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Intrathecal Bupivacaine and Bupivacaine with Different Doses of Clonidine in Lower Limb Orthopedic Surgeries-A comparative study in a tertiary healthcare Centre.

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I. INTRODUCTION:

Spinal anesthesia is used for providing sensory and motor block for lower limb surgeries. The onset and the duration of anesthesia can be prolonged with addition of adjuvant drugs. This is by the help of opiate receptors in the brain and substantia gelatinosa of spinal cord that revolutionized the concept of pain relief.[1] An ideal adjuvant continued because opioid adjuvants were associated with side effects such as pruritis, nausea, and delayed respiratory depression. Clonidine, an imidazoline compound, is a selective agonist for α_2- adrenoceptors with an α_2:α_1 selectivity ratio of approximately 220:1.[2] The antinociceptive properties of clonidine were first described in 1974 by Paalzow.[3]

Analgesic effects of intrathecal clonidine are due to interruption of nociceptive stimulus in the periphery, in the spinal cord and in supraspinal sites. It blocks conduction of C and Aδ fibers by increasing potassium conductance.[4]

Many studies conducted in the past have used clonidine in doses of 15–150 μg intrathecally, but higher doses were associated with hemodynamic instability and systemic side effects.[5]

Our present study using low doses of clonidine as an adjuvant to bupivacaine in lower limb surgeries. The aim of our study was to evaluate the efficacy of intrathecal clonidine in doses of 15mcg and 30 mcg, and to find the dose of clonidine that would produce optimal analgesia with minimal hemodynamic instability and motor block.

II. MATERIALS AND METHODS:

The present study was conducted in a randomized, double-blind manner after the approval of hospital ethical committee. A written informed consent was obtained from all patients. A total 75 adult patients of either sex belonging to physical status American Society of Anesthesiologists (ASA) Classes I and II scheduled to undergo lower limb orthopedic surgery, under subarachnoid block, were randomly allocated into either of three study groups of 25 patients each in a random manner. Patients in Group A received 12.5 mg with 0.5 ml of normal saline, in Group B patients received intrathecal bupivacaine 12.5 mg with clonidine 15 μg (0.1 ml), and 0.4 ml of normal saline and patients in Group C received bupivacaine 12.5 mg with clonidine 30 μg (0.2 ml) and 0.3 ml of normal saline intrathecally. A total volume of 3 ml was made in all groups using normal saline. The preservative free drugs were choosen. The anesthesiologist and the patients were blinded to the study solutions.

Patients with a history of significant coexisting disease, any contraindication to regional anesthesia, history of anaphylaxis to local anesthetic and allergy to the drugs to be used, history of disease predisposing to altered sensation such as diabetes mellitus and neuropathies, with spinal deformities, morbidly obese patients. Patients with coagulation disorder, local skin infection or disease, patients with increased intracranial pressures and patients with atrioventricular blocks were excluded from the study.

A thorough preanesthetic check-up was conducted a day prior to surgery. All routine investigations such as complete hemogram, urine routine, random blood sugar, renal function test, electrocardiography (ECG), and chest radiograph were done. Special relevant investigations were conducted wherever indicated. Patients were familiarized with visual analog scale (VAS) preoperatively .Patients were kept nil per oral for at least 6 h before surgery. All patients were premedicated with oral alprazolam 0.5 mg and ranitidine 50 mg at night before surgery and in the

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morning on the day of surgery with sips of water. After shifting to OR patient's baseline parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), peripheral oxygen saturation (SpO_2), and ECG was recorded. Clonidine was measured by the help of insulin syringe and mixed with bupivacaine. These solutions were prepared in a 5 ml syringe by an separate anesthesiologist after achieving intravenous access and preloading with 15 ml/kg of lactated Ringer's solutions.

Under strict aseptic conditions lumbar puncture was performed in sitting position at the level of L_3–L_4 or L_4–L_5 intravertebral space using 25G Quincke's spinal needle after infiltrating the skin with 0.5–1 ml of 2% lidocaine. After obtaining free flow of cerebrospinal fluid, study drug was injected intrathecally at approximately @ 0.20 ml/s. After administering the drug, spinal needle was taken out, the patient turned to site of surgery by tilting the table position immediately, and position of operation table was kept horizontal after 7 minutes.

The onset and duration of sensory block, highest dermatomal level of sensory block, motor block onset, time to complete motor block recovery, and duration of spinal anesthesia were recorded.

The onset of sensory block was defined as the time between injection of intrathecal anesthetic and the absence of pain at the T_{8-9} dermatomes, assessed by pinprick.

