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Optimization of Bupivacaine Induced Subarachnoid Block by Clonidine: Effect of Different Doses of Oral Clonidine

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Abstract

Background: Various drugs are used for premedication to reduce anxiety and to provide hemodynamic stability. The study was designed to investigate the optimum dose of oral clonidine administered preoperatively with regard to its anxiolytic efficacy and its effect on hemodynamics and sedation. We studied the effect of three different doses of oral clonidine on surgeries below umbilicus which were administered intrathecal bupivacaine.

Methods: A placebo controlled double blind study was conducted on 120 patients scheduled for surgeries below umbilicus. Group 1 received oral placebo, group 2 received oral clonidine 3 μg kg^{-1}, group 3 received oral clonidine 4 μg kg^{-1} and group 4 received oral clonidine 5 μg kg^{-1} along with 0.5% heavy bupivacaine 0.3 μg kg^{-1} intrathecally in each group. Outcomes assessed were anxiolysis through VAS, level of sensory block, time to reach highest sensory segment, regression to L1 segment, sedation score, bradycardia and hypotension.

Results: There was improved block duration and sedation with the different doses of clonidine. Time for the sensory block to regress to L1 and rescue analgesia was longest in 4 followed by groups 3 and 2. There was significant dose dependent decrease in VAS anxiety score between group 1 and other clonidine groups in intraoperative and post-operative period. However, the episodes of bradycardia and hypotension were highest in 4 group.

Conclusion: Preoperative oral clonidine 4 μg kg^{-1} appears to be the optimum dose for optimization of spinal anaesthesia with bupivacaine as it prolongs the sensory block maximally with minimal side effects.

Introduction

Preanesthetic medication lessens preoperative anxiety, provides amnesia for preoperative and perioperative events and maintains hemodynamic stability by attenuating autonomic reflexes [1]. Use of α-2 adrenoreceptor agonist like clonidine has a lot of advantages as a premedication agent due to the wide spread distribution of α-2 receptors throughout the central nervous system and rest of the body. Clonidine reduces sympathetic activity, the incidence of shivering, [2] dries up secretions; minimizes fluctuations in the hemodynamic profile during anesthetic induction [3] and decreases anesthetic requirements for both opioid and volatile anesthetics [4]. Premedication with oral clonidine provides significant benefits for preoperative anxiety [1] and analgesia. Clonidine can be given via oral, intramuscular, intravenous, intrathecal and epidural routes.

Although prolongation of local anesthetic-induced sensory and motor block is well documented after co-administration with intrathecal clonidine [5,6], the effect of oral clonidine remains controversial [5,7]. The proposed study aims to investigate the effect of three different doses of oral clonidine on subarachnoid block, anxiolysis, sedation, hemodynamic stability and their side effects, in patients undergoing surgeries below umbilicus in order to find out its optimum dose as a premedication agent with spinal anaesthesia Bupivacaine.

Materials and Methods

After getting approval from institutional ethical committee, informed consent was taken from the patients or patient's kin (in case of illiterate). This study was performed in 120 patients aged 18-40 years of either sex, for below umbilical surgeries under spinal anaesthesia. Patients with contraindications to spinal anaesthesia, allergy to local anesthetics, patients of ASA grade III and IV, refusal to consent and pregnant patients were excluded (Table 1).

Groups	Bupivacaine (0.3 μg kg^{-1} intrathecal)	Clonidine (μg kg^{-1} oral)
1	0.5%	Nil
2		3
3		4
4		5

Table 1: Anaesthesia Treatment to different groups

The patients were divided into following groups (n=30 each) and according to the medication they received one hour prior to surgery.

All patients were evaluated during preoperative assessment. Visual analogue scale (VAS) for anxiety [8] was explained to the patient at the

pre-operative visit (0 mm = being completely calm, 100 mm=possible worst anxiety). VAS and vital parameters were assessed and recorded before administration of oral clonidine and termed as baseline values. In the pre-operative room, after securing intravenous access with 18G or 20 G intracath, either placebo or oral clonidine in three different doses were given randomly 60 minutes prior to shifting to operative room by the person who was unknown to study. No oral gastric tube was used during surgery.

