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ORIGINAL RESEARCH ARTICLE

Assessing the Efficacy of Intrathecal Ultra-Low Dose Buprenorphine with Hyperbaric Bupivacaine in Infraumbilical Surgeries: A Randomised Control Study

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ABSTRACT

Introduction: Pain management is one of the defining roles of an anesthesiologist. Across the world, infraumbilical surgeries are carried out under subarachnoid blocks. However, one of the major limiting factors of spinal anesthesia is limited block duration. The addition of opioids and other adjuvants prolongs the block duration but a high dose of intrathecal opioids is associated with adverse events. This study was carried out in an attempt to evaluate ultra-low dose buprenorphine administered intrathecally and its effect on bupivacaine spinal anesthesia.

Material and Methods: The present prospective double-blind study was undertaken on ninety American Society of Anaesthesiologists I and II patients between 18 and 60 years of age undergoing subarachnoid block for lower limb surgery. Group 1 (n = 45) patients were administered 3 mL of injection bupivacaine heavy 0.5% with 30 mcg of buprenorphine while group 2 (n = 45) was administered 3 mL of injection bupivacaine heavy 0.5%. The following parameters were observed: Onset times and duration of sensory and motor block, time for a 2-segment dermatomal recession, hemodynamic parameters and side effects if any. Data were analyzed by appropriate statistical tests and $p < 0.05$ were considered significant.

Results: The two groups were comparable in terms of the demographic profile, and onset of sensory blockade mean time taken to achieve the highest level of sensory blockade. Most patients in both groups achieved a maximum sensory level of T4 (n = 29 *vs* n = 26). However, 2-segment regression time and time for complete sensory recovery was significantly higher in patients who received intrathecal buprenorphine (145.36 ± 7.34 *vs* 78.956 ± 7.845; $p < 0.0001$) and (327.31 ± 11.151 *vs* 160.31 ± 16.258; $p < 0.0001$). Both groups were comparable in terms of grade III motor block onset and duration (12.620 + 0.79 *vs* 12.827 + 0.77; $p = 0.2215$) and duration of motor block (122.58 + 9.117 *vs* 119 + 16.396; $p = 0.2039$). There was no significant difference in terms of side effects between the two groups.

Conclusion: Intrathecal buprenorphine is a viable alternative for prolonging sensory block in spinal anesthesia without affecting motor blockade and no significant adverse events.

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INTRODUCTION

"Pain" is derived from the Latin word "poena," which refers to punishment.[1,2] One of the primary roles of the anaesthesiologist is to alleviate the patient's pain throughout perioperative procedures and liberate the patient from this punishment. Post-operative pain results in a wide range of systemic issues, including hypertension, tachycardia, myocardial ischemia, atelectasis, hypoxemia, ileus, urine retention, and poor glycemic control. This additional stress makes the patient more vulnerable to infections, leading to prolonged hospital stays and higher costs, and delays the patient from resuming his usual activities.[3]

Pain therapy is largely opioid-based across the world, delivered intravenously, intramuscularly, epidurally, and intrathecally, either alone or in conjunction with local anesthetics. Opioids can also be supplied non-parenterally, *via* buccal, sublingual, oral, rectal, and transdermal methods, which have swarmed the market of late. Gaseous and volatile anesthetics have also been used; however, their use is limited in the postoperative period. Excessive opioid use can lead to perioperative adverse effects such as respiratory depression, drowsiness, postoperative nausea and vomiting (PONV), pruritus, urine incontinence, ileus, and constipation, leading to delayed hospital discharge.[4] As a result, anaesthesiologists are increasingly relying on regional anesthesia, multimodal analgesic approaches, and novel medications.

The subarachnoid block is a simple and technique that involves injecting the local anesthetic with or without adjuvant in the subarachnoid space. This technique provides profound muscle relaxation, decreases operative blood loss and causes minimal side effects, but is

restricted by limited block duration.[5,6] This has been overcome by the use of intrathecal adjuvants. Owing to the side-effects associated with opioids the world welcomed with open arms the alpha-2 agonists and is shutting the doors on opioids.

