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Intrathecal Clonidine Co-Administered With Hyperbaric Bupivacaine in Infra-Umbilical Surgery - A Dose Response Study.

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ABSTRACT

Background: Clonidine, the α_2 – adrenergic agonist, has a variety of different action including the ability to potentiate the effect of local anaesthetic without any significant undesirable effects. The intrathecal use of different doses of clonidine when co-administered with hyperbaric bupivacaine provides prolongation of pain free period than hyperbaric bupivacaine alone. Objectives: Our present study was targeted to find out the optimum intrathecal dose of clonidine as an adjunct to hyperbaric bupivacaine.**Methods:** Patients with ASA physical status I & II scheduled for elective infra umbilical surgery under spinal anaesthesia were randomly divided into four equal groups (n = 30) by a computerized randomization chart. Groups BC_{15}, BC_{30}, and BC_{45} received mixture of 10 mg hyperbaric bupivacaine plus clonidine in the doses of 15, 30, and 45 µg respectively intrathecally and the control group (Group B) received 0.5% hyperbaric bupivacaine 10 mg and normal saline as placebo. All analysis was two tailed and P value < 0.05 was considered statistically significant. Data analyzed with the help SPSS software version 16.0 for Windows, SPSS Inc. Chicago. **Results:** It was observed that intrathecal clonidine to hyperbaric bupivacaine dose dependently prolongs both sensory blockade of spinal anesthesia and time to request for first supplemental analgesia in post operative period. **Conclusion:** Because of the absence of significant adverse effects, we conclude that, within the tested dose range, 30 µg of clonidine is the preferred dose, when prolongation of spinal anesthesia is desired.

Keywords: Analgesia, Bupivacaine, Clonidine, Infra-umbilical surgery.

INTRODUCTION

Single shot spinal anaesthesia is the most commonly employed regional technique for intra and post operative pain relief in infra umbilical surgery. The popularity of this technique is due to its simplicity and high success rate. However, commonly used local anaesthetic, hyperbaric bupivacaine, provides adequate pain relief for 75-150 minutes.[1] From the very earlier time of spinal anaesthesia research workers have been tried several drugs as an adjuvant to local anaesthetics. α_2–adrenergic agonist, clonidine, has a variety of different action including the ability to potentiate the effect of local anaesthetic without any significant undesirable effects.[2]

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It prolongs the sensory block and reduces the amount of local anaesthetics required to produce post operative analgesia.[1] The intrathecal use of different doses of clonidine when co-administered with hyperbaric bupivacaine would provide prolongation of pain free period than hyperbaric bupivacaine alone.[3] Intrathecal clonidine has been used in a wide dose range of 15– 400 µg either alone or in combination with different local anaesthetics or opioids.[2]The question is about optimum dose. De kock et al. Found that addition of clonidine has significant effects on the duration of sensory and motor blockade, when compared with ropivacaine alone. The lower dose of clonidine (15 µg) to 8 mg ropivacaine preserves the advantage of this low dose of local anaesthetic (short-lasting motor block, early ambulation, and micturition) while improving the quality of anesthesia.[4] Dobrydnjov I et al. 2003 found that the addition of clonidine 15 µg and 30 µg to bupivacaine prolonged time to first analgesic request and decreased postoperative pain with minimal risk of hypotension but clonidine 15 µg

produced an effective spinal anesthesia for inguinal herniorrhaphy.[5] Sites BD et al 2003 found little difference between 25 µg and 75 µg of clonidine in terms of pain control and adverse side effects.[6] The aim of our present study was to find out the optimum dose of clonidine when administered intrathecally as an adjunct to hyperbaric bupivacaine for adequate pain relief in patients undergoing lower abdominal surgery.

