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Original Research Article

Comparative Evaluation of Low Dose Intrathecal Buprenorphine and Clonidine in Potentiating Post-Operative Analgesia by Subarachnoid Block for Lower Limb Orthopedic Surgery- A Randomized Double Blind Controlled Study

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Abstract

Introduction: In attempt to prolong post-operative analgesia by intrathecal block, it is necessary to use adjuvant with local anaesthetic agents. High doses of intrathecal adjuvant cause side effects. So to avoid this, in our study we used low doses of intrathecal buprenorphine and clonidine as adjuvant to local anaesthetics for lower limb orthopedic cases.

Methods: Ninety ASA I and II patients who were scheduled for femur fracture surgeries, either open or closed reduction with implantation, were enrolled in our study and randomly divided into three groups (30 of each).Patients in Group A - received intrathecal bupivacaine 0.5% (Heavy) 2.8 cc + 0.2 cc NS, Group B –intrathecal bupivacaine 0.5% (Heavy) 2.8cc+ buprenorphine 30 mcg (0.2cc), and Group C received intrathecal bupivacaine 0.5% (Heavy) 2.8cc + Clonidine 30mcg (0.2cc).The purpose of this study was to compare Buprenorphine and Clonidine in terms of their intra- and post-operative effects, their side effects, and their effects on the onset of pain,24-hVAS, and the amount of additional analgesic required when they were added to the local anesthetics in the spinal anesthesia we administered to elective femur fracture surgery patients.

Results: The duration of sensory and motor blockade and post-operative analgesia was significantly longer in both study groups when compared to the control group (group A), but significantly prolonged in buprenorphine group compared to clonidine group (group B vs. group C, $P < 0.05$). The total requirement of rescue analgesic was less in both study groups compared to the control group, but it was significantly lesser in buprenorphine group when compared to clonidine. Side effects such as bradycardia and hypotension were observed to be more with clonidine(n=9),10 patients in group B experienced PONV in comparison to 5 in group C, whereas sedation score of >3 was seen in 7 patients of buprenorphine group.

Conclusion: We conclude that both intrathecal buprenorphine and clonidine effectively prolong the duration of post-operative analgesia, but intrathecal buprenorphine is more effective in prolonging pain free period when compared to clonidine with insignificant side effects.

Keywords: Buprenorphine, Clonidine, Intrathecal, Post-operative analgesia.

Introduction

Post-operative recovery largely depends on the control of pain following surgery. Pain which is an unpleasant sensory and motor experience often hinders ambulation due to potential tissue damage[1]. In the present times, regional anesthesia is preferred because of its economic feasibility, rapid onset, accuracy, and relative ease of administration. Subarachnoid block using 0.5% hyperbaric bupivacaine is the most commonly used technique in patients undergoing lower limb and lower abdominal surgeries[2].

Opioids administered via intrathecal route along with local anesthetics (LA) synergize the analgesic effect of LA to relieve post-operative pain [1]. They prolong the duration of subarachnoid block and post-operative analgesia and potentiate recovery with reduced hospital stay. Buprenorphine, a semi synthetic opioid, is a μ-receptor agonist, an effective analgesic and is 25–100 times more potent than morphine[3]. At higher doses side effects such as pruritus, drowsiness, nausea, vomiting, and delayed respiratory depression are encountered. To overcome these adverse effects, other non-opioid adjuvant including alpha agonists such as clonidine and dexmedetomidine are being used[4].

Clonidine, an alpha-2 receptor agonist has been widely studied as adjuvant to LA and the results are very promising[4]. Yet, there are certain shortcomings, such as brady cardia and hypotension, which need to be considered [5]. Higher doses of buprenorphine and clonidine exert certain limitations, so to overcome these adverse effects with high intrathecal doses; we conducted this study using low doses of these drugs.

The primary objective was to evaluate the subarachnoid block in terms of the duration of sensory and motor blockade while the secondary objectives were to study the duration of post-operative analgesia, the hemodynamic parameters, and the total rescue analgesic requirement over 24h.

