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Effect of Oral Clonidine as a Premedication in Patients Receiving Spinal Anaesthesia with Hyperbaric Bupivacaine

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Abstract

Background: Spinal anaesthesia is the most commonly used technique for infraumbilical surgeries. Hyperbaric Bupivacaine has limited duration of action. Clonidine has been used to prolong the duration of local anaesthetic. Hence, we studied the effects of oral clonidine premedication on spinal anaesthesia with hyperbaric Bupivacaine vs placebo with reference to sedation, onset and duration of sensory and motor blockade including its effects on hemodynamic status and also on postoperative analgesic requirement. *Objectives:* To study the effect of oral clonidine premedication on spinal bupivacaine anaesthesia with respect to - The onset time, duration of sensory and motor blockade, Effect on haemodynamic status, Sedation, Duration of analgesia, Need for further analgesics in the first 24 hours postoperatively. *Materials & methods:* 60 adult (18-65 yrs) ASA physical status class I and II patients scheduled for lower abdominal, perineal and lower limb surgeries under spinal anaesthesia were recruited into the study. Patients were randomized to receive either 150 µg clonidine or placebo tablet using a random number table. Prespinal heart rate, blood pressure, oxygen saturation and sedation score recorded. Subarachnoid block performed with 3.0 ml of 0.5% hyperbaric Bupivacaine. Sensory & motor block assessed along with hemodynamic parameters and interventions required intraoperatively. Postoperatively heart rate, systolic and diastolic blood pressure, time of first request of analgesic and number of analgesics required in 24 hours were recorded and statistically analysed with p value < 0.05 considered as significant. *Results:* Clonidine group had higher incidence of sedation, faster onset of sensory block without any effect on the onset of motor block, prolonged duration of both sensory and motor block, reduction in blood pressure and heart rate with minimal requirement of haemodynamic interventions, reduced analgesic requirement in the early postoperative period compared to the Placebo group. *Conclusion:* Oral clonidine premedication in patients receiving hyperbaric bupivacaine spinal anaesthesia produces moderate sedation, hastens the onset of sensory block, prolongs the duration of sensory and motor block. Although causes reduction in blood pressure and heart rate, the haemodynamic interventions required is minimal. It also reduces analgesic requirement in early postoperative period.

Keywords: Clonidine; Bupivacaine; Spinal anaesthesia; Sedation; Sensory & motor block; haemodynamic interventions; postoperative rescue analgesics.

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Introduction

Regional anaesthesia has been known to be a better technique for lower limb and lower abdominal surgeries especially in patients with respiratory impairment [1]. It causes minimal intervention of airways, reduces the metabolic changes associated with surgery and at the same

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time provides residual postoperative analgesia [1]. Spinal anaesthesia is the most commonly performed regional anaesthetic technique, [1] due to its safety, reliability, rapid onset of neural blockade and the ease with which it is performed.

As expertise and time are required for epidural anaesthesia, it would be very useful to prolong the duration of spinal analgesia by alternative techniques or methods for prolonged surgeries. Several agents have been used to hasten the onset and prolong the duration of spinal anaesthesia. Vasoconstrictors like phenylephrine, opioids, dextran-40, carbonated local anaesthetics, proteins, potassium, clonidine etc. are some of the well-known agents [2].

Clonidine, an alpha 2 adrenoceptor agonist was introduced into clinical practice as an antihypertensive medication during early 1970. It has been shown to be an effective premedicant, providing preoperative sedation [3,4], perioperative haemodynamic stability [5,6], decrease in the dose of narcotics required to prevent reflex cardiovascular response to tracheal intubation or surgery [7] decrease in minimum alveolar concentration (MAC) of inhalational anaesthetics [8], and postoperative analgesia [9,10].

Regional anaesthesia too is benefited by using clonidine added to local anaesthetic for epidural, spinal, or peripheral block [11]. Clonidine has also been used in alleviating postoperative pain as an adjuvant to opioids [12].

In view of large number of literatures supporting the beneficial effect of clonidine in central neuraxial blockade, we aimed to study the effect of oral clonidine premedication (0.15 mg) during spinal anaesthesia (3 ml of 0.5% hyperbaric bupivacaine).