MATERIALS AND METHODS

After the approval of the Institutional Ethics Committee of Burdwan Medical College and Hospital, Burdwan this prospective, randomized, double blind, controlled study was carried out under department of anaesthesia. Those were having Local infection on injection site, Spinal deformities, Bleeding diathesis, History of hypersensitivity to local anaesthetics, known cardiovascular, renal, metabolic, neurological and psychiatric disorders were excluded from the study. Obtaining written informed consent from each subject, 120 healthy subjects of either sex, aged 20 – 50 years, ASA physical status I & II scheduled for elective lower abdominal surgery under spinal anaesthesia were selected. They were randomly divided into four equal groups (Group B, BC_{15}, BC_{30} and BC_{45}) by a computerized randomization chart (n = 30). Groups BC_{15}, BC_{30}, and BC_{45} received mixture of 10 mg hyperbaric bupivacaine plus clonidine in the doses of 15, 30, and 45 µg respectively intrathecally. Patients belonging to control group (Group B) received 0.5% hyperbaric bupivacaine 10 mg. Maximum volume of the study agents were made 2.5 ml by adding normal saline. Patients as well as the anaesthesiologist, administering spinal anaesthesia and monitoring data were blinded about the study drugs. All patients received Alprazolam 0.25 mg orally night before surgery. Ondansetron (4 mg) and Ranitidine (50mg) intravenous were given 1 to 2 hours before operation. All the patients were preloaded with 15 ml/kg Ringer's lactate solution. Spinal anaesthesia was administered under proper aseptic condition, in sitting position through L3-L4 or L4-L5 interspaces using 26G Quincke needle. 2.5 ml study solutions were administered after clear free flow of CSF. The patients were administered O_2, 3 L/min through facemask. Surgical intervention started 10 minutes after the administration of spinal anaesthesia when spread of sensory and motor block was confirmed. Pulse, SpO_2, ECG monitored continuously. Blood pressure monitored at 5 minutes interval. Pulse rate and mean arterial blood pressure (MAP) was recorded at interval of 5, 10, 20, 30, 40, 50, 60, 80, 100, 120, 240, 480, 720 and 1440 minutes and also the baseline values. Any fall in blood pressure >20% decrease in systolic blood pressure or systolic arterial blood pressure < 100mm of Hg considered as hypotension and treated with bolus dose of Mephentermine 3 mg or fluids as appropriate. No other analgesic was given to the patients intra-operatively. The intensity of the pain assessed using a 100-point VAS.[7] Duration of anaesthesia measured the time interval from intrathecal injection to the regression of the sensory block below L1. The duration of analgesia defined as the time from intrathecal drug administration to the first request for analgesia. Rescue analgesic (inj. diclofenac sodium 75 mg intramuscular) was given when the numerical pain score is >40 or the patient asked for that. Height of sensory block was assessed by pin prick method over dermatomal segments. Motor block was assessed by modified Bromage scale.[8] Time duration (in minutes) was measured from the injection of study drug to regaining of full motor power and joint movement. Incidence of side effects and adverse reactions like nausea and vomiting, hypotension, bradycardia and sedation (scored by modified Wilson Sedation Scale[9]) were noted.

Data was summarized by descriptive statistics, key proportions being expressed along with 95% confidence interval. Categorical variables were compared between groups by Chi-square test or Fisher's exact test as applicable. The comparison of normally distributed continuous variables among the groups was performed by means of one-way analysis of variance, and with Bonferroni correction. All analysis was two tailed and P value < 0.05 was considered statistically significant. All the data were analyzed with the help of statistical package for social sciences (SPSS software version 16.0 for Windows, SPSS Inc. Chicago).

RESULTS

There was no significant difference in the demographic characteristics of the patients in different study groups. Distribution of age, sex, body weight, height and duration of operation in different study groups were comparable (p>0.05) to each other [Table 1].

Table 1: Demographic data in different groups.

	B (Bupivacaine 10mg)	BC15 (Bupivacaine 10 mg plus clonidine 15µg)	BC30 (Bupivacaine 10 mg plus clonidine 30µg)	BC45 (Bupivacaine 10 mg plus clonidine 45µg)
Age (Yr)	40.40(6.36)	41.10(5.97)	42.00(7.58)	40.30(7.65)
Sex(Female/Male)	16/14	14/16	16/14	15/15
Body Wt (kg)	55.66	56.67	57	57.43
Height (cm)	149.93±5.19	151.33±5.42	151.97±4.13	151.97±4.04

Initially baseline mean arterial blood pressure (MAP) was comparable among the groups. After 20 to 30 minutes, patients of group BC45 showed drop in MAP comparing with other groups. This tendency persisted till 100 minute's observation. Some of the patients belonging BC_{30} group were observed a lower value in MAP at 50 and 60 minute's data [Fig-1]. Three patients in control group, three patients in group BC_{15}, four patients in group BC_{30} and ten patients in group BC_{45} required vasopressor support to treat the incidence of hypotension [Table 4].