Materials and Methods:

Patients of either gender, in age group 20–60 years with a BMI<30kg/m2, belonging to the American Society of Anesthesiologists (ASA) physical status I and II scheduled for femur fracture surgeries under spinal anesthesia were enrolled for this study while patients who refused to participate in the study or those with pre-existing hypotension, bradycardia, significant coagulopathies, and /orallergies to LA were excluded from this study. A written informed consent was obtained from all enrolled patients (SKNMC/ethics/App/2021/786). All patients who were enrolled in the study were randomly divided into three groups using the chit-in-a box technique.

Group A had 30 patients who were administered intrathecalbupivacaine 0.5% (Heavy) 2.8cc + 0.2 cc NS. Group B with 30 patients were given intrathecal bupivacaine0.5 % (Heavy) 2.8 cc + buprenorphine 30 mcg (0.2 cc). Group C also had 30 patients and were administered intrathecal bupivacaine 0.5% (Heavy) 2.8cc+ Clonidine 30mcg (0.2cc).

All patients involved in this study underwent a detailed preanesthetic evaluation. The anesthesia and surgical plan were explained to patients in their language, so as to ensure that they could comprehend and a written informed consent was then obtained. Patients were also explained about the use of their data for research purpose and a written consent was obtained for the same. On the day of surgery, each patient was reviewed in the pre-operative room, overnight fasting of

minimum 8h was ensured, the patency of IV cannula was confirmed and their baseline pulse rates, and blood pressures were noted.

All standard monitors such as pulse oximeter, ECG leads, and non-invasive blood pressure monitoring were attached. Patients were preloaded with ringer's lactate at the rate of 10ml/kg and inj. ondensetron 4mg IV was administered. The patients were then positioned for subarachnoid block. Under strict aseptic precautions, lumbar puncture was done at L3–L4 interspace using 26-gauge Quincke spinal needle. After ensuring free flow of CSF, patients received the group specific drug. The observing anaestheist was blinded to the intrathecal administration of the drug.

Sensory blockade was assessed using the pin prick method and was graded using the 3-point scale[6]. 0-normal, 1-loss of sensation to pinprick, 2-loss of sensation to touch.

The duration of sensory block was defined as the time interval between completions of LA administration to complete recovery of sensation (grade0). Sensory blockade was assessed every 2 min until T8 dermatome was achieved. The highest level of sensory block was evaluated by pinprick at midclavicular line anteriorly every 2min for 15min after the injection, thereafter every 5min for next 15min.

Motor blockade was recorded by using Modified BromageScale[7]

Intraoperatively, hemodynamic variables such as pulse rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, oxygen saturation, and respiratory rate were initially measured at 5,10,15,20,25,30 intervals and every 15min thereafter until the end of surgery and then half hourly during the post-operative period in PACU and every 2 hourly after discharge from PACU to the ward until the first rescue analgesic was given.

The duration of post-operative analgesia was recorded using a Visual Analog Scale(VAS) 0–10[8]. VAS was assessed everyhalf an hour until the first 6h and then hourly until 24h. Once the patient begins to experience pain with VAS ≥ 4 (VAS 1–3is a bearable pain which the patient can accept), it is considered the end point of analgesic action of the drugs and study was terminated. Rescue analgesic – Inj. Diclofenac 1.5mg\kgIMgiven.

0 - No pain1–3-Mildpain

4–6-Moderatepain >6 – Severe pain and sedation score. The time for first rescue analgesic was taken as the duration of post-operative analgesia.

Residual sedation was assessed using the Ramsay Sedation Score as given under[9].

Patients were observed for complication ssuch as nausea, vomiting, pruritis, bradycardia, hypotension, convulsion, hematoma, dryness of mouth and respiratory depression.