The highest level of sensory block was evaluated by pinprick at midclavicular line anteriorly every 5 min for 20 min after injection and there after every 30 min. The duration of sensory block was defined as the time of regression of two segments in the maximum block height, evaluated by pinprick. Motor block onset was assessed with bromage score. Time for motor block onset was assumed when bromage score becomes three. Modified bromage scale was followed according to which: 0 – able to raise the whole lower limb at the hip, 1 – able to flex the knee but unable to raise the leg at hip, 2 – able to plantarflex ankle but unable to flex the knee, and 3 – no movement of lower limb. Complete motor block recovery was assumed when Bromage score became zero. The duration of spinal anesthesia/mean time to analgesic request was defined as the period from spinal injection to the first occasion when the patient complained of pain in the postoperative period.

Surgery was allowed to commence on achieving adequate sensory block height (T8–9). Sensory block was recorded every 5 min after intrathecal injection till 20 min from the time of injection. Motor block was recorded till the Bromage score became three. SBP, DBP, HR, RR, and SpO_2 were recorded 5 min before intrathecal injection and then every 5 min for first 30 min and then at 45, 60, 75, 90, 120, 150, 180 min till the end of the surgery. Intravenous fluid (Lactated Ringer's solution & 0.9% Normal Saline) was given to maintain the blood pressure. If SBP was more than 30% below the baseline or 90 mm Hg, intravenous ephedrine6 mg, was given repeatedly. If HR was less that 50 beats/min, 0.6 mg of atropine sulfate was administered intravenously. The incidence of hypotension (fall in mean arterial pressure >20% of the baseline), bradycardia (HR <50 beats/min), hypoxemia, and excessive sedation was recorded. At the completion of surgery all hemodynamic parameters (HR, SBP, DBF, RR, and SpO_2), sensory and motor block was recorded, and then, the patient was shifted to the recovery room.

Immediately after shifting the patient to postoperative recovery room, HR, SBP, DBF, RR, and SpO_2 was recorded every 30 min, either till 3 h or till the time of analgesic request, which ever was longer. Pain scores using VAS was assessed in the postoperative period. Postoperative pain was treated using intravenous paracetamol 1 g every 6 hourly in all patients. For severe pain (VAS >5) Inj.Tramadol 50-100 mg was given intravenously. Side effects such as sedation, nausea, vomiting, respiratory depression, or any other complications were noted. All observations were recorded by an anesthesiologist who was blinded to the group allocation of the patient.

A sample size of 25 patients in each group was selected to achieve a power of 80% and accepting an α error of 0.05, to be able to detect a difference of at least 50 min in the mean time of analgesic request in clonidine groups.

After completion of the study, observations obtained were tabulated and analyzed using statistical methods. The blind was opened at the end of the study for the purpose of evaluating the ethical efficacy of the treatment given to the patient. At the end of study all collected data were analysed using Statistical Package for Social Sciences version 16.0 statistical analysis software. The values were represented in number (%) and mean ± SD. Analysis of variance (ANOVA) was used for parametric data while Student's t-test and Chi-square test was used for non parametric data. $P < 0.05$ was considered statistically significant.

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III. OBSERVATIONS AND RESULTS:

There were no intergroup differences as regards to the demographic profile and ASA physical status of patients enrolled in our study. The mean age of patients in Group A was 42.04 ± 14.67, in Group B was 44.12 ± 16.82, and in Group C was 46.10 ± 19.07. The mean height of patients in Group A was 168.58 ± 5.98, in Group B was 163.96 ± 5.17 and in Group C was 167.34 ± 5.75. The mean weight of patients in Group A was 64.4 ± 9.51, in GroupB was 65.53 ± 6.16 and 66.42 ± 6.53 in Group C. There were 14 male and 11 female in Group A, 16 males and 09 females in Group B and 15 males and 10 females in Group C which was statistically insignificant. The groups were also comparable in the duration of surgery with Group A lasting 79.00 ± 18.97 min, Group B for 69.8 ± 26.64 and Group C lasting for 72.80 ± 25.14 min. There were no significant differences between the three groups regarding preoperative HR, SBP, and DBP, RR, and oxygen saturation.

The mean time of onset of sensory block was 6.80 ± 2.84 min in Group A, 5.80 ± 1.87 min in Group B and 5.20 ± 1.00 min in GroupC, which was significantly shorter in Group C. The difference in time of onset of the block was not significant between Group B and Group C.

The mean duration of sensory block was significantly prolonged in Group B and GroupC, with Group A having 128.40 ± 33.00 min, 140.40 ± 43.05 min in Group B, and 175.20 ± 37.43 min in Group C.

The mean time of onset of motor block was significantly shorter in Group B (5.60 ± 1.65) and C (5.0 ± 0) as compared to Group I (12 ± 2.50). However, there was no statistically significant difference between Group B and Group C.

The duration of motor block was significantly prolonged in Group C(171.60 ± 38.20) as compared to Group A (113.20 ± 35.79) and Group B (115.20 ± 38.41) whereas no significant difference in the motor block was found in between Group A and Group B.