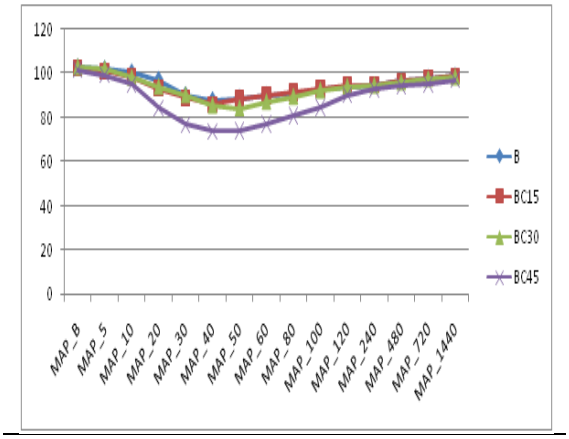

Figure 1: Shows change in mean MAP over different period of time. Time interval (in minutes) is placed along the abscissa and MAP (mm Hg) is placed along the ordinate.

Change in heart rate during observation is shown in [Figure 2]. No patient of any group was shown to have bradycardia and required any intervention.

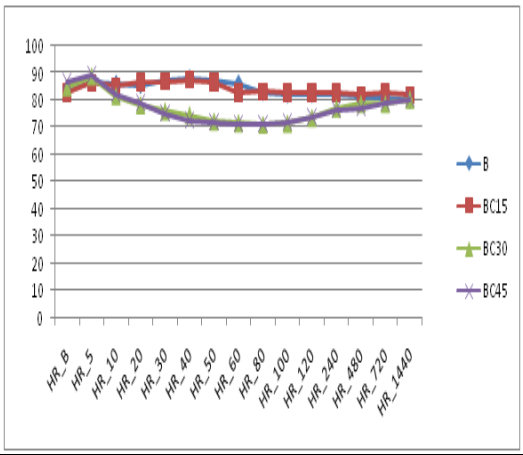

Figure 2: change in mean of the heart rate over different period of time. Time interval (in minutes placed along the abscissa and heart rate along the ordinate.

Maximum level of sensory block obtained after spinal anaesthesia among the different study group did not show significant difference [Table 2].

Table 2: Maximum spread of sensory block after spinal anaesthesia in different groups.

Maximum sensory level obtained	B	BC_{15}	BC_{30}	BC_{45}
T6	12	12	13	14
T7	15	15	16	15
T8	3	3	1	1

The duration of sensory anaesthesia was measured by calculating the time interval between intrathecal injection and regression of sensory block to L1 dermatome by pin prick method. The mean values were 102.67(±10.807) in-group B, 109.67 (±16.238) in-group BC_{15}, 133.00 (±13.429) in group BC_{30} and 150.33 (±13.257) in group BC_{45}. Both the values in group BC_{30} and BC_{45} were significantly higher than group B and group BC_{15} ($p<0.05$). Patients of group BC_{45} also showed a significantly higher value than group BC_{30}. Duration of motor block was assessed by modified Bromage scale post-operatively. The mean duration of complete motor recovery was 185.33 (±12.794) in group B, 186.00 (±13.544) in group BC_{15}, 242.00 (±22.345) in group BC_{30} and 250.00 (±17.811) in group BC_{45}. Both the group BC_{30} and BC_{45} showed significantly prolonged duration of motor block than control group B and group BC_{15}. Duration of analgesia was assessed either patient's request for rescue analgesia or when visual analogue scale score (VAS) is more than 40 from the time of injection. The mean values are 132.00 (±21.877) in group B, 139.00(±21.512) in group BC_{15}, 266.67(±28.325) in group BC_{30} and 273.33 (±27.080) in group BC_{45}. When there mean values were compared it was found that there is no significant difference between control (group B) and group BC_{15}. And values in group BC_{30} and BC_{45} were also comparable. The duration of analgesia in both BC_{30} and BC_{45} group was significantly prolonged than in group B and group BC_{15} [Table 3].