Statistical Analysis

Sample size was calculated based on the previous study by Arora et al. [10]. To attain a confidence level of 95% and the test power of 80%, a minimum of 25 patients were needed in each group. Considering the dropouts a sample of 30 was taken in each group and 90 patients were enrolled for the study. All values are reported as mean ± standard deviation (SD). Chi-square/Fischer exact test was used to find the significance of study parameters on a categorical scale between two or more groups. Unpaired Student's t-test was

Used for intergroup comparison of various data obtained such as the duration of sensory and motor blockade and duration of post-operative analgesia. Differences were considered statistically significant when $P < 0.05$. Consort flow chart for the study is given(Fig.1)

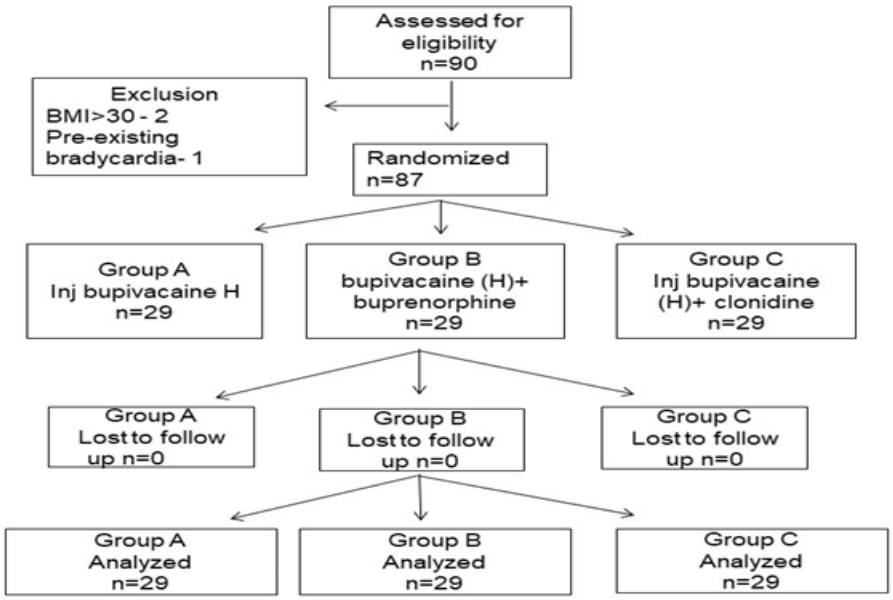

Figure 1: consort flow chart for the study

Results:

By comparing the mean ± SD and calculating unpaired t-test(P>0.05), there was no statistically significant difference in the demographic data of our study group (Table 1). The mean duration of sensory action of group B was longer 436.93 ±9.61 min than group C 321.52±7.12 min (P<0.00001). Similarly, the mean duration of motor action was also significantly longer in group B (404.21 ± 13.37 min) than group C (287.28±10.73min) with P<0.00001. The mean duration of post-operative analgesia in group B was 512.5±22.49 and in group C was 390.86±27.65. This was also statistically significant (Fig.2). Similarly, the average VAS scores were higher in group C than group B in early as well as late post-operative period. The total dose of rescue analgesic (Inj. Diclofenac 1.5 mg\kg IM given) required is depicted in the graph below (Fig.3).

All three groups exhibited side effects that were not statistically significant, P>0.05 (Table2). Ingroup C 12 patients of 29 had Intra-operative hypotension, whereas only 7 out of 29 patients in group B had hypotension. Ten patients in group B experienced PONV, whereas only 5 patients of 29 in group C complained of PONV. Somnolence was slightly higher in group B, 8 patients had sedation score of >3 in group B while 3 in group C.

Table 1: Demographic Details

	Group A	Group B	Group C	P value
Age (years)	34.52±11.82	31.69±10.80	32.0 ±10.22	P=0.569 Not significant
BMI (kg/m^2)	24.91±2.59	24.32±2.21	24.29±2.28	P=0.536 Not significant
ASA I II	17 12	16 13	16 13	
Duration of surgery	106.62±14.31	102.10±31.27	101.83±15.49	P=0.324 Not significant

