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Use of Intravenous Clonidine for Prolonging Spinal Anaesthesia

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Results: The mean duration of sensory blockade in clonidine group and saline groups were 206.20 and 136.20 minutes respectively. The motor blockade in clonidine group lasted for 157.60 and 129.60 minutes in saline group. The highest spinal level achieved was between T4 to T8 level and between T2 to T8 in clonidine and saline groups respectively. The incidence of bradycardia and hypotension was comparable.

Conclusion: Intravenous clonidine significantly prolonged the duration of spinal blockade.

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I. Introduction

Several additives like clonidine are added to prolong spinal blockade. Many trials have shown that by using various additives intrathecally the duration of spinal anaesthesia can be increased. Previous studies have demonstrated that by adding small dose of vasoconstrictors intrathecally with anaesthetic agent, sensory block may be prolonged[1, 2].

Clonidine is a selective 2 adrenergic receptor agonist, which is known to produce sedation, analgesia and haemodynamic stability. It is also known that clonidine prolongs spinal anesthesia when added to intrathecal local anesthetic agents or when administered as an oral medication[3-5]. However, it is not clear whether the effect of clonidine is mediated locally at the level of the spinal cord or whether the effect is mediated systemically. In order to test the hypothesis that the effect might be mediated systemically rather than locally, the study was designed. Previous studies have used oral clonidine. However, it is likely that IV clonidine will achieve higher plasma concentrations and more rapidly than oral clonidine and intrathecal injection may or may not have the same effects.

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II. Materials and Methods

The approval of the double blind randomized study was provided by the Institutional Ethics Committee. Written informed consent was taken for all the cases. The aim was to study onset of analgesia, duration of sensory and motor block after spinal blockade. In addition, the hemodynamic effects after giving intravenous clonidine were also noted. Previous study by Rhee et al[6] showed duration of sensory block of 196 ± 42 minutes in clonidine group versus placebo having duration of sensory block of 125 ± 25 minutes. The duration of motor block in clonidine group versus placebo was 153 ± 26 minutes versus 131 ± 29 minutes respectively. For alpha error of 0.05 and power of study to be 80%, expected sample size was 88. Considering dropout etc, the study was done in 100 patients. We had a set of computer generated 50 exclusive random numbers for each group. They were then chronologically numbered and were allotted the group depending on the group they belonged as per randomization. Thus, the allocation was random and 50 cases were selected for each group. The study drug solutions were not made by the anaesthesiologist evaluating the patient and were not aware of the group to which the patient belonged. This study was planned for a period of about six months.

In group C, 3 mcg/ kg of Clonidine diluted in 10ml of normal saline was administered intravenously for a period of 10 minutes immediately after laying down the patient in supine position following the spinal blockade with 15 mg (3 ml) of 0.5% hyperbaric bupivacaine. In group S, only 10 ml of normal saline was administered intravenously over a period of 10 minutes after patient was placed supine. Patient belonging to ASA grade I and II, with age between 20 to 65 years with height between 150 – 180 cm undergoing inguinal surgery under spinal anaesthesia were included. As height influences the dosage of drug in spinal anaesthesia, for a constant dosage, height range of

patients in 150-180 cm was chosen. Patients known to have allergy to clonidine and bupivacaine and pregnant and lactating women were excluded from the study. Preoperative pulse and blood pressure were recorded. All patients were preloaded with 500 ml of lactated Ringer's solution. Onset of analgesia was assessed by pinprick until highest level of sensory blockade was achieved and thereafter every 10 minutes during surgery. Duration of sensory block was defined as duration between injection of spinal anaesthetic agent to regression of spinal level up to L1 dermatome, while duration of motor block was defined as duration between injection of intrathecal drug and recovery of knee flexion and ability to move the posterior aspect of knee 10 cm above the surface of bed. Heart rate and mean arterial pressure (1/3 Systolic Blood Pressure + 2/3 Diastolic Blood Pressure) were measured and recorded every two minutes for first 10 minutes, during surgery. The lowest heart rate and blood pressure was also noted. Bradycardia (heart rate less than 45 beats per minute) (bpm) and hypotension (mean blood pressure less than 70% of base line) were treated appropriately. Patients were observed until the sensory block regressed below L1 dermatome and knee flexion had recovered. This was the end point of study.

III. Statistical Analysis

Demographic data was analyzed by Pearson's chi-square test. Duration of spinal anaesthesia, mean heart rate and blood pressure and the occurrence of cardiovascular side effects if any between the two groups was analyzed using unpaired 't' test. 'p' value less than 0.05 was considered significant.

IV. Results

As estimated, the study was completed in six months. All 100 patients who were enrolled completed the study.