Table 3: Duration of operation, motor and sensory block and duration of analgesia

	B	BC15	BC30	BC45
Duration of Operation	69.83 (±11.02)	65.50 (±15.39)	63.67 (±10.90)	67.67 (±10.63)
L1 Regression time (minutes)	102.67 (±10.807)	109.67 (±16.238)	133.00 (±13.429)	150.33 (±13.257)
Time to full motor recovery (minutes)	185.33 (±12.794)	186.00 (±13.544)	242.00 (±22.345)	250.00 (±17.811)
Duration of analgesia (minutes)	132.00 (±21.877)	139.00 (±21.512)	266.67 (±28.325)	273.33 (±27.080)

One patient in group B, one in group BC_{15} and two patients in group BC_{45} were complaints of nausea and vomiting during study period. One patient in either group BC_{30} and BC_{45} were found to be sedated

(score 2, according Wilson sedation scale). Three in group B, three in group BC_{15}, four in group BC_{30} and ten patients in group BC_{45} had hypotension and required vasopressor support. No patient in any of the group was complaint of dryness of mouth and sedation. So there was significantly higher incidence of hypotension in group BC_{45} in comparison to other groups [Table 4].

Table 4: Shows distribution of the events of side-effects in different study groups.

Groups	Nausea & Vomiting	Sedation	Dry mouth	Hypotension and vasopressor needed	Urinary retention
B	1	0	0	3	0
BC_{15}	1	0	0	3	0
BC_{30}	0	1	0	4	0
BC_{45}	2	1	0	10	0

DISCUSSION

Clonidine is a α_2-adrenergic agonist with a selectivity ratio of about 200:1 in favour of α_2 receptors. It stimulates inhibitory α_2-adrenoceptors to reduce central neural transmission in the spinal neurons. Intrathecal use of clonidine when co-administered with hyperbaric bupivacaine provides prolongation of pain free period than hyperbaric bupivacaine alone.[10]

In our present study we compared three different dose of intrathecal Clonidine (15, 30 and 45µg) along with hyperbaric bupivacaine (10 mg) in the group BC_{15}, BC_{30}, BC_{45} and a control group B (bupivacaine 10 mg). There was no significant difference ($p \geq 0.05$) in the demographic characteristics of the patients in different study groups [Table 1].

All the patients had a cephalic spread of sensory anaesthesia up to the thoracic dermatome. The range was from T8 to T6 [Table 2]. Strebel S. et al. in their dose response study[2] and did not found any significant difference in spread of anaesthesia with the increase in dose of clonidine and in control group also. Clonidine did not affect the cephalad spread of sensory anaesthesia of hyperbaric bupivacaine with increase in dose in our study.

Duration of sensory block (regression of sensory anaesthesia to L1 dermatome), ware 102.67 (±10.807) in-group B, 109.67 (±16.238) in group BC_{15}, 133.00 (±13.429) in group BC_{30} and 150.33 (±13.257) in group BC_{45} [Table 3). Both the values in group BC_{30} and BC_{45} were significantly higher than group B ($p<0.001$) and group BC_{15} ($p<0.001$). Patients of group BC_{45} also showed a significantly higher value than group BC_{30}. Kaabachi O. et al. used bupivacaine 0.2- 0.4 mg/kg body weight and clonidine 1µg/kg body weight in adolescent between 10- 16 year of age.[11] They found sensory regression 107±42 min in control group and 136± 56 in clonidine group. Dobrydnjov I. et al. in their study with clonidine 15 µg and 30 µg, found similar prolongation in duration of sensory anaesthesia in a dose dependant manner.[12]

The mean duration to complete recovery from motor block in our study were 185.33(±12.794) min in group B, 186.00(±13.544) min in group BC_{15}, 242.00 (±22.345) min in group BC_{30} and 250.00 (±17.811) min in group BC_{45} [Table 3]. The differences were less significant between group BC_{30} and BC_{45}. Significantly prolonged motor blockade after intrathecal clonidine has been reported with doses >75 µg.[13-15] Strebel S. et al. observed a significantly larger proportion of patients with intense motor blockade that resolved after 8 –10 hours in patients who received 150 µg intrathecal clonidine.[2] Kaabachi O. et al. found a similar prolongation of motor block as our study with clonidine 1µg/ kg than control group.[11] But in all study, including our study duration of motor block increases with increase in dose of intrathecal clonidine.

