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Research Article

Comparison of Two Different Doses of Buprenorphine as Adjuvants to Intrathecal Levobupivacaine in Lower Abdominal Surgeries

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ABSTRACT

Background: Levobupivacaine because of its longer duration of action and better safety profile has gained popularity in regional anaesthesia. Intrathecal opioids synergise with Local anaesthetics and potentiate subarachnoid block. We conducted this study with the primary aim to compare analgesic efficacy of two different doses of buprenorphine as adjuvant to isobaric Levobupivacaine and the secondary aim to compare the onset and duration of sensory and motor blockade, hemodynamic variability and adverse effects if any.

Methods: One hundred and twenty patients of American society of anaesthesiologist (ASA) I and II were divided in 3 groups of 40 each. Group A :0.5%levobupivacaine, group B: 0.5%levobupivacaine with 60 mcg buprenorphine Group C:0.5 %levobupivacaine with 90mcg buprenorphine. Duration of analgesia, onset of sensory and motor block, VAS scores, haemodyanamic parameters and adverse effects were noted.

Results: The duration of analgesia was significantly prolonged in group C (11±0.41) h than group B (8.5±0.61) hour and Group A (4.8 ±40) hour ($p < 0.001$). Onset and duration of Sensory and motor blockade was not significantly different. VAS score was significantly lower in group C ($p<0.001$), hemodynamic parameters were well preserved with higher incidence of PONV in group C (10%).

Conclusion: Addition of buprenorphine to intrathecal Isobaric Levobupivacaine prolonged the duration and quality of postoperative analgesia after lower abdominal surgery. Increasing the dose of buprenorphine from 60mcg to 90mcg provided longer duration of analgesia with minimal adverse effects like dizziness and PONV which were not significant to hinder recovery.

Introduction

In the era of regional anaesthesia sub-arachnoid block is the preferred choice of anaesthesia as it is easy to administer technically, with fast onset of sensory and motor anaesthesia and often results in adequate muscle relaxation.

Prolonging the pain free period enhances post-operative recovery and improves patients' satisfaction. Opioids are the most studied adjuvants as they act synergistically with local anaesthetic agents and intensify the sensory block, providing longer postoperative analgesia [1].

Levobupivacaine an amino amide derivative of n-alkyl substitute of pipecoloxylidide family and is long-acting with clinical profile similar to racemic bupivacaine with better safety profile [2-3].

Buprenorphine with high binding affinity at μ and kappa receptors produces a longer duration of sensory blockade. Its high lipid solubility decreases its rostral spread causing fewer side effects [4-5].

The authors declare no conflicts of interest.

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Our study was primarily aimed to compare the duration of analgesia of two different doses of intrathecal buprenorphine. The secondary aim was to compare the onset and duration of sensory and motor blockade, haemodynamic variability and adverse effects if any.

We hypothesize that addition of 90 mcg of buprenorphine to levobupivacaine while administering spinal anaesthesia would provide longer postoperative analgesia than 60 mcg of buprenorphine added to levobupivacaine or levobupivacaine when used alone. Though there may be an increased incidence of postoperative nausea and vomiting (PONV) with higher dose of buprenorphine.

Methods

After obtaining institutional ethical committee approval (SKNMC/Ethics/App/2019/599) we enrolled patients posted for lower abdominal surgeries in the age group of 18-60 years with American society of anaesthesiologist's physical status I and II. All patients who consented to participate in the study and use their data for the research purpose and publish it were further assessed. Ours is a prospective randomized double-blind study, conducted completely in accordance with the guidelines of Helsinki from September 2019 to March 2020.

Patients with significant coagulopathies and contra-indications for spinal anaesthesia, pre-existing systemic diseases, psychiatric disorders, history of drug abuse, allergy to local anaesthetics and opioids were excluded. Patients were randomly allocated into 3 groups using closed envelope method based on computer generated numbers using EPI-INFO software. The consort flow chart of the study is depicted in Fig 4. Group A received isobaric 0.5% levobupivacaine 3ml with 0.5ml normal saline (NS), group B received 0.5% isobaric levobupivacaine with buprenorphine 60mcg, and group C received 0.5% isobaric levobupivacaine with buprenorphine 90mcg. Total volume was made upto 3.5ml in all the three groups.

After a thorough pre-anaesthetic evaluation, VAS scale was explained to the patient preoperatively. In the operating room, baseline parameters were recorded and intravenous access was secured with 20G intracath and patients were preloaded with 10ml/kg of crystalloid. Using strict aseptic precautions subarachnoid block was administered using 26Gauge Quinke needle.