As seen in Table 1, the patients were comparable in both groups with respect to demographic data. As depicted in table 2, mean pre-operative and lowest intra-operative pulse rate between the groups was comparable. As seen in table 3, the difference in pre-operative and intra-operative lowest mean arterial pressure (MAP) in between two groups was not statistically significant. Table 4 depicts that two patients in group C developed hypotension, which was comparable to incidence of hypotension in group S where only one (2%) patient developed hypotension. In group C, only two (4%) patients had developed bradycardia and only one (2%) patient in group S had presence of bradycardia. The incidence of bradycardia in two groups was comparable.

As shown in table 5, the highest spinal level achieved was between T4 to T8 level in group C and the median highest spinal level achieved was T6 that was present in 25 (50% in a group) patients. In group S 30 (60% in a group), patients achieved highest level of T6. The difference between two groups was statistically not significant.

The difference of mean duration of sensory and motor blockade between two groups was highly significant as evident in table 6.

V. Discussion

Small dose of vasoconstrictors intrathecally the duration of sensory block can be prolonged[7]. Clonidine is a selective 2 adrenergic receptor agonist, which is known to produce sedation, analgesia and hemodynamic stability. It is also known that clonidine prolongs spinal anesthesia when added to intrathecal local anesthetic agents or when taken orally.

By considering this in mind, intravenous clonidine would reach peak plasma concentration more rapidly than oral clonidine and it may have the same effect even if administered after intrathecal injection of local anaesthetic agents.

K. Rhee et al, performed a similar study in 78 patients The demographical data was comparable as in our study.[6] Victor Whizar-Lugo et al did a study for comparing dexmedetomidine and clonidine for prolonging spinal anaesthesia[8]. The demographical data of this study was comparable to our present study. In the study by I. Van Tuijl et al healthy women (ASA I or II) presenting for an elective Caesarean section with 150–195 cm height and 50–120 kg weight were studied.[9] Intravenous administration of 2 adrenoceptor agonists frequently leads to an initial increase in arterial blood pressure and systemic vascular resistance and a secondary decrease in heart rate resulting in transient reduction in cardiac output[9]. These effects are probably due to activation of alpha 1 receptors and post-junctional vascular alpha-2 adrenoceptors. This first short period of increase in blood pressure is within minute followed by a longer period characterized by a decrease in heart rate and arterial blood pressure due to centrally mediated decrease in sympathetic action[10, 11]. The reduction in sympathetic tone results in a reduction of heart rate, systemic metabolism, myocardial contractility and systemic vascular resistance. The result of these effects is a net decrease in myocardial oxygen consumption, which most probably explains the positive effects seen with alpha 2 adrenoceptor agonists in the treatment of angina pectoris.

Clonidine attenuates cardiovascular reactions and provides circulatory stability by its action at central alpha2-adrenergic receptors. However, intravenous clonidine especially when infused rapidly and at high plasma concentrations, may result in vasoconstriction and increased arterial blood pressure by peripheral alpha 2 adrenergic stimulation. In this study, 3 mcg/kg of clonidine mixed in 10 ml of normal saline was administered intravenously for 10 minutes to avoid stimulation of peripheral alpha 2 adrenergic receptors.

K. Rhee et al showed comparable pre-operative pulse rate and intra-operative lowest pulse rate[6]. Study by Victor Whizar-Lugo et al showed similar results.[8] Liu et al used oral clonidine for prolongation of lidocaine spinal anesthesia in human volunteers and found no significant change in pulse rate.[12] Stephan Strebel et al performed a study using various doses of intrathecal clonidine for prolongation of spinal anaesthesia in orthopedic surgeries and found no significant change in haemodynamic parameter after using clonidine up to 150 mcg/kg dose.[13] However, study done by L. Niemi using 3 mcg/kg intrathecal clonidine on effects of duration of bupivacaine spinal anaesthesia showed mean arterial pressure and heart rate significantly lower in the clonidine group compared to the control group.[4]

In our study, pre-operative mean blood pressure was comparable. The incidence of hypotension in the study done by Victor Whizar-Lugo et al for comparing intravenous dexmedetomidine and intravenous clonidine for prolonging spinal anaesthesia was similar to our present study.[8] In study by Liu et al on use of oral clonidine to prolong lidocaine spinal anesthesia in human volunteers, no significant decrease in blood pressure in clonidine and control group was found.[4]

In one another study Stephen Mannion et al used Intravenous Clonidine for prolonging postoperative analgesia after psoas compartment block for hip fracture surgery and also showed no significant decrease in blood pressure.[14]

In a study done by L. Niemi on effects of intrathecal clonidine on duration of bupivacaine spinal anaesthesia in patients undergoing knee arthroscopy found there was significant increase in incidence of hypotension and bradycardia with use of clonidine 3 mcg/ kg.[4]

Descending noradrenergic antinociceptive pathways originating in the brainstem are believed to be associated with analgesic effects by suppression of spinal nociceptive impulses. Alpha 2a adrenoceptors have been identified in substantia gelatinosa of the dorsal horn of the spinal cord. Stimulation of these alpha 2a adrenoceptors inhibits the firing of nociceptive neurons stimulated by Aδ and C fibers and is considered to be one of the main mechanisms of descending endogenous pain modulation[15].