The time of analgesic request in Group A was 148.16 ± 43.99 min, 190.60 ± 38.08 in Group B and 200.80 ± 59.85 min in Group C. The time of analgesic request was significantly prolonged in Group B and Group C ($P < 0.05$). The vital signs such as HR, SBP, DBP, RR, oxygen saturation were comparable in all the three groups throughout the postoperative period.

Among side effects, hypotension occurred in three patients in Group C, which was statistically significant as compared to Group A and Group B. Two patients had bradycardia in Group C which was statistically not significant. The incidence of sedation was higher in clonidine groups, two patients in Group B, and eight patients in GroupC, which was statistically significant. None of the patients in any group developed respiratory depression or pruritis.

IV. DISCUSSION:

Intrathecal clonidine is an α_2 adrenergic agonist having potent antinociceptive properties. It results in the prolongation of sensory and motor blockade and a reduction in the amount or concentration of local anesthetic required to produce prolonged perioperative analgesia, thereby reducing the incidence of side effects.

The dosages used in our study are based on data from various studies, where hemodynamic stability and a significantly reduced incidence of side effects have been reported in dosages ranging between 15 and 150 µg of clonidine.[6,7,8]

The onset of sensory block was significantly early in Group B and Group C as compared to Group A. The duration of sensory block (in minutes) was significantly prolonged in clonidine groups, i.e., Group B (140.40 ± 43.05) and C (175.20 ± 37.43) as compared to Group A (128.40 ± 33.00).

The results of our study are in accordance with observations of various studies which concluded that the duration of sensory block was significantly prolonged by the addition of intrathecal clonidine.[7,9,10,11,12] The possible mechanisms involved in potentiating the sensory block include suppression of the activity of wide dynamic range of neurons and release of substance P in the dorsal horn of spinal cord by activation of pre- and post-synaptic α_2 adrenergic receptors on small primary afferents; release of norepinephrine and acetylcholine in spinal cord dorsal horn; direct inhibition of impulse conduction in A delta and especially C fibers, possibly by increasing potassium conductance.[13,14]

The time of analgesic request was significantly prolonged in clonidine groups as compared to study group. Our results are in agreement with the results of other studies which observed prolonged duration of spinal anesthesia in clonidine groups with same doses.[7,8]

Chiari et al. in dose-response study using intrathecal clonidine during first stage of labor found 50–200 µg of intrathecal clonidine produces dose-dependent analgesia. Although duration of analgesia were more potent with 100 and 200 µg than with 50 µg, but higher incidence of hypotension was observed with doses of 200 µg.[15]

With regard to variation in mean arterial pressure, we observed relative stable hemodynamics in all groups in our study as we ensured adequate preloading before subarachnoid block and optimal intraoperative volume replacement. Niemi observed significant reductions in mean arterial pressures in doses of 3 µg/kg clonidine, which was a larger dose as compared to our study.[11] Sia also used 15 µg and 30 µg of clonidine and observed higher incidence of hypotension in 30 µg clonidine group.[16]

Clonidine after neuraxial or systemic administration affects arterial blood pressure in complex manner. The α_2 adrenergic agonist produce sympatholysis and reduced arterial blood pressure by acting on specific brainstem nuclei and sympathetic preganglionic neurons in the spinal cord. On the other hand, α_2 adrenergic agonist cause direct vasoconstriction by acting on the peripheral vasculature.[10]

In accordance with our study, two other studies showed similar results in which no patient developed bradycardia with the dose of 15 µg clonidine.[7,8] Klimscha et al. reported a significant fall in HR with 150 µg of clonidine which can be due to higher dose used.[17] Bajwa et al. also did not observe bradycardia by the addition of clonidine even up to 45 µg. This can be explained on the basis of low doses of clonidine and bupivacaine used.[18]

We did not observe sedation with use of clonidine. Markedly increased sedation scores were observed by with higher doses clonidine.[10,11] Kothari et al. also found 35%–45% patients drowsy by addition of 50 µg of clonidine to bupivacaine.[19] Clonidine is reported to cause a significant decrease in power of theta, α, and β bands of the electroencephalography. This hypnotic response may be mediated through locus coeruleus where α_2 adrenergic receptors are abundant.[20]

A potential limitation of our study was that we did not observe dose-response relationship using various doses of clonidine intrathecally for postoperative analgesia.

V. CONCLUSION:

Clonidine is a useful additive when used in appropriate dosage. Clonidine led to a rapid onset, prolonged duration of sensory and motor block along with prolonged and adequate postoperative analgesia with moderate sedation. Clonidine 30 µg is associated with prolonged recovery of motor block and causes hypotension and bradycardia. Clonidine 15 µg is associated with a stable hemodynamic profile and can be a useful adjuvant in spinal anesthesia.

Conflicts of interest
There are no conflicts of interest.

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