Buprenorphine is one opioid that was used extensively in the past but its use reduced significantly with the advent of drugs like dexmedetomidine. However, interest in the use of buprenorphine as an analgesic has increased in recent years. Its unique agonist-antagonist properties make it a useful analgesic with the potential to lower abuse liability in humans. Buprenorphine has been used as an analgesic in the postoperative period for the treatment of moderate-to-severe pain. Buprenorphine has also been found to have antihyperalgesic properties, which might make it an agent to consider for the prevention and reduction of central sensitization. In addition, its high affinity for the mu receptor along with its slow dissociation from the receptors has led to new challenges when controlling postoperative pain in patients on buprenorphine maintenance therapy.[7]

Buprenorphine administered intrathecally has been used in the past although higher doses are associated with the above-mentioned side effects. The paucity of data on the usage of ultra-low dose intrathecal buprenorphine has left a void in the utility of the drug at the investigated dose. Hence, this study was proposed to assess and ascertain whether ultra-low dose buprenorphine can be an alternative to the newer drugs in terms of efficacy, duration of analgesia and safety.

MATERIAL AND METHODS

This prospective, single-centric, double-blinded, randomized, Helsinki protocol-compliant clinical study was conducted after obtaining written informed consent and approval from the institutional ethics committee.

We enrolled 90 American Society of Anaesthesiologists' physical status I/II patients aged 18 to 60 years undergoing elective infraumbilical surgeries under subarachnoid block. Those patients refusing to be part of a trial, local site infection, hemodynamic instability, coagulopathy, uncontrolled systemic illnesses and neurological or spine anomaly.

Patients were randomly assigned into two groups by a computer-formulated randomization technique, using consecutively numbered opaque sealed envelopes, which were organized by a volunteer not a part of the trial. The enrolled study participants were randomized into 2 groups of 45 subjects each.

Group 1

Patients receiving 30 mcg buprenorphine mixed in 3 mL 0.5% (pc) bupivacaine heavy.

Group 2

Patients receiving 0.5 pc bupivacaine heavy 3 mL.

The method of concealment was consecutively opaque sealed envelope technique. A pre-operative visit was done a day before surgery. A detailed survey of the current, coexisting medical illness along with general, systemic and airway examination was done. All necessary investigations were conducted and investigation reports were reviewed. Demographic data such as age, sex, height, weight, body mass index (BMI) and American Society of Anaesthesiologists (ASA) physical class were noted. American Society of Anaesthesiologists fasting guidelines were adhered to for all patients. Patients and attendants were informed and explained about the procedure and written and well-informed consent was obtained.

All patients were provided with patient information sheets. All the patients included in this study received a tablet of alprazolam 0.25 mg and a tablet of pantoprazole 40 mg the night before surgery. All standard monitor like electrocardiograms, pulse oximeters, and non-invasive blood pressure (NIBP) was applied to all patients and baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and baseline oxygen saturation (SPO2) were recorded.

Hemodynamics were noted at baseline. All the patients were put in the left lateral position and spinal anesthesia was administered at the L3-L4 intervertebral space. Using a 25-gauge Quincke's spinal needle and patient was repositioned to a supine position. Vitals were recorded every 2 minutes following dural puncture and drug injection for 10 minutes then every 15 minutes till the end of surgery, and thereafter half-hourly in the postoperative phase till the first rescue analgesic.