Recent evidence suggests that the antinociception produced by alpha 2a adrenoceptor agonists may be due in part to acetylcholine release in the spinal cord. Since the spinal cord is the major site of analgesic action of alpha 2a adrenoceptor agonists, the epidural and intrathecal routes have been considered preferable to the intravenous route. This is, however, questioned by data showing a similar effect of orally administered clonidine when compared to intrathecally applied clonidine in the context of spinal anaesthesia[16]. Also due to its lipid solubility clonidine will readily penetrate extra vascular sites as well as central nervous system and can cause same effect as does by intrathecal clonidine

In our study, median highest spinal level in clonidine group was T6 that was present in 25 patients of total 50. In saline group, total 30 patients achieved highest level of T6 in out of 50 patients. The difference between two groups was not statistically significant.

In similar study done by K. Rhee et al, the median highest level of spinal blockade was T5 in both clonidine and control group. The highest spinal level achieved in this study was comparable to our present study.[6]

The motor blockade in clonidine and saline group lasted for 157.60 and 129.60 minutes respectively, while the duration of sensory blockade was 206.20 and 136.20 minutes The difference of mean duration of sensory and motor blockade between two groups was statistically significant.

In study by K. Rhee et al, the duration of sensory and motor blockade was prolonged approximately by one hour and 25 minutes respectively. This prolongation in duration of spinal blockade was comparable to our study. The difference in prolongation of duration of spinal blockade between two groups was statistically significant.[6]

Victor Whizar-Lugo et al have done a study for comparing intravenous dexmedetomidine and intravenous clonidine for prolonging spinal anaesthesia against placebo group. They found significant increase in duration of sensory and motor spinal blockade with using intravenous clonidine 4 mcg/kg. The prolongation in duration of sensory blockade was approximately one hour and motor blockade was approximately 20 minutes with clonidine.[8] In another study done by L. Niemi on effects of intrathecal clonidine on duration of bupivacaine spinal anaesthesia and also found there was significant increase in duration of spinal anaesthesia with use of clonidine 3 mcg/ kg.[4]

VI. Conclusion

Administration of intravenous clonidine in patients undergoing spinal anaesthesia using 0.5 % Bupivacaine, significantly prolonged the duration of spinal anaesthesia without significant increase in incidence of haemodynamic side effects like hypotension and bradycardia.

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Table 1 : Demographical data

Parameters	Group C	Group S
American Society of Anaesthesiologists Grade (ASA) status I (number)	35	38
ASA status II (number)	15	12
Male (number)	39	34
Female (number)	11	16
Age (yrs) Mean ± SD	37.58 ± 12.609	38.70 ± 12.968
Weight (kg) Mean ± SD	61.86 ± 7.49	60.88 ± 8.573
Height (cm) Mean ± SD	165.20 ± 6.719	162.52 ± 9.811

Table 2 : Pulse rate (beats per minute)

Pulse rate (beats per minute)	Group C	Group S	P value
Preoperative	86.16 ±8.775	84.94 ±9.483	0.506
Intraoperative Lowest	60.98 ±8.959	60.06 ±9.142	0.612

Comparable

Table 3 : Mean arterial pressure (mm Hg)

Pulse rate	Group C	Group S	P value
Preoperative	99.14 ±5.792	99.20 ±5.379	0.957
Intraoperative Lowest	75.74 ±8.773	74.74 ±5.900	0.505

Comparable

Table 4 : Incidence of haemodynamic side effects

Side Effect (No of patients)	Group C	Group S	Total
Hypotension	2	1	3
Bradycardia	2	1	3

Table 5 : Highest spinal level

Level (No of patients)	Group C	Group S	Total
T2	0	1	1
T4	13	9	22
T6	25	30	55
T8	12	10	22

Table 6 : Duration of spinal blockade

	Group C	Group S		P value
Sensory blockade (minutes)	206.20 ± 19.155	136.20 ±	15.104	0.000
Motor blockade (minutes)	157.60 ± 14.365	129.60 ±	14.422	0.000

Significant