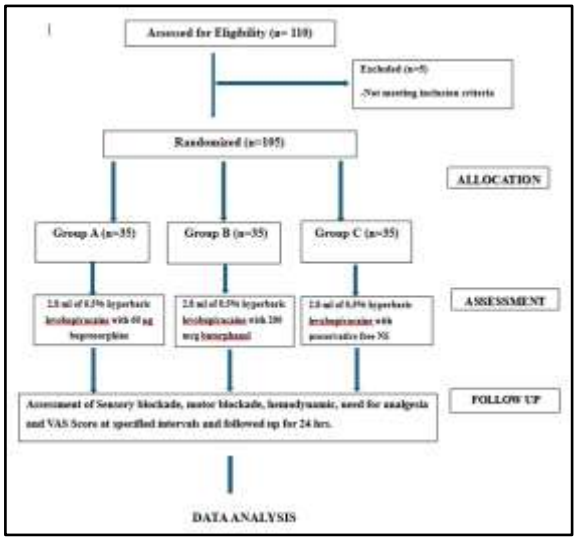

Figure 1: Consert Flow Diagram

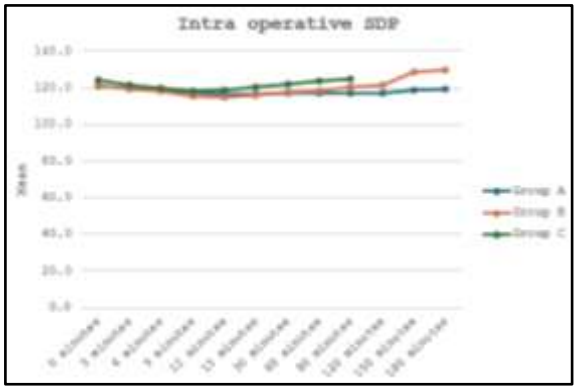

Figure 2: Intraoperative SBP between study groups

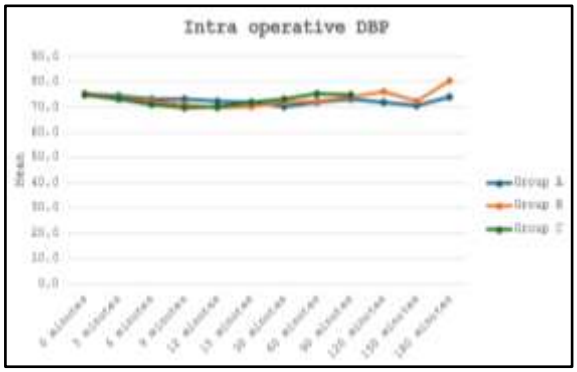

Figure 3: Intraoperative DBP between study groups

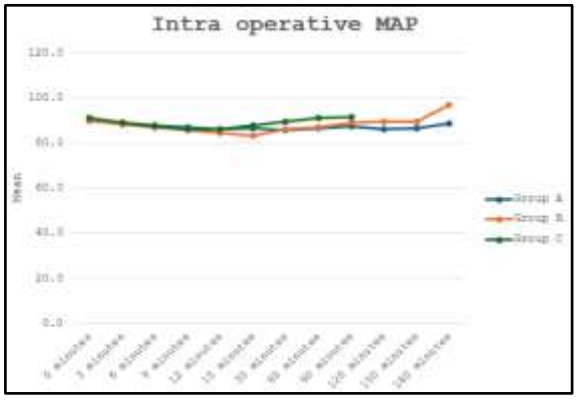

Figure 4: Intraoperative MAP between study groups

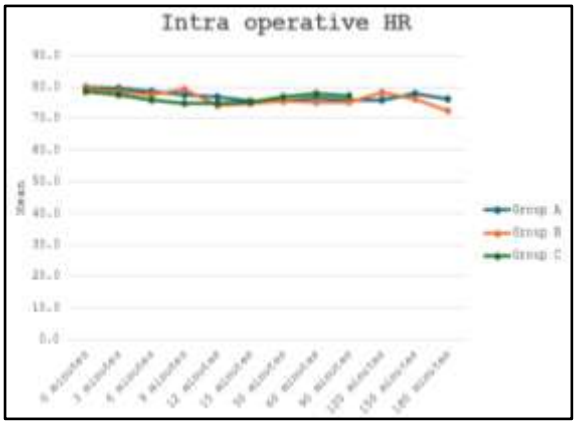

Figure 5: Intraoperative HR between study groups

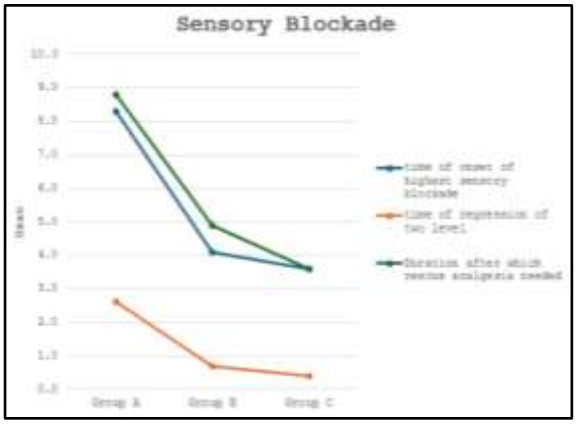

Figure 6: Sensory blockade between study groups

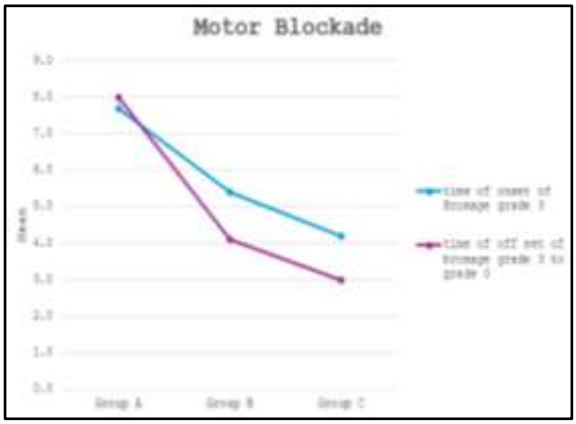