Fall of systolic blood pressure below 20% of the baseline values was corrected by fluid boluses and an aliquot of mephentramine 6 mg intravenous (IV) in patients not responding to fluid therapy. An onset of sensory and motor block was observed. Sensory blockade was assessed by a gentle pinprick with a blunt tip hypodermic needle. The onset of sensory block was considered when blockade reached T8 (or as per surgical need). The Bromage scale was used to observe motor blockade, wherein Bromage 0: Full flexion of knees and feet, Bromage 1 (Partial): Just able to move knees, Bromage 2 (Almost complete): Able to move feet only and Bromage 3 (complete): Unable to move feet and knees.[1] Onset of motor blockade was considered adequate when bromage scale grade 3 was achieved. The highest level of sensory block height achieved, time for 2 segment regression, duration of sensory blockade and motor blockade were noted.

Recovery time for the sensory blockade was defined as two dermatome regressions of anaesthesia from maximum level. Motor block duration was defined as the time to return to grade 1 on the bromage scale, pain was noted by visual analogue scale (VAS). VAS score of 4 or more were administered inj. diclofenac sodium 75 mg intramuscularly and time for first rescue analgesic were noted. This were recorded as the duration of analgesia.

Statistical Analysis

For each group, (i.e., a total sample size of 90, assuming equal group sizes), to achieve a power of 80% hand a level of significance of 5% (two-sided), for detecting a true difference in means between the test and the reference group of 0.8500, (i.e., 3.45–2.6) units. Assuming a pooled standard deviation of 1.5 units, the study would require a sample size of: 45 (Including the dropouts).

Graphpad Instat 3 statistical software for Windows was used to conduct the statistical analysis. Continuous variables are presented as mean ± SD, median (IQR), and minimum-maximum values. Categorical variables are displayed as percentages and absolute values. The Mann-Whitney U test was employed for variables that were not normally distributed, whereas the unpaired t-test was used to compare continuous variables that were normally distributed. The Fisher's exact or chi-square tests were used to assess categorical variables. For within-group comparisons, a paired t-test was used to test any significant change in hemodynamic parameters at various time points from the baseline.

RESULTS

The CONSORT flow diagram (Figure 1) depicts the flow of the participants in the three groups. Demographic variables revealed that both groups were comparable (Table 1). Primary outcome measures were onset of sensory and motor block, highest sensory level achieved, time for 2-segment regression, duration of sensory and motor blockade, and time for first rescue analgesic. Hemodynamic parameters (HR, SBP, DBP, NIBP) and SpO2 were recorded at baseline (prior to shifting in the operating room), immediately after administration of study drugs, immediately after administering subarachnoid block (SAB) at 3 minute intervals for 10 minutes or till the maximum level of block is achieved, at 15 minutes interval till end of surgery and hourly till first rescue analgesic.

The two groups were comparable in terms of onset of sensory blockade (2.98 ± 0.15 *vs* 3.06 ± 0.29; $p = 0.1038$), mean time taken to achieve the highest level of sensory blockade (11.527 ± 1.56 *vs* 11.469 ± 0.67; $p = 0.573$). Most patients in both groups achieved a maximum sensory level of T4 (n = 29 *vs* n = 26). However, the 2-segment regression time was significantly higher in patients who received intrathecal Buprenorphine (145.36 ± 7.34 *vs* 78.956 ± 7.845; $p < 0.0001$). Time for complete sensory recovery was also significantly higher in the buprenorphine group over the control (327.31 ± 11.151 *vs* 160.31 ± 16.258; $p < 0.0001$) (Table 2).

In terms of motor blockade, it was observed that the two groups were comparable in terms of time for grade III motor blockade (12.620 ± 0.79 *vs* 12.827 ± 0.77; $p = 0.2215$) and duration of motor block (122.58 ± 9.117 *vs* 119 ± 16.396; $p = 0.2039$) (Table 3).

Both the groups were also compared for hemodynamic status over the course of the block (Figure 2) and for any associated side effects. Both groups did not show any significant difference with regard to differences in heart rate and mean arterial pressure. In terms of side effects, the most common adverse event was hypotension with the intergroup difference being non-significant (Table 4).

