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COMPARISON OF EFFECT OF INTRATHECAL BUPRENORPHINE VERSUS CLONIDINE AS ADJUVANT TO 0.5% BUPIVACAINE IN LOWER LIMB SURGERIES.

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ABSTRACT

Background and aims: There are very few reported clinical trials with direct comparison of buprenorphine and clonidine on subarachnoid block characteristics. The aim of the present study was to compare the effect of buprenorphine 75 µg and clonidine 50 µg as an adjuvant to 15 mg of 0.5% bupivacaine in lower limb surgeries with respect to the subarachnoid block characteristics, postoperative analgesia and side-effects.

Methods: One hundred patients of 18 to 60 years, either sex and American Society of Anesthesiologist (ASA) I/II undergoing elective lower limb surgeries under planned spinal anesthesia were included and randomly allocated into two equal groups (n = 50 each) to receive intrathecal 0.5% bupivacaine (heavy) with either clonidine 50 µg (group C) or buprenorphine 75 µg (group B) . The patients were evaluated with respect to various sensory and motor block characteristics, duration of postoperative analgesia and adverse effects.

Result: Both the groups were comparable with respect to demographic profile. There was significant prolongation in the duration of sensory block (119.26 ± 24.56 *vs* 79.40 ± 15.67; p = 0.0), motor block (277.90 ± 37.56 *vs* 198.80 ± 42.21; p = 0.0) and postoperative analgesia (355.80 ± 63.85 *vs* 283.20 ± 51.84; p = 0.0) in group C compared with group B. There was clinically significant earlier onset of maximum sensory block (9.20 ± 5.69 *vs* 11.90 ± 4.78; p = 0.018) and motor block (5.10 ± 3.39 *vs* 11.90 ± 4.78; p = 0.018) in group C compared with group B however the results were statistically significant only for time to attain maximum sensory block. The incidence of shivering was significantly lower in group C compared with group B.

Conclusion: Intrathecal 50 µg clonidine seems to be an attractive alternative to 75 µg buprenorphine as an adjuvant to spinal bupivacaine in terms of duration of sensory and motor blockade, postoperative analgesia and having less side-effects

KEYWORDS : Adjuvants, buprenorphine, clonidine, bupivacaine .

INTRODUCTION: Though subarachnoid block is widely used for lower limb surgeries, it has practical limitations in prolonged surgeries. Weaning of the effects of subarachnoid block is very embarrassing for the anesthesiologist, discomforting for the surgical team, and excruciatingly unbearable for the patients. From time to time, various methods including the addition of adjuvants to local anesthetics (LAs) have been tried but with a varying success. Adjuvants are pharmacological agents possessing little pharmacological effect by themselves,

but enhance or potentiate the action of other drugs when given at the same time. Synergistic action between several analgesic drugs and local anesthetics has been demonstrated. Clinical studies have evaluated the efficacy of both opioids and alpha 2 adrenergic agonists as an adjuvant to intrathecal bupivacaine and found them to be effective. Opioids and local anesthetics administered together intrathecally are known to improve the quality of intraoperative analgesia and also provides postoperative pain relief for longer duration. Intrathecal α2 agonist like clonidine are extensively being evaluated as an alternative to neuraxial opioids and has proven to be a potent analgesic with relief from somatic as well as visceral pain both intra and post operatively with fewer side effects. The present study was thus undertaken to compare the effects of buprenorphine (75 µg) added to 15 mg of 0.5% bupivacaine to that of clonidine (50 µg) added to the same in orthopedic lower limb surgeries for prolongation of intra and post operative analgesia.The secondary outcomes included any variation in hemodynamic parameters and side effects if any associated with administration of these two drugs when used as intrathecal adjuvant with bupivacaine.

Materials and Methods :

After approval from the hospital ethical committee, written informed consent was taken from all 100 American Society of Anesthesiologist Physical Status I and II patients, aged between 18 and 60 years , of either sex undergoing elective lower limb surgery under intrathecal block. The patients with cardiovascular, neurological, respiratory, renal or endocrine diseases contraindications to spinal anesthesia, allergy to any of the study drugs and pregnant patients were excluded from the study. Patients were kept fasting for 6 hours preoperatively and no premedication was given. The patients were instructed in the use of numerical rating scale (NRS) of pain scale (NRS; 0-No pain, 10-Worst possible pain).