Figure 7: Motor blockade between study groups

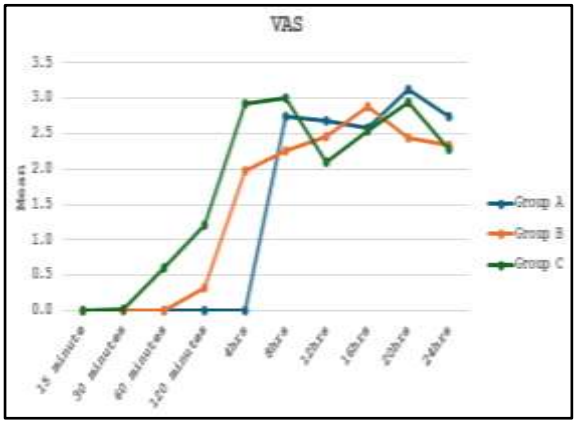

Figure 8: Distribution of VAS between study groups

Table 1: Demographic profile of group Buprenorphine, group Butorphanol and control group

Parameters	Group A	Group B	Group C	p value
Age (yrs)(mean±SD)	35.9±13.4	39.7±12.5	37.6±9.4	0.399
Weight (kg)(mean±SD)	61.5±9.4	58.9±9	58.4±9.3	0.176
Sex (male : female) (%)	65.7%/34.3%	71.4%/28.6%	54.3%/45.7%	0.315
ASA (Gr 1/2) (%)	65.7%/34.3%	42.9%/57.1%	48.6%/51.4%	0.137
Duration of surgery (mean±SD)	1.8±0.6	1.8±0.5	1.6±0.2	0.811