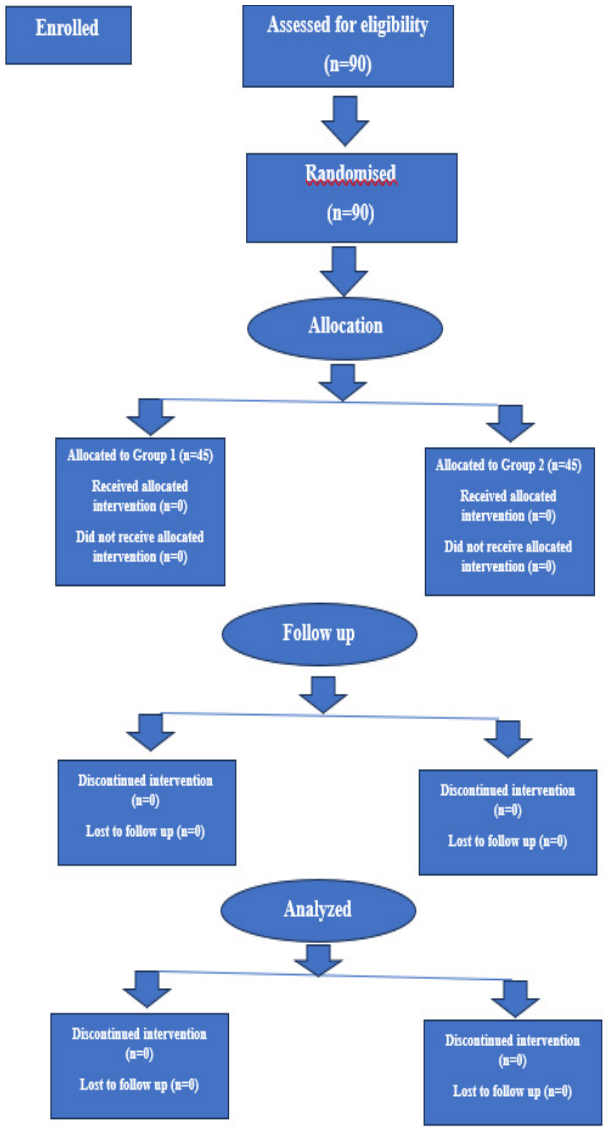

Figure 1: CONSORT Diagram

Table 1: Demographic profile

Parameter	*Group 1*	*Group 2*	*p-value*
Age	29.23 ± 9.45	28.40 ± 4.29	0.663
Sex			
Male	24	23	0.702
Female	21	22	
BMI	25.40 ± 3.38	24.85 ± 3.50	0.487
ASA			
I	37 (92.5%)	35 (87.5%)	0.712
II	3 (7.5%)	5 (12.5%)	

Table 2: Sensory characteristics

Parameter	*Group 1*	*Group 2*	*p-value*
Onset of sensory block (minutes)	2.98 ± 0.15	3.06 ± 0.29	0.1038
Time to achieve the highest level of sensory block (Minutes)	11.527 ± 1.56	11.469 ± 0.67	0.573
Time for 2-segment regression (Minutes)	145.36 ± 7.34	78.956 ± 7.845	<0.0001
Time for complete sensory recovery	327.31 ± 11.151	160.31 ± 16.258	<0.0001

Table 3: Motor block characteristics

Parameter	*Group 1*	*Group 2*	*p-value*
Time for grade III block (minutes)	12.620 ± 0.79	12.827 ± 0.77	0.2215
Time for complete motor recovery	122.58 ± 9.117	119 ± 16.396	0.2039

DISCUSSION

As an anaesthesiologist one of the most gratifying experiences is relieving the patient from the agony of pain. While numerous additives and adjuvants have been employed to prolong the usual duration of analgesia following subarachnoid block, each additive brings with it a set of challenges that often leave the anaesthesiologist bewildered. The quest for a safe intrathecal additive that minimizes local anesthetic dose while retaining subarachnoid block effectiveness appears to be never-ending. The results of our study demonstrate that administering ultra-low dose buprenorphine along with bupivacaine enhanced analgesic effects while causing negligible adverse events and a motor block equivalent to that caused by local anesthetic minus adjuvant.