Preoperative evaluation was carried out in all patients with detailed history, general physical examination including height and weight, evidence of any special deformity or any neurological disease and mental status of the patient. Pulse rate, blood pressure, respiratory rate and oxygen saturation in room air were noted and systemic examination was performed. The patients were randomly divided into two groups of fifty each (n = 50) using a computer random number sequence.

After wheeling the patients in a prepared operation theater on the day of the surgery, monitoring devices like electrocardiography (ECG), pulse oximetry (SpO2), non-invasive blood pressure were attached and baseline vitals recorded. Equipments and drugs necessary for resuscitation and general anesthesia administration were kept ready A senior postgraduate of anesthesiology well experienced in administering subarachnoid block and who was unaware of the study design performed the procedures and carried out all the observations . An 18 gauge intravenous cannula was secured on the dorsum of either arm and pre-loading done with 10 ml/kg of Ringer lactate solution. The patients were randomly assigned using computer generated random list into two groups to receive intrathecally either: group C: 15 mg hyperbaric bupivacaine 0.5% + 50 µgm clonidine or group B: 15 mg hyperbaric bupivacaine 0.5% + 75 µgm buprenorphine . After all aseptic preparation, subarachnoid block was given at the L2-3/L3-4 interspace using a Quincke needle (25-gauge) with the patient in lateral position. After confirming free flow of clear cerebrospinal fluid, the study drug was injected slowly as per group allotment and the patient was turned supine. All the patients received oxygen 3-4 L/min through a facemask during perioperative period. All the onset and duration times were recorded with respect to completion of intrathecal injection as time 0.

Onset of sensory block was taken as the time from injection of the study drug in the subarachnoid space until the time when maximum sensory level was achieved. The sensory blockade was assessed with bilateral pin prick method with sterile 25 G hypodermic needle in midclavicular line.The highest dermatome showing sensory analgesia was taken as the upper segmental level of block when it remained same even after 5 min. Total duration of sensory block was taken as an interval from intrathecal administration of the study drug to regression of sensory block to S-1 level.

The level of motor block was assessed by modified Bromage scale: 0:

Patient able to move hip, knee and ankle, 1: Able to move knee and ankle, cannot move hip, 2: Able to move ankle, can not move hip and knee, 3: Unable to move hip, knee or ankle. The onset and duration of motor block was defined as the tome to attain Bromage 3 and return of motor power to Bromage 0 respectively.

Pulse rate, blood pressure, respiratory rate, oxygen saturation, sedation and visual analog scale (VAS) were monitored continuously every 2 minutes for first 10 minutes, every 5 minutes for 30 minutes, every 30 minutes for 180 minutes and every 60 minutes till complete recovery from block and till demand for first rescue analgesic by patient. A fall of systolic blood pressure of less than 80 mm Hg or more than 20% of baseline was considered as hypotension and treated with rapid infusion of intravenous fluid Ringer lactate 250 ml and 6 mg intravenous ephedrine if there was no response to intravenous fluid administration. Heart rate of less than 50 beats per minute was considered as bradycardia and treated with injection atropine sulfate 0.6 mg intravenously.In the postoperative period the level of sedation was assessed using Ramsay Sedation Score: I: Patient is anxious, agitated and restless or both, II: Patient is cooperative oriented and tranquil, III: Patients respond to verbal commands only, IV: Patient exhibits brisk response to glabellar tap or loud auditory stimulus, V: Patient exhibits sluggish response to glabellar tap or loud auditory stimulus, VI: Patient exhibits no response. The patients were assessed for postoperative pain and injection diclofenac sodium 1.5 mg/kg was given as the rescue analgesic when numerical rating scale (NRS) $\geq$ 3. The time to requirement of first rescue analgesia was taken as the duration of analgesia. Intraoperative side effects like sedation, nausea and vomiting, shivering, bradycardia and dryness of mouth requiring active treatment were also noted.

RESULTS:

Both the groups were comparable with respect to age, weight,height,ASA physical status and duration of surgery.(Table 1). Mean duration of surgery was 144 ± 18.45 minutes in clonidine group and 146 ± 10 .26 minutes buprenorphine group, which was insignificant statistically. The subarachnoid block characteristics have been depicted in Table 2. Fortyone (82%) patients in clonidine group achieved the maximum sensory level within 10 minutes, while only 26 (52%) patients in buprenorphine group could achieve this in 10 minutes . All the patients in both the groups achieved grade III motor blockade, only the difference was time required to achieve this. Almost 82% (41 patients) in clonidine group attained a grade III motor blockade within 6 minutes of commencement of motor blockade, compared to only 11 patients (22%) in
Buprenorphine group .