Oral clonidine tablets were available in 100 µgms. These tablets were grounded before giving it to the patients and properly weighed according to weight of the patient.

In operating room, non invasive monitors were applied, and patients were preloaded with 10-15 ml kg^{-1} ringer lactate solution. VAS for anxiety was recorded for the second time. Baseline heart rate, blood pressure (MAP), respiratory rate and SpO2 were noted. Under aseptic conditions, the patients were given spinal anaesthesia, bupivacaine with 25G spinal BD needle at L3-L4 level in sitting or lateral position. The final position was made after waiting for 20 minutes and following parameters were assessed-

1. Highest level of sensory block achieved and time to reach highest level of sensory block by pin prick test.

2. Time taken for sensory block regression to L1 level.

3. Hemodynamic parameters (Mean arterial pressure and Heart rate) were recorded every two min for the first 10 minutes and every 10 minute for next one hour.

4. Oxyhemoglobin saturation (SpO2).

5. Any adverse events like bradycardia, hypotension, respiratory depression and dry mouth.

Sedation was assessed by an observer who was unknown to the study using Sedation score: [1=Awake, 2=Drowsy but responding to verbal stimuli (mild), 3 = Responding to moderate touch (moderate) 4=Responding to firm touch (severe)]

In the event of any complication, standard protocols were followed. Bradycardia (<50 beats min^{-1}) was treated with atropine (0.005 mg kg^{-1} i.v.). Hypotension (MAP<70 mm Hg) was treated with 500 mL of Ringer's lactate over 30-minute period and if hypotension persisted, then mephentermine was administered in 6-mg intravenous increments. The patients were followed for the first 24 hrs to find out time for requisition of supplementary analgesia by the patient and to asses other complications.

Statistical Analysis

The sample size was n=30 in each of the four groups. The obtained data was analyzed using chi square test or student 't' test as appropriate, with the p value reported at the 95% confidence interval. p value <0.05 was considered statistically significant. The parameters were expressed as mean ± S.D. The results obtained in the study are presented in tabulated manner and analyzed using Microsoft Excel and SPSS for analyzing the collected data. The authors wanted to conduct the study in order to get some substantial significant result pattern. Power of study was kept 80% (β=0.8).

Results

Four study groups of 30 patients each were comparable with respect to demographic profile. No significant differences were observed in age, weight and height (Table 2). Duration of surgery did not differ among the study groups.

n=120	Group 1	Group 2	Group 3	Group 4
Age (years)	34.87 ± 5.41	34.33 ± 7.32	34.13 ± 6.60	33.80 ± 6.83
Weight (kgs)	59.67 ± 7.49	58.20 ± 8.74	58.07 ± 7.92	56.93 ± 8.09
Height (cms)	153.87 ± 6.45	151.07 ± 9.62	152.60 ± 6.72	151.73 ± 8.27
Duration of surgery (mins)	108.78 ± 14.49	102.67 ± 9.77	102.48 ± 12.42	110.34 ± 10.76

Table 2: Patient's profile (Mean ± SD), values are mean ± SD of n=30

Clonidine treated patients (Groups 2, 3 and 4) and control group did not show any difference in onset of sensory block that is time to reach maximal level of sensory blockade (Table 3). There was no significant difference in the highest level of sensory level achieved in all groups (T6-T8).

The mean time for the sensory block to regress to L1 was significantly prolonged in all three groups receiving oral clonidine than group I (p<0.001). Statistically, significant difference in sensory block L1 and rescue analgesia were found in both group 3 and 4 when compared with group 2 (p<0.05), maximum effect was seen with 4 µg kg^{-1} clonidine and then it was almost stationary after increasing the dose (Table 3).

Groups	1	2	3	4
Highest sensory segment	7.27 ± 1.03	6.27 ± 1.28	6.23 ± 1.50	6.07 ± 1.39
Sensory block L1	147.33 ± 24.04	173.13 ± 15.5	191.33 ± 19.95	192.13 ± 19.7
Rescue analgesia	152.67 ± 16.68	183.20 ± 19.5	200.67 ± 15.80	201.33 ± 18.46

Table 3: Time taken to reach onset and regression of block

Preoperatively, there was no difference in anxiety levels in all groups. A clear decrease in anxiety was observed in intraoperative and postoperative period. There was significant difference in VAS anxiety score between group I and other groups (clonidine) in intraoperative period as compared to preoperative and postoperative period. There was no significant difference in VAS score among clonidine groups (Table 4).