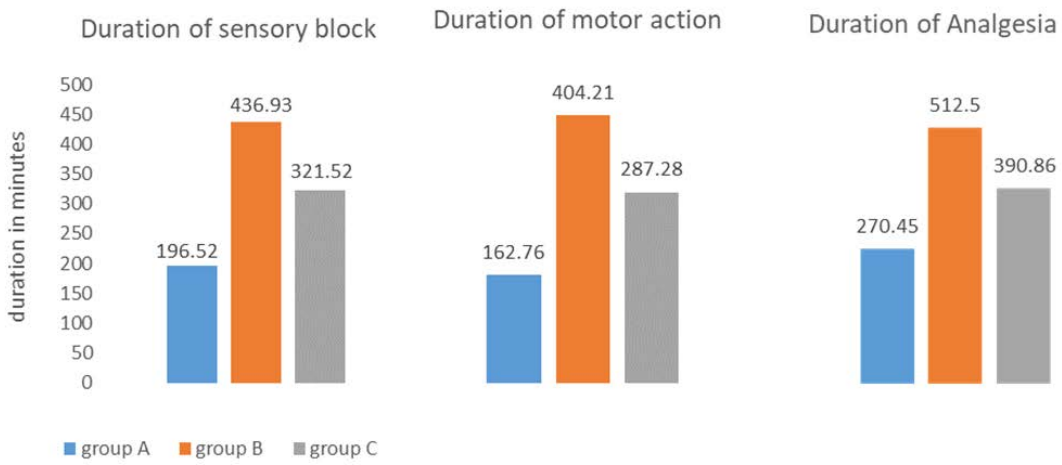

Figure 2: Duration of sensory and motor block

Table 2: adverse effects

	Group An=29	Group Bn=29	Group Cn=29
Bradycardia<60bpm	2	3	9
Hypotension<20% baseline	3	7	12
PONV	4	10	5
Somnolence Sedation score ≥3	NIL	8	3
Pruritis	NIL	NIL	NIL

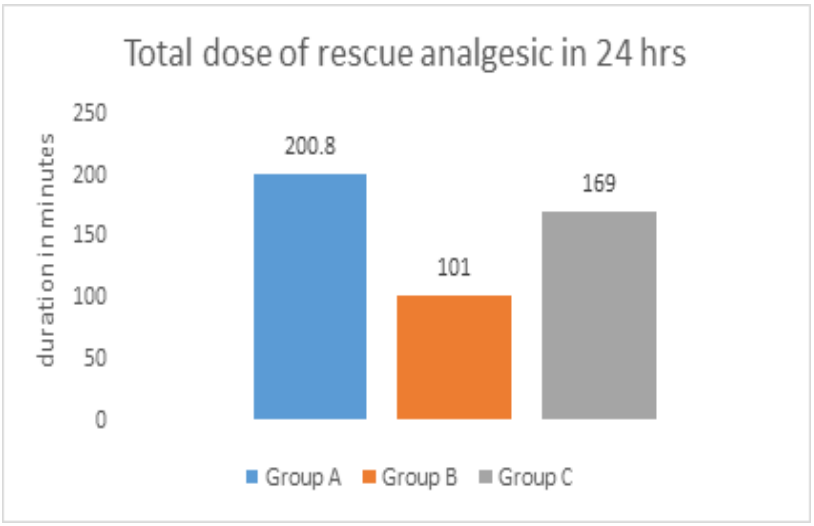

Figure 3: The total dose required in 24hr

Discussion:

Better post-operative analgesia with 30µgms of buprenorphine than 30 µgms of clonidine. To the best of our knowledge this the first study comparing 30 µgms of buprenorphine with 30 µgms of clonidine and using low doses of adjuvant demonstrated very promising results which can definitely be used in high risk (ASA III and IV) cases where the adverse effects of these drugs need to be avoided yet the extent of analgesia has to be prolonged.

Buprenorphine is known to exert its action by binding to opioid receptors with

especially high affinity for μ and kappa receptors while some action is also exerted via delta receptors[11, 12]. Due to its lipid soluble characteristics buprenorphine is rapidly absorbed into the spinal venous plexus reducing the risk of respiratory depression associated with rostral spread[13].

Clonidine, after administration, affects arterial BP by its opposing action at multiple sites. Blood pressure typically decreases in hypertensive patients more than in normotensive patients. Clonidine also reduces heart rate partly by presynaptic mediated inhibition of norepinephrine release at the neuro receptor junction and partly by a vagomimetic effect[5]. Also, combining α2-adrenergic receptor agonists with LA can potentially increase the degree of sympatholysis and result in hypotension. Clonidine is believed to prolong the motor blockade produced by local anesthetic agents by local vasoconstriction action on vascular smooth muscle(α-receptors), which decreases absorption of local anesthetic from subarachnoid space there by prolonging the duration of action[14,15,16].