Buprenorphine is a relatively older opioid classified under the phenanthrene morphine class. It has partial agonist activity at the μ-and kappa opioid receptor and competitive antagonist activity at the k-opioid receptor.[8] Higher doses administered intrathecally have also been evaluated in the past by multiple authors but these patients experienced complications such as post-operative nausea and vomiting especially during ambulation and the potential of this drug to cause delayed respiratory depression necessitating monitoring and apprehensions with intrathecal administration; which translated into the delayed discharge of these patients from the hospital, increase in hospital costs and significant agony to the patients and relatives alike.[9-11] These reasons prompted us to explore a lesser investigated ultralow dose of intrathecal buprenorphine

Our investigation demonstrated that ultra-low dose intrathecal buprenorphine did not hasten the onset of sensory or motor blockade. Neither did the addition of the study drug affect the block height nor did it affect the time to achieve the highest sensory level. Another factor that could possibly influence the block level and time to achieve the highest block level was patient height. Patient height was comparable between the two groups with no statistical difference (161.40 ± 8.441 *vs* 159.00 ± 9.386; p = 0.2055). At the presently evaluated dose, the only factors that were affected were the time for two dermatomal sensory regressions and the total duration of analgesia, which were prolonged significantly over the control group. The favorable effect of intrathecal buprenorphine on sensory blockade has been demonstrated by multiple authors who used higher doses of intrathecal buprenorphine. This prolongation of the sensory blockade can be attributed to the fact that buprenorphine dissociates slowly from a μ-opioid receptor, it has a long duration of action and less addiction potential.[7-12]

Fauzia *et al.* conducted a study with an intrathecal buprenorphine dose similar to ours and our study concurred with them in terms of time to achieve maximum sensory level and maximum sensory level achieved. However, the authors found an earlier onset of sensory blockade in the buprenorphine group as compared to the control.[12] However, investigators including Irfan *et al.*, Kaur *et al.* Shruthijayaram *et al.* and Singh *et al.* who had used a higher intrathecal buprenorphine dose also did not report earlier sensory block onset, while concurring with the rest of the findings as ours including the similar highest level of sensory block and prolonged 2-segment dermatomal recession time and total sensory block time.[8,9,11,13] Adate *et al.* also compared 60 and 90 mcg intrathecal buprenorphine. Authors focussed on sensory parameters only and these parameters were similar to our study in the view that bupregesic prolonged the duration of a sensory block with no effect on the time of onset of the block.[14]

However, the authors did report that the addition of higher doses of intrathecal buprenorphine resulted in

Table 4: Incidence of adverse events

Complication	*Group 1*		*Group 2*		*p-value*
	No. of patients	*percentage*	*No. of patients*	*percentage*	
Hypotension	20	44.44%	18	40 %	> 0.05
Bradycardia	04	08.88 %	05	11.11 %	> 0.05
Nausea & vomiting	06	13.33%	05	11.11 %	> 0.05
shivering	03	6.67 %	04	08.88%	> 0.05
Pruritus	00	00	00	00	
Respiratory depression	00	00	00	00	
PDPH & neurological complication	00	00	00	00	

early onset and prolonged motor blockade especially at higher doses, with few of them reporting the extension of motor blockade close to 4 hours and even above. This problem has been addressed by our study in which the duration of motor blockade was equivalent to local anesthetic without adjuvant.[8-13] The implication of this finding lies in the fact that in the current day scenario of enhanced recovery after surgery and daycare surgeries; early recession of motor blockade, early mobility and hastened discharge from the hospital hold the key to the patient returning to his activities of daily living and cost-effectiveness.