Duration of analgesia were assessed either patient's request for rescue analgesia or when visual analogue scale score (VAS) is more than 40 from the time of spinal injection. The mean values were 132.00 (±21.877) in-group B, 139.00(±21.512) in group BC_{15}, 266.67(±28.325) in group BC_{30} and 273.33 (±27.080) in group BC_{45} [Table 3]. The time interval increased with increase in dose of clonidine. Though it was less significant between group BC_{30} and group BC_{45}. Dobrydnjov I. et al. in their study observed a similar prolongation of duration of analgesia.[12] Strebel S. et al. and Kaabachi O. et al, observed a higher mean value of duration of analgesia which was prolonged with increase in dose of intrathecal clonidine.[2,11]

Inhibition of substance-P release is believed to involve in the analgesic effect. Analgesic action through α_2-adrenoceptor shown by partial reversal of epidural clonidine analgesia and sedation, by the α_2-adrenergic antagonist, yohimbine, although the effect on blood pressure and heart rate were not reversed.[16] This supports the possible mechanism of action is mediated through α_2-adrenoceptors. The receptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial laminae of the spinal cord, and within several brainstem nuclei implicated in analgesia, supporting the possibility of analgesic action at peripheral, spinal, and brainstem sites.[17] Clonidine does produce a minor degree of nerve conduction blockade at high concentrations, however, with some preference for C-fibers,[18]

which are important neuronal structure for pain transmission. Some experimental data suggest that intrathecal injection of clonidine increases cerebrospinal fluid acetylcholine concentrations[19] and intrathecal injection of cholinesterase inhibitors enhances analgesia.[20,21] In humans, epidural clonidine increases CSF acetylcholine conc., and spinal injection of the cholinesterase inhibitor neostigmine enhances clonidine-induced analgesia.[22] It has been observed that, addition of intrathecal clonidine, decreased MAP significantly compared with plain bupivacaine.[23] The commonly administered doses (≥1 µg/kg) produce hypotension, bradycardia and sedation. A smaller dose of intrathecal clonidine is not usually associated with systemic side effects such as bradycardia, hypotension, or sedation.[24] In the present study incidence of hypotension was 10% in group B, 10% in group BC_{15}, 13.33% in group BC_{30} and 33.33% in group BC_{45}. 3 patients in control group, 3 patients in group BC_{15}, 4 patients in group BC_{30} and 10 patients in group BC_{45} required inj. mephentermine to treat the incidence of hypotension (table-4). Change in mean arterial blood pressure (MAP) has been shown in figure-1. The α2-adrenergic agonists produce sympatholysis and reduce arterial BP through effects at specific brainstem nuclei and on sympathetic preganglionic neurons in the spinal cord.[16] Furthermore, combining with local anaesthetics it potentiates the degree of sympatholysis and resulting hypotension. Pulse rate was relatively stable in the patients of all groups. However, patients in group BC_{30} and BC_{45} showed relatively lower values. No patient of any groups required active management for bradycardia. There was no incidence of dryness of mouth and urinary retention in any patients. One patient in-group B, one in-group BC_{15} and two patients in-group BC_{45} were complaints of nausea and vomiting during study period. One patient in either group BC_{30} and BC_{45} were found to be sedated (score 2, according Wilson sedation scale[9]). Sedation, a central effect of α_2-adrenergic drugs, occurs after systemic, epidural, or intrathecal administration of clonidine in humans. Sedation were observed with higher dose (3 µg/kg).[25]

CONCLUSION

Intrathecal clonidine clearly increases the duration of both sensory and motor block as well as postoperative pain relief. De Kock et al. recommended a dose of 15–45 µg of clonidine as optimal for supplementing spinal anesthesia.[24] In our study 15, 30 and 45 µg of clonidine plus bupivacaine (10 mg) and bupivacaine (10 mg) alone were compared. Analgesia was significantly increased by addition of intrathecal clonidine. Importantly, increasing the dose of clonidine from 15 to 45 µg there was an increase in the duration of analgesia, motor block as well as the duration of sensory block. This prolongation was less significant between 30 µg and 45 µg of clonidine. Whereas, incidence of hypotension were more with the dose of 45 µg. The mean height and weight of the patient of our study population was lower than that of the values in De Kock et al.[24] This might be an important factor behind the better hemodynamic response and other side effect profile with 30 µg of clonidine than 45 µg, the later was appeared better in their study.

Thus, we conclude that, addition of intrathecal clonidine to hyperbaric bupivacaine dose dependently prolongs both sensory blockade of spinal anesthesia and time interval to first request for supplemental analgesia. And within the tasted dose range 30 µg is the optimum dose in terms of effect versus side effects for adult patient posted for infra umbilical surgery.

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