Sensory block was assessed by pinprick with 18 G blunt needle in caudo cephalic direction. Onset of sensory block (no sensation at T10 dermatome), maximum level of sensory block attained, time to attain maximum sensory block and total duration of sensory block (regression to T10 dermatome) were noted. Motor block was assessed as per modified Bromage scale (0 = no paralysis, able to flex hips/knees/ankles; 1= able to move knees, unable to raise extended legs; 2= able to flex ankles, unable to flex knees and 3 = unable to move any part of the lower limb). Maximum level of motor block attained, time to achieve maximum level of motor block and total duration of motor blockade (from the time of intrathecal administration of the drug to motor recovery to Bromage score 0) was noted. Sensory and motor assessment were performed every 2 min for up to 10 min after spinal anaesthesia. If the sensory or motor blockade was inadequate, the patient was administered general anaesthesia and was excluded from the study.

The vital parameters were recorded prior to induction and later at an interval of 5 mins until the end of the procedure. A fall in mean blood pressure >25% from baseline, or to <60 mm Hg, was defined as hypotension and was treated with Inj mephentermine 6 mg stat. A drop in HR <50 bpm was defined as bradycardia and was treated with 0.6 mg of Inj atropine; and a fall in SpO2 to <93% was defined as hypoxia and treated with supplemental oxygen using a face mask. Postoperatively haemodynamic parameters were monitored every 30 min until the sensory and motor variables were back to normal.

VAS score was assessed every 15 min for 120 min, then half hourly for 180 min, hourly for 12 h, and thereafter every 3 h until 24 h of surgery. Injection Paracetamol 1gm IV was administered as rescue analgesic as per request by the patient (VAS >3) in all groups. Total duration of analgesia was estimated from the time of subarachnoid administration of the drug until the patient demanded first rescue analgesic. Patients were monitored for any side effects like hypotension, bradycardia, PONV, sedation, urinary retention, pruritus or headache for 24 hours.

The primary objective of the study was to compare the duration of analgesia among the three groups. The secondary objective was to assess the quality of sensory and motor blockade, peak sensory and motor level, time to reach peak sensory and motor block and the degree of motor block in the three groups. Intraoperative haemodynamic effects were also compared among the groups.

A sample size of 90 was estimated based on the study by Dr. Rashmi et al [6] to achieve a power of 80% and alpha error of 0.5. 120 patients were included in the study considering the dropouts and is represented in the consort diagram (Figure 1).

Statistical Package for Social Sciences 20 software was used for statistical calculation. Paired and unpaired t test were used for data analysis and analysis of variance. Data are presented as mean ± standard deviation and $P< 0.001$ was considered significant. The categorical data were analysed using the Chi-square test.

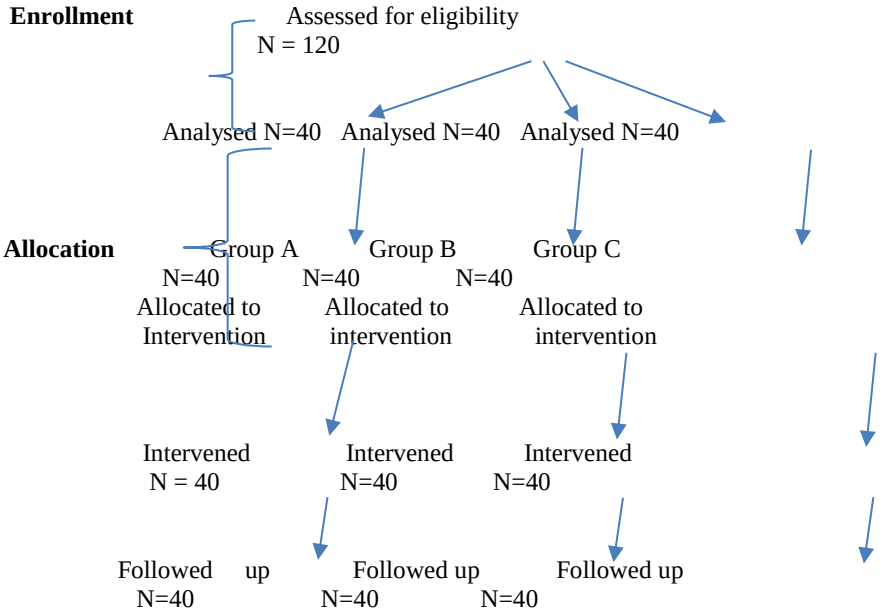

Figure 1- Consort flow chart of the study

Results

All participants completed the study. Demographically no significant difference was observed among the groups (Table 1).

In the present study the onset of sensory and motor block in three groups is not significant. Regression of sensory block in Group B (499.35±30.36) and Group C (607.80±32.52) is significantly slower than group A (284.75±8.68) p (<0.001), also there is significantly slow regression of sensory block in Group B(90mcg) than Group C(60mcg) p (<0.001).