Another aspect that is a major concern among adjuvants, especially the in-vogue alpha-2 agonists is the occurrence of hypotension. This has been tackled by intrathecal buprenorphine and even more so by our study wherein ultra-low dose buprenorphine was used. Most studies except by Rabiee *et al.* displayed better and more stable hemodynamics as against many other adjuvants.[15]

In terms of side effects of intrathecal buprenorphine, the common side effects that have been associated with buprenorphine either intrathecal or intravenous include the typical opioid-related side effects such as pruritis, post-operative nausea and vomiting, respiratory depression, etc. In addition to these, we also observed all patients for side effects associated with subarachnoid block viz, hypotension, bradycardia and post-dural puncture headache. Most of the researchers who have studied higher doses of intrathecal buprenorphine have highlighted post-operative nausea and vomiting as one of the major adverse events. In our research, although a few subjects did exhibit this problem the difference was not significant when compared with the control group or the non-adjuvant group, thereby addressing this major concern which often hampers early patient discharge.

A major concern in patients being administered opioids include sedation and respiratory depression. Concerns about late respiratory depression from neuraxial opioids perhaps have been the main reason for reluctance in the widespread use of these analgesic techniques but in the case of buprenorphine which is a lipid-soluble, non-ionized drug, it reaches the cisterns of the brain in 3 to 6 hours after intrathecal administration absorbed into the spinal venous plexus *via* the arachnoid granulations and there is minimal increase in the spinal fluid concentration thus a minimal risk with rostral spread.[16] According to Stoelting the patients receiving intrathecal opioids should be under close surveillance for adequacy of breathing but suggests that neuraxial administration of narcotics as in our study does not obligate observation in intensive care units.[17] None of the patients had sedation scores different from the control group. Nor did any of our patients experience respiratory depression.

No study, including ours, is devoid of any limitations. We evaluated a single dose of buprenorphine and this

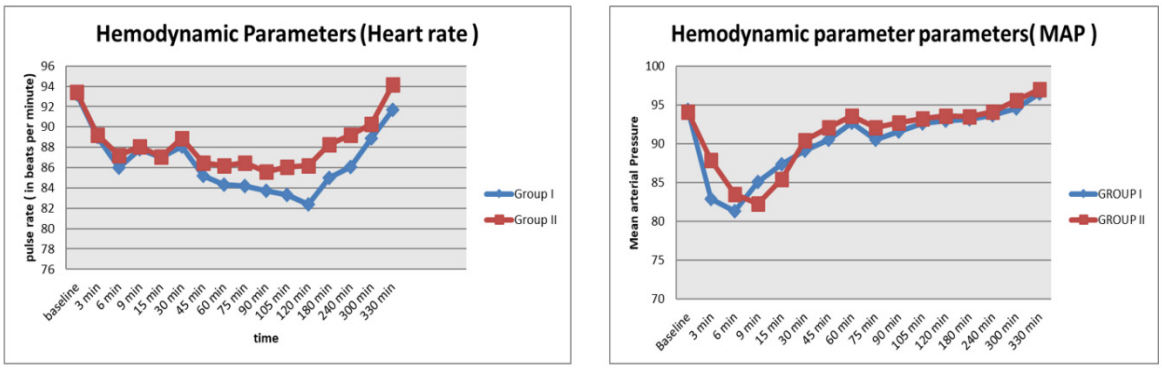

Figure 2: Hemodynamic trends

dose should ideally be compared in a multiarmed study with other higher doses or with other adjuvants. Even though the sample size was based on previous studies, a larger study is needed to generalize the results and find further explanations for unexplained findings.

CONCLUSION

Intrathecal 30 mcg buprenorphine as adjuvant intensified and prolonged the duration of bupivacaine-induced sensory spinal block without affecting the onset, intensity and duration of motor blockade. A combination of low-dose buprenorphine to bupivacaine can be safely employed for patients who undergo lower abdominal, perineal and lower limb surgeries without significant hemodynamic changes and adverse effects.

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