There was no significant difference in the preoperative heart rate and mean arterial blood pressure (MAP) values in groups. During intra-operative period, decrease in MAP was observed in all clonidine groups and reduction was statistically significant when compared with control group. Maximum change in mean blood pressure was found in patients receiving 5 μg kg^{-1} oral clonidine group and statistically this change was significant when compared with group 2 ($p<0.001$) (Table 4). There was slight difference between group 3 and 4. Same results were observed in post-operative period when MAP of group I was compared with clonidine groups ($p<0.05$). MAP remained at lower level in group 4 as compared to group 2 ($p<0.001$). There was no significant difference between groups 2 and 3.

Compared to baseline, HR was reduced intra and post-operatively. Negligible differences were noticed in the control and clonidine groups. Regarding comparison among clonidine groups intraoperatively, 4 group showed maximum reduction in heart rate and difference was statistically highly significant when compared with group 2 ($p<0.001$) (Table 4). No difference was observed between groups 3 and 4.

VAS Score	Group 1	Group 2	Group 3	Group 4
Preoperative	67 ± 21	70 ± 19	66 ± 10	65 ± 22
Intraoperative	68 ± 20	40 ± 17**	38 ± 11**	36 ± 18**
Postoperative	64 ± 21	61 ± 20	58 ± 11	54 ± 18**
Blood Pressure				
Preoperative	97.57 ± 1.55	99.2 ± 1.58	98.6 ± 1.55	98.53 ± 1.14
Intraoperative	92.57 ± 1.72	85.1 ± 2.24	82.67 ± 2.34	80.53 ± 2.22**
Postoperative	93.73 ± 1.44	88.03 ± 2.46	87.27 ± 2,46	82.53 ± 1.76**
Heart Rate				
Preoperative	81.53 ± 2.57	84.1 ± 1.94	80.7 ± 3.02	83.23 ± 1.96
Intraoperative	72.67 ± 2.31	68.03 ± 2.33	60.1 ± 1.99	58.1 ± 2.26**
Postoperative	78.33 ± 2.38	70.03 ± 2.4	66.06 ± 2.88	60.4 ± 1.77**

Table 4: VAS Score, Blood pressure and heart rate **P <0.001.

Intra operatively, sedation was observed in 5, 11 and 15 patients in 2, 3 and 4 groups respectively though all patients responded well to verbal stimuli (grade 2). No sedation was observed in control group and this difference was statistically significant when compared with 3 and 4 group (Table 5). Among clonidine groups, difference between 2 and 4 was significant and 3 versus 4 was non-significant.

(n=120)	Group 1		Group 2		Group 3		Group 4	
	No.	%	No.	%	No.	%	No.	%
Sedation								
Intraoperative	0	0	5**	16.65	11	36.63	15**	50
Postoperative	0	0	2	6.67	5*	16.65	8*	26.67
Bradycardia	1	3.33	2	6.67	2	6.67	5	16
Hypotension	1	3.33	1	3.33	2	6.67	4	13.3
Dry mouth	0	0	1	3.33	2	6.67	2	6.67
Respiratory depression	0	0	0	0	0	0	0	0

Table 5: Incidence of Side Effects No: reflects number of patients with side effects, **P <0.001; *P <0.05.

In post-operative period also, maximum sedative effect was seen in 4group and difference was significant when compared to control group, difference among clonidine groups was significant.

Compared to the placebo-treated groups (Group 1), the number of episodes of bradycardia and hypotension were higher in the clonidine-treated groups. Throughout the study period, four patients (13%) in the group 4, two (6%) in the group 3, but one (3%) in the both control and group 2 were treated for hypotension. The frequency of

bradycardia in Group 4 (16%) was significantly higher than in Group 2, 3 and control ($P < 0.05$).

There was no incidence of respiratory depression in any patient (Table 5). SpO2 was maintained above 95% in all patients. Two patients in groups 3 and 4, one in group 2 and none in group I complained of dry mouth (Table 5).