Thirty-six (72%) patients in clonidine group had two segment regression time of sensory level in 90 to 120 minutes .It was found that 42 (84%) patients in buprenorphine group depicted a two segment regression time within 90 minutes, and all patients depicted the same within 120 minutes (2 hours). Motor blockade was maintained for 241 to 300 minutes by

Table 1: Demographic Profile

Variable	Group C (Clonidine; n = 50)	Group B (buprenorphine; n = 50)
Age (years)	44.20 ± 12.34	43.65 ± 11.40
Height (cm)	164.28 + 5.61	163.18 + 4.35
Weight (kg)	58.10 ± 7.13	59.60 ± 5.26
Sex (M/F)	11:39	12:38
ASA I/II	42/8	44/6
Duration of Surgery (min)	144±18.45	146±10.26

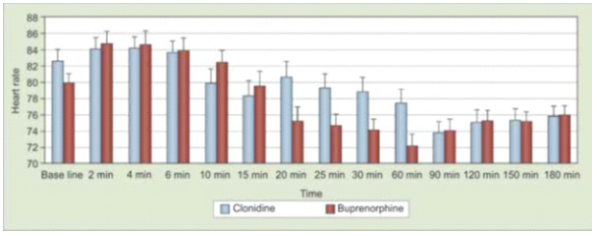
Table 2: Subarachnoid block characteristics

Variable (minute)	Group C (clonidine; n = 50)	Group B (buprenorphine; n = 50)	p-value
Onset time of highest SBL	9.20 ± 5.69	11.90 ± 4.78	0.018*
Highest SBL	T7 (T3–T10)	T8 (T5-T10)	0.05
Motor block onset time	5.10 ± 3.39	8.32 ± 2.78	0.06
Sensory block duration	119.26 ± 24.56	79.40 ± 15.67	0.00*
Motor block duration	277.90 ± 37.56	198.80 ± 42.21	0.00*
Duration of postoperative analgesia	355.80 ± 63.85	283.20 ± 51.84	0.00*

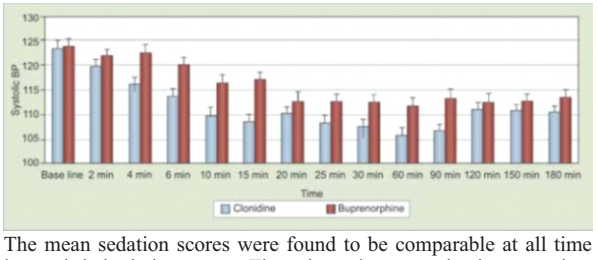
*Significant

maximum number of patients, 29 (58%) in clonidine group as compared to only 4 patients (8%) in buprenorphine group, where duration of motor blockade lasted for < 240 minute in 46 (92%) of patients. Twenty-five patients (50%) in buprenorphine group and 16 (32%) in clonidine group had duration of analgesia in between 241 to 300 minutes . Nineteen (38%) of patients in clonidine group had analgesia for 301 to 360 minutes, which was observed in only in 11 (22%) patients in buprenorphine group . A duration of 361 to 480 minutes analgesia was observed in 13 (26%) patients in clonidine group while none in buprenorphine group had
analgesia more than 360 minutes.

Graph 1 : Mean pulse rate



Graph 2 : Mean systo;ic blood pressure



The mean sedation scores were found to be comparable at all time intervals in both the groups . Thus, the patients remained cooperative, calm and tranquil at all time intervals. Maximum number of patients in both the groups exhibited a score of 2 to 3 at all the time intervals. Mean pulse rate noted at various time intervals were found to be statistically comparable ($p > 0.05$) between the groups at all respective time intervals (Graph 1). Mean systolic blood pressure was statistically less in clonidine group than buprenorphine group from 6 to 90 minutes after intrathecal drug administration (Graph 2).

The incidence of adverse effects is shown in Table 3.