Table 2: Sensory Blockade between Study Groups

Sensory Blockade	Group A	Group B	Group C	p value	Intergroup p value		
					Group AB	Group BC	Group AC
Time of onset of highest sensory blockade in minutes	8.3±1.5	4.1±1	3.6±0.8	<0.001*	<0.001*	<0.001*	<0.001*
Time of regression of two level in Hours	2.6±0.5	0.7±0.3	0.4±0.2	<0.001*	<0.001*	<0.001*	<0.001*
Duration after which rescue analgesia needed in Hours	8.8±0.8	4.9±0.9	3.6±0.5	<0.001*	<0.001*	<0.001*	<0.001*

Note: p value significant at 5% level of significance (p<0.05)*

Table 3: Pairwise Intergroup Comparison

Sensory Blockade	p value between		
	Group A & B	Group B & C	Group A & C
Time of onset of highest sensory blockade	<0.001*	<0.001*	<0.001*
Time of regression of two level	<0.001*	<0.001*	<0.001*
Duration after which rescue analgesia needed	<0.001*	<0.001*	<0.001*

Note: p value significant at 5% level of significance (p<0.05)*

Table 4: Total analgesia dose required between Study Groups

Total analgesia dose required (Inj. TRAMADOL 100mg IV)	Group A		Group B		Group C		p value
	N	%	N	%	N	%	
1	21	60.00%	0	0.00%	0	0.00%	<0.001*
2	14	40.00%	7	20.00%	0	0.00%	
3	0	0.00%	28	80.00%	18	51.40%	
4	0	0.00%	0	0.00%	17	48.60%	
Total	35	100.00%	35	100.00%	35	100.00%	

Note: p value significant at 5% level of significance (p<0.05)*

Table 5: Motor blockade between study groups

Motor Blockade	Group A	Group B	Group C	p value	Intergroup p value		
					Group AB	Group BC	Group AC
Time of onset of Bromage grade 3	7.7±1.2	5.4±1.4	4.2±0.8	<0.001*	<0.001*	<0.001*	<0.001*
Time of off set of Bromage grade 3 to grade 0	8±0.8	4.1±0.7	3±0.6	<0.001*	<0.001*	<0.001*	<0.001*

Note: p value significant at 5% level of significance (p<0.05)*

Table 6: Pairwise Intergroup Comparison

Motor Blockade	p value between		
	Group A & B	Group B & C	Group A & C
Time of onset of Bromage grade 3	<0.001*	<0.001*	<0.001*
Time of off set of Bromage grade 3 to grade 0	<0.001*	<0.001*	<0.001*

Note: p value significant at 5% level of significance (p<0.05)*

Table 7: Distribution of VAS between Study Groups

VAS score	Group A	Group B	Group C	p value
15 minutes	0±0	0±0	0±0	-
30 minutes	0±0	0±0	0±0.2	0.371
60 minutes	0±0	0±0	0.6±0.7	<0.001*
120 minutes	0±0	0.3±0.5	1.2±0.4	<0.001*
4hrs	0±0	2±1.4	2.9±1	<0.001*
8hrs	2.7±1.2	2.3±0.7	3±0	0.001*
12hrs	2.7±0.5	2.5±1	2.1±0.3	0.001*
16hrs	2.6±0.7	2.9±0.9	2.5±0.6	0.116
20hrs	3.1±0.7	2.4±0.8	2.9±0.2	<0.001*
24hrs	2.7±0.4	2.3±1	2.3±0.5	0.012*

Note: p value significant at 5% level of significance (p<0.05)*

Table 8: Pairwise Intergroup Comparison

VAS	p value between		
	Group A & B	Group B & C	Group A & C
15 minutes	-	-	-
30 minutes	-	0.441	0.441
60 minutes	-	<0.001*	<0.001*
120 minutes	0.001*	<0.001*	<0.001*
4hrs	<0.001*	<0.001*	<0.001*
8hrs	0.034*	0.374	0.001*
12hrs	0.324	0.001*	0.055
16hrs	0.198	0.986	0.147
20hrs	<0.001*	0.471	0.002*
24hrs	0.042*	0.017*	0.935