Regression of motor block in Group B (509.3±27.8) and Group C (618.45±29.2) is significantly at a slower pace than Group A (317.35±22.44) p (<0.001), also there is significantly slow regression of motor block in Group C(90mcg) than Group(60mcg) p (<0.001) (Table 2).

The mean duration of postoperative analgesia was much longer in Group C (11±0.41) h than group B (8.5±0.61) h and Group A (4.8 ±40) h which was statistically significant. (p<0.0001) (Figure 2).

The total no. of rescue analgesics over 24 hrs in group C was significantly lower than Group B and group A. (p 0.001) (Figure 2). The mean duration of postoperative analgesia is more in Group C (11±0.41) than group B (8.5±0.61) and Group A (4.8 ±40) which was statistically significant. (p<0.0001) (Figure 2). The total no. of rescue analgesics over 24 hrs in group C was significantly lower than Group B and group A p (0.001) (Figure 3).

The mean VAS at 2, 4, 6, 8 and 24 h in all the 3 groups was calculated and the pain scores were significantly lower in patients of both buprenorphine groups (Group B, Group C) as compared to the control group up to 24 h (p < 0.001) (Figure 4).

The incidence of adverse effects is represented as percentage of patients, shows hypotension in 15% and 10% in group C and B respectively. While bradycardia was noted in 7.5% and 5% patients of group C and B respectively. Incidence of PONV was more with 90microgms of buprenorphine (10%) than 60 micrograms (7.5%) and no adjuvant group (5%).

Statistically significant rise in heart rate in-group A as compared to groups B and C at 4 h, 12 h, 18 h, and 24 h after surgery was noticed, it was clinically insignificant requiring no intervention. In addition, statistically significant difference in mean blood pressure (MBP) among the groups at 4 h and 12 h was noted but needed no intervention. The MBP was comparable between the groups in the rest of the study period (Table 3).

Table 1- demographic profile

Parameters	Group A	Group B	Group C	P value
Age(years)	30.9 ± 7.67	30.2 ±3.04	32.31±2.55	NS
Weight(kg)	60.23 ± 12.87	60.93±5.0	61.86±5.42	NS
Height(cm)	154.9±5.2	155.7±4.3	156.3±5.4	NS
ASA I/II	28% / 72%	48%/62%	73% / 26%	NS
Duration of surgery(min)	150±9.6	150.5±10.3	152.5±9.9	NS

NS: non-significant

Table 2- characteristics of sensory and motor block

Variable (min)	Group A, n(40) M±SD	Group B, n(40) M±SD	Group C, n(40) M±SD	P value
Onset of sensory block.	3.60±0.28	3.64±0.28	3.62±0.28	NS
Onset of motor block.	4.08±0.41	4.06±0.41	4.06±0.42	NS
Regression of sensory block	284.75±8.68	499.35±30.36	607.80±32.52	<0.001
Regression motor block	317.35±22.44	509.3±27.8	618.45±29.2	<0.001

Table 3- Adverse effects noted in three groups.

	Group A	Group B	Group C
Hypotension	2(5%)	4(10%)	6(15%)
Bradycardia	0	2(5%)	3(7.5%)
Pruritis	0		
vomiting	2(5%)	3(7.5%)	4(10%)
Respiratory depression	0	0	0

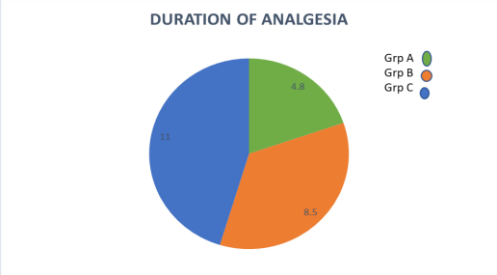

Figure 2- Duration of analgesia

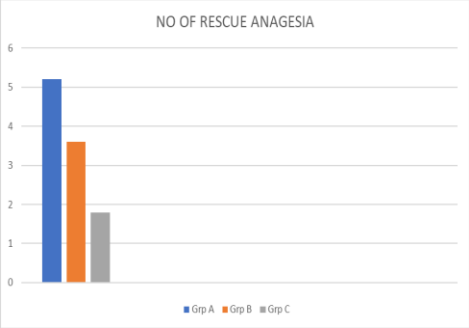

Figure 3- dose of rescue analgesic consumed in 24 hours

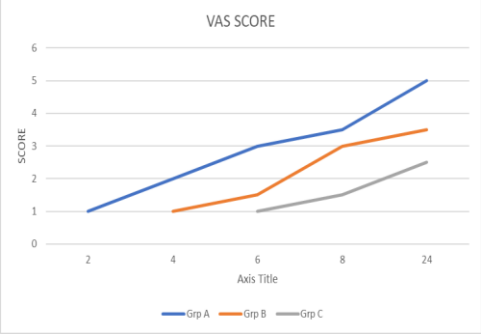

Figure 4- mean VAS scores in three

Groups at different time Intervals.