Table 3: Adverse effects

Variable	Group C (clonidine;n = 50)	Group B (buprenorphine;n = 50)	p-value
Bradycardia	4 (8%)	3 (6%)	0.698
Hypotension	5 (10%)	3 (6%)	0.298
Prurtis	1 (2%)	4 (8%)	0.341
Shivering	1 (2%)	7 (14%)	0.028*
Nausea & vomiting	2 (4%)	3 (6%)	0.649
Retention of urine	1 (2%)	3 (6%)	0.312
Respiratory depression	0 (0%)	0 (0%)	
Dryness of mouth	8 (16%)	2 (4%)	0.112

*Significant

DISCUSSION:

Spinal anesthesia is the fastest, predictable and most reliable form of anesthesia for infraumbilical surgeries. The quest for safer anesthesia procedure with reduction of LA dose by addition of adjuvants seems to

be never ending. The results of current study have established that the addition of buprenorphine and clonidine to this LA bupivacaine produced better anesthetic and analgesic effects with minimal side effects when compared to administration of bupivacaine alone for lower limb surgeries.

Bupivacaine, apart from providing sensory and motor blockade, also provides some pain relief in the initial postoperative period. But the duration of analgesia is not lengthy enough to relieve pain for extended period in postoperative setting after wearing off of the local anesthetic effect. Relief of intraoperative and postoperative pain is professionally rewarding and is a subject that has gained attention in past few years. Pain during surgery or in the postoperative period increases morbidity by causing (1) Sympathetic stimulation increased heart rate, blood pressure, altered regional blood flow, increased oxygen consumption and (2) stress response due to hormonal surge and depressed immune functions. Benefits of pain prevention and control are moral and ethical, thus postoperative pain treatment must be included in the anesthetic planning even before induction of anesthesia.

Buprenorphine is an opioid of the phenanthrene morphine class with extremely high binding affinity at the μ-and kappa receptor. It has partial agonist activity at the μ-and kappa opioid receptor, partial or full agonist activity at the opioid receptor-like 1/nociception and delta opioid receptor and competitive antagonist activity at the κ-opioid receptor. Low dose intrathecal buprenorphine increases sensory block, duration of analgesia without affecting motor block and is associated with minimal side-effects. Intrathecal buprenorphine in doses of 75 μg induces rapid onset of analgesia and lacks the side effects that can be attributed to higher doses.Dixit et al stated that 60 μg buprenorphine given intrathecally to pregnant patients prolonged the duration of analgesia with negligible side effects.

Clonidine is a selective partial agonist for α2 adrenergic receptors and it is the most studied drug used for neuraxial anesthesia. It is more potent after neuraxial than systemic administration indicating spinal site of action and favoring neuraxial administration. It is moderately lipid soluble, easily penetrates the blood brain barrier leading to spinal and supra spinal receptor binding and thus provides effective and long lasting post-operative analgesia. Antinociceptive action of Clonidine exists for somatic and visceral pain. Clinical efficacy of Intrathecal Clonidine to relieve visceral pain in well-established but Clonidine is also associated with few side effects like bradycardia, hypotension and dry mouth. So, 50μg dose of Clonidine was chosen in our study, as higher doses (150ug) are also associated with significant risk of hypotension as reported by Chiari et,al.

The demographic data, such as age, sex, height, and weight were comparable among the groups thereby not having any influence upon the outcomes. The meantime to achieve maximum SBL in our study was 9.20 ± 5.69 and 11.90 ± 4.78 in group C and B respectively. The faster onset time in our study compared to the earlier studies by other authors might be due to the higher dose of clonidine (50 μg) and buprenorphine (75 μg) in our study. The median highest dermatome of T8 in group C in our study is in conjunction with those of De Kock et al and Dobrydnjov et al.

CONCLUSION:

In conclusion, 50 μg clonidine seems to be an attractive alternative to 75 μg buprinorphine as an adjuvant to spinal bupivacaine in lower limb orthopedic surgery especially those of longer duration. In our study, we found that clonidine is better in terms of quality of intraoperative analgesia, sensory and motor blockade, postoperative analgesia and have less side-effects. We found that shivering was significantly less with clonidine in comparison to buprenorphine which could be beneficial for patient during intraoperative and postoperative period. Further due to long motor blocked with clonidine, it is better for long duration orthopedic surgery while buprenorphine may be better in day care orthopedic surgeries like knee arthroscopy.

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