DISCUSSION

According to Commiskey et al critical review The opioid analgesic, butorphanol is a prototypical agonist-antagonist opioid analgesic agent with a published affinity for opioid receptors in vitro of 1:4:25 (μ:δ:κ) which indicates that a substantial selective action of butorphanol on the κ-opioid receptor.[2] Buprenorphine, an opioid with mixed agonist-antagonist activity at classical opioid receptors, Partial agonism at the mu opioid receptor and, in some cases, antagonism at the kappa or delta opioid receptor.[3] Kumar et al used 25 μg fentanyl and 250 μg butorphanol given intrathecally along with 12.5 mg of hyperbaric bupivacaine provide effective anesthesia for lower limb surgeries. They found Intrathecal bupivacaine-butorphanol mixture provides longer duration of sensory blockade and superior analgesia than intrathecal fentanyl-bupivacaine mixture.[4] According to Singh et al Addition of buprenorphine (60mcg) and fentanyl(10mcg) as adjuvants to intrathecal 0.75% ropivacaine (2.8ml), buprenorphine is better as compared to fentanyl in prolonging the duration of sensory block and achieving a better outcome in terms of pain relief.[5] In our study Patients in the buprenorphine group required rescue analgesia after 8.8±0.8 hours, significantly longer than those in the butorphanol (4.9±0.9 hours) and control groups (3.6±0.5 hours) ($p < 0.001$). The buprenorphine group exhibited a longer time to reach the highest level of sensory blockade (8.3±1.5 min) compared to butorphanol (4.1±1 min) and the control group (3.6±0.8 min) ($p < 0.001$). Similarly, two-segment regression time was prolonged in the buprenorphine group (2.6±0.5 hours) compared to the butorphanol (0.7±0.3 hours) and control groups (0.4±0.2 hours) ($p < 0.001$). According to Poornima et al onset of sensory blockade and with butorphanol was faster but the duration of sensory blockade was more in buprenorphine compared to butorphanol whereas motor blockade is comparable in both groups. Buprenorphine group required rescue analgesia at 4hrs postoperatively whereas butorphanol group required rescue analgesia at 2nd hr Hence they conclude that buprenorphine would be beneficial for lower limb orthopedic surgeries as it provides prolonged duration of analgesia.[6] In our study The duration of motor blockade also differed significantly among groups, with buprenorphine extending motor block duration to 8±0.8 hours, longer than butorphanol (4.1±0.7 hours) and the control group (3±0.6 hours) ($p < 0.001$). According to Downing et al Buprenorphine caused a greater decrease in diastolic arterial pressure than did morphine, but arterial systolic pressure and heart rate were not influenced by either drug. No serious side-effects were encountered in this study.[7] In our study Intraoperative hemodynamic parameters, including systolic and diastolic blood pressure, heart rate, and oxygen saturation, remained stable across all study groups. However, significant variations in mean arterial pressure (MAP) were observed at later time intervals, with both opioid adjuvants (buprenorphine and butorphanol) contributing to greater hemodynamic stability compared to the control group.

Patients receiving buprenorphine required significantly fewer rescue analgesic doses postoperatively compared to the butorphanol and control groups. Only 60% of patients in the buprenorphine group needed a single dose of tramadol, compared to 80% in the butorphanol group and 100% in the control group ($p < 0.001$. Paul et al mentioned in their study All clinically used opioids are μ-opioid receptor agonists, and the major adverse effects are directly or potentially connected to this receptor.[8] In our study we used both partial mu receptor agonists so there was very less side effects seen among both drugs.

Limitations and Future Research

The study was limited to a 24-hour postoperative observation period, preventing an assessment of long-term effects such as pain, nausea, vomiting etc. Additionally, variations in duration, type of lower limb surgeries and opioid receptor sensitivity among patients may influence analgesic responses. Future research should focus on larger, multicenter trials with extended follow-up periods to evaluate the long-term efficacy and safety of intrathecal opioid adjuvants.

CONCLUSION

Both buprenorphine and butorphanol serve as effective intrathecal adjuvants to 0.5% levobupivacaine, each offering unique advantages. Buprenorphine provides superior analgesia with

extended pain relief and reduced postoperative opioid requirements, whereas butorphanol facilitates faster recovery and earlier ambulation. The choice of adjuvant should be tailored to the patient's surgical needs and recovery goals to optimize perioperative pain management.

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