Arora et al. also, in their study had compared similar doses of 50 mcg of buprenorphine and 50mcg clonidine as adjuvant to bupivacaine in lower limb orthopedic surgeries in ASA I and II patients[10].

Pravinet al. used 60 mcg of both clonidine and buprenorphine each as adjuvant to 15 mg bupivacaine for intrathecal administration and noted that buprenorphine provided longer duration of post-operative analgesia when compared to clonidine (818.9 ± 135 min vs. 686.5 ± 41.9min) [16]. While the average duration of analgesia with buprenorphine and clonidinein our study was 512.5 min and390.86 min, respectively. The reduced duration of analgesia in our study as compared to the study by Pravin et al. reflects a dose dependent increment in duration of analgesia by both drugs.

Ramya et al. studied 45 mcg of buprenorphine and 22.5 micrograms of clonidine in subarachnoid block and reported a longer pin free period with buprenorphine [17]. The duration of post-operative analgesia reported was similar or rather lesser (448.47 ± 78.08 min) than the duration inferredin our study (512.5 min). Hence, it can be concluded that lower dose of buprenorphine can be used to provide similar post-operative analgesia as with a 1.5 times higher dose, while the dose of clonidine projected a dose dependent potentiation of duration of analgesia when compared to the study by Ramya et al. At the offset of longer duration of analgesia, the associated adverse effects also show a rise. In their study, they report an incidence of PONV in 17.5% in buprenorphine group while 7.5 %in clonidine group. The VAS scores in concurrence with duration of pain free period showed lower scores with buprenorphine in comparison to clonidine, while the scores in control group were high as expected in the early post-operative period.

Borse et al. studied 150mcg of buprenorphine with bupivacaine and reported lower VAS scores when buprenorphine was added[18]. Grandhe et al. studied two different doses of clonidine and reported a dose dependent improvement in VAS scores with higher doses of clonidine[15]. They concluded that patients treated with 1.5mcg/kg clonidine had lower VAS scores than patients treated with 1mcg/kg clonidine.

We studied the influence of study drugs on hemodynamic parameters and found that the clonidine causes more of hypotension and bradycardia while buprenorphine was more efficient in maintaining hemodynamic parameters.

Pravin et al. reported hypotension in 2.5% patients and bradycardia in 5% cases of the study population. They had used 60 mcg

of both buprenorphine and clonidine in lower limb orthopedic surgery. Thakur et al. compared two doses of clonidine and reported a more pronounced hypotension with 30 mcg of clonidine when compared to 15 mcg of clonidine[4]. The dose of 15mcg does not potentially prolong the duration of postoperative analgesia hence not advisable though the incidence of hypotension is less.

The adverse effects encountered with buprenorphine are those of somnolence and PONV. The incidence of hypotension and bradycardia are not notable. In our study, 12% cases in buprenorphine group had sedation score of 4 or more while 5% patients of clonidine group had sedation score of 3 or more. Pathak and Engti studied 75 mcg buprenorphine with fentanyl for subarachnoid block and reported higher sedation scores with buprenorphine[1]. Pravin et al. reported somnolence in 7.5% patients of buprenorphinegroup and 2.5% cases of clonidine group.[19]

Total consumption of rescue analgesic is significantly reduced in buprenorphine group when compared to clonidine group and control group. Ramya et al. also reported similar results in their study where 66% cases of buprenorphine group demanded 2 doses of rescue analgesic while 77% cases of clonidine group needed 3 doses of rescue analgesics.

We authors accept certain limitations of the study. Studies with larger sample size including ASA III and IV cases need to be conducted. Furthermore, the onset of sensory and motor block was not considered as a study parameter which needs to be studied with such lower doses of adjuvant.

Conclusion

To conclude, 30mcg of buprenorphine is more effective than 30 mcg clonidine in potentiating subarachnoid block when used as adjuvant to 0.5% bupivacaine (H) in lower limb orthopedic surgeries. The incidence of hypotension and bradycardia was lower in buprenorphine group when compared to clonidine, while the complaints of PONV andsedation were more in buprenorphine group than clonidine but not significant enough to hamper post-operative ambulation.

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