Discussion

Levobupivacaine is a recently introduced local anaesthetic agent, with a pharmacological profile similar to that of commonly used bupivacaine. It is relatively more cardio stable, less neurotoxic than bupivacaine, and hence more favourable to be used in high-risk patients [2]. Several studies are available reporting the comparison of buprenorphine with other agents as additives to bupivacaine [6-7]. In the wide database available, this is the only study conducted to find the optimum dose of buprenorphine as adjuvant to levobupivacaine in subarachnoid block. We conducted this study with 60 and 90 µgms doses of buprenorphine as adjuvant to levobupivacaine. These lower doses are selected in order to minimise the adverse effects of opioid.

Buprenorphine is an opioid that exerts its action primarily via µ and kappa receptors but also has a partial action at delta receptors [7]. It has both spinal and supraspinal component of analgesia and is compatible with cerebrospinal fluid producing no adverse reactions when administered intrathecally. It has been used intrathecally in a dose of 75–150 µg with appreciable efficacy.

Behr et al. in their study added buprenorphine 150 µgms to levobupivacaine for brachial plexus block. They compared intramuscularly administered buprenorphine with perineural buprenorphine and found that perineuraly administered buprenorphine was more efficacious in prolonging postoperative analgesia. There were significant (P< 0.05) differences in the onset and duration of the sensory block and in duration of postoperative analgesia [8].

Dixit et al in their study with subjects undergoing caesarean section also stated that the onset of sensory action was faster with buprenorphine as adjuvant. While in our study we did not notice any significant difference in onset of sensory and motor block [9]. This difference

might be because of the change in the local anaesthetic and its baricity. Both the above mentioned studies used hyperbaric bupivacaine while we conducted our study with levobupivacaine. Similar to study results Bidikar et al in their study stated that there was no difference in the onset time and time to achieve maximum sensory block (9.5±2.3 mins vs 8.9±1.6 mins) when fentanyl was used as adjuvant to levobupivacaine in subarachnoid block for caesarean sections [10].

Singh et al. studied intrathecal buprenorphine versus fentanyl as adjuvant to 0.75% ropivacaine in lower limb surgeries and concluded that buprenorphine is better as compared to fentanyl in prolonging the duration of sensory block and achieving a better outcome in terms of pain relief [11]. Thus buprenorphine is more effective in potentiating subarachnoid block when compared to fentanyl. In our study we could witness a dose dependent improvement in characteristics of subarachnoid block with higher dose of buprenorphine.

In the current study, the mean duration of analgesia following surgery was significantly prolonged in both the buprenorphine groups (8.5 ± 0.61 h in group B and 11±0.41 h in group C) as compared to 4.8 ± 40 h in the control group ($p<0.0001$). Tulsyan et al compared 150 and 300µgms of buprenorphine as adjuncts to levobupivacaine in lumbar plexus block and found that the duration of post-operative analgesia was prolonged with both doses of buprenorphine but the difference in the duration of pain free period among both groups was not statistically significant (9.76 hrs vs 10.13hrs). Also the sedation was more pronounced in both groups and more so with 300µgms of buprenorphine (RSS score 1.93 vs 1.46) [12]. This study shows a stagnation of duration of analgesia with higher doses of buprenorphine along with increase in incidence of adverse effects. Hence the use of lower doses of 60 and 90 µgms of buprenorphine can be justified.

Our study shows significantly lower VAS scores with the use of either doses of buprenorphine, also the incremental doses of buprenorphine showed reduced VAS scores in 1st 24 hours. The cumulative rescue analgesic doses per patient and the total number of rescue analgesics doses in each group was significantly less in groups in which buprenorphine was administered (i.e., groups B and C), as compared to control group (group A) in our study. These observations are also consistent with studies by Behr et al. (2012) and Paliwal and Karnawat (2013) (using either 150 µg or 300 µg of buprenorphine), where the authors have stated that the requirement of rescue analgesics was less when compared with the control group [13].

Rashmi et al studied 45 µgms and 60 µgms as adjuvant to bupivacaine in caesarean section and reported similar results. They also stated that the quality of analgesia was also better with higher dose as was witnessed in our study also [14].

Authors admit certain limitations of the study. The first one being a selection bias of non- inclusion of ASA III and IV patient group which would be more vulnerable to hemodynamic variations and respiratory depression.

Only lower abdominal surgeries have been included in the study. Other variety of surgeries requiring higher level of subarachnoid block should have been included in the study.

Conclusion

To conclude we state that the addition of buprenorphine to isobaric levobupivacaine potentiates the effect of subarachnoid block. Among the two study doses (60, 90) 90mcgs proves to be more effective as it prolongs the postoperative pain free period without significant side effects.

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