Discussion

Clonidine is absorbed almost completely after oral administration after 1-2 hours of administration. The peak blood-pressure reducing effect of clonidine occurs approximately 90 min after oral administration and peak plasma concentrations are observed between 1 and 3 hr [9,10]. Oral route is generally considered most suitable because it is effective, convenient, non-invasive, painless, therefore has the best patient compliance and is relatively safe in recommended doses.

In the present study, oral clonidine in all three doses augment sensory block with bupivacaine spinal anaesthesia. Ota et al. [11] reported that oral clonidine 150 μg, prolonged the duration of tetracaine's sensory analgesia by 93% and the effect was dose dependent with maximum effect at 150 μg. In another study, 200 μg oral clonidine, prolonged the duration of the tetracaine-induced sensory block by only 20-30% [12] while in our study, clonidine prolonged regression time in a dose dependent manner maximum up to dose of 4 μg kg^{-1}. The exact mechanism of clonidine for prolongation of sensory block with spinal anaesthesia is not known. It may due to spread of drug into the spinal cord via systemic circulation and causing direct spinal activation. This evidence is also supported in animal experiments [13]. It is assumed that proposed mechanism of direct spinal activation could also be the reason for the quality of sedation provided by the preoperative use of clonidine [14].

The current study established that clonidine in doses 4 and 5 μg kg^{-1} produces significant sedation as well as anxiolysis measured through VAS as compared to placebo. These studies are in harmony with many studies that has been conducted in the past [10,14]. Thomson et al. [15] concluded that 5 μg kg^{-1} of oral clonidine provides anxiolysis, sedation and quality of premedication which is comparable to the conventional premedication. Ahmed et al. [16] also demonstrated significant anxiolysis during intraoperative period with 150 μg of oral clonidine.

Kriton et al. [17] showed that patients were more sedated with 2-2.5 μg kg^{-1} and 4-4.5 μg kg^{-1} of oral clonidine than placebo in the study and the effect was dose dependent with maximum effect at latter doses. The results are in concordance to the present study, where C4 group showed maximum patients with sedation though all patients had grade 1 type of sedation, hence, it can be assumed that sedative effect is directly related to dose. Moreover, both elderly and young patients show same kind of response with higher doses of clonidine, since there are elderly patients in former study and the patients in our study were comparatively young. Although the sedative effect of clonidine has been related to doses, the optimal dose for anxiolysis, without deep sedation, has not been reported. Various previous studies have supported the use of oral clonidine doses between 100-300 μg for premedication to allay anxiety [14,16].

Regarding hemodynamics, in the present study, clonidine groups showed significant decrease in MAP and heart rate from baseline both intraoperatively and postoperatively and maximum decrease was observed at the dose of 5 μg kg^{-1}. Hypotensive effects of clonidine are due to its central effect or its direct action on peripheral α2 adrenoreceptors and this effect has been found to be dose dependent. Dose response studies of oral clonidine have reported the dose dependent reduction of tonic sympathetic outflow and depression of blood pressure and heart rate [17,18]. Results of our study correlate well with many previous studies [19,20].

Many studies have shown the use of oral clonidine as a premedication agent for general anaesthesia because of its potent hypnotic effects. However, for general anaesthesia the optimal dose is considered to be 4-5 μg kg^{-1} [21,22]. However, Pouttu et al. [23] indicated that similar dose of oral clonidine, when used as premedication for spinal anaesthesia, tend to enhance bradycardia. Our present study also supports this finding and suggests that an oral clonidine dose ≤4 μg kg^{-1} does not cause significant hemodynamic responses, such as hypotension and bradycardia, during spinal anaesthesia.

In conclusion, oral clonidine prolongs the duration of bupivacaine spinal anaesthesia. A dose-response relationship seems to exist with a plateau effect at a dose of 4 μg kg^{-1}. Bradycardia occurred more frequently with 5 μg kg^{-1} oral clonidine, compared with 4 μg kg^{-1}. Therefore, the optimal dose of oral clonidine which produces a clinically useful prolongation of bupivacaine spinal anaesthesia without adverse cardiovascular effects appears to be approximately 200 μg for 50 kg patient or 4 μg kg^{-1}.

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