Materials and Methods

After institutional approval and informed written consent 60 adult ASA class I & II patients scheduled for lower abdominal, perineal and lower limb surgeries under spinal anaesthesia were recruited into the study. The study was conducted from October 2005 to September 2006. Exclusion criteria were Patients with spinal deformities, coagulopathies, local sepsis, Patients with known cardiovascular disease or on cardioactive drugs, Patient's refusal, Patients in whom lumbar puncture could not be performed at L_{3-4} level, Patients in whom supplementation of regional block was required.

Our study was a prospective, double blind, randomized, placebo-controlled study. Patients were randomized to receive either 150 μg clonidine or placebo tablet using a random number table. Blinding was achieved by pharmacy prepared sealed packets containing either study drug or placebo.

A routine pre-anaesthetic evaluation was conducted on the evening before surgery and relevant investigations done. Informed written consent was obtained after explaining the anaesthetic procedure. The patients were pre-medicated with tablet diazepam 10 mg at bed time on the previous night before surgery. They were kept nil orally for 6 hours prior to surgery for solid food and 2 hours for clear liquids.

On the day of surgery, before premedication, heart rate, systolic and diastolic blood pressure, and sedation were recorded. These were taken to be "baseline" readings. Sedation was assessed using the Ramsay scale [13]. Premedication consisted of either clonidine 0.15 mg or placebo, and was administered orally with sips of water 90 minutes before anaesthesia.

After the patient was shifted to the operation theatre, heart rate, systolic and diastolic blood pressure and SpO_2 were recorded using a 3 leads ECG, automated non-invasive blood pressure monitors and pulse oximeter. Sedation score was recorded. These were taken as "prespinal" values. Intravenous line was secured with an 18-gauge cannula and all patients were given 500 ml of ringer's lactate before performing spinal anaesthesia. Under strict aseptic precautions, with the patient in sitting posture, lumbar puncture was performed through a midline approach at L3-4 interspace using either a 23 or 25G Quincke's bevelled spinal needle. Once a free flow of cerebrospinal fluid was obtained, 3.0 ml of 0.5% hyperbaric Bupivacaine was injected. Patients were made to lie supine immediately after the completion of the injection and were retained in that position for at least 20 minutes before positioned for surgery. Sensory block was evaluated by pinprick every minute for first 20 minutes followed by every 10 minutes interval thereafter and the following parameters recorded - Time for the loss of pinprick sensation at T 10 dermatomal level, Highest level of sensory block achieved, Time to achieve highest sensory level, Time for 2 segment regression of sensory anaesthesia from highest level.

Motor block was assessed using Modified Bromage scale [14], and following parameters recorded - Time for onset of Bromage 3 motor block, Time taken for the recovery of motor block to Bromage 2.

Blood pressure and heart rate were recorded every 2 minutes for the first 20 minutes, every 10 minutes till the end of 1 hour, every 15 minutes for 2nd hour, followed by every 30 minutes until 360 minutes from the time of premedication (270 minutes from time of spinal anaesthesia). Time intervals at which hypotension and bradycardia occurred were noted. Hypotension (Systolic blood pressure < 90 mmHg) [15,16] was treated with injection Mephenteramine 6 mg increments intravenously. Bradycardia (Heart rate < 60 beats/ minute) was treated with injection Atropine 0.6 mg intravenously. Any desaturation (SpO_2< 90%) was treated with oxygen supplementation at 5 litres/ minute via face mask.

After surgery, patients were shifted to postoperative recovery room and following parameters recorded - Heart rate, systolic and diastolic blood pressure up to 360 minutes from the time of premedication, time of first request of analgesic, and number of analgesics required by the patient in 24 hours.

Data obtained are presented as mean±standard deviation. Age, sex distribution, ASA class, needle used for SAB and position of surgery were compared using Contingency coefficient (CC). Height, weight and sedation score were compared using Student's t-test. Intergroup comparison of onset and duration of sensory as well as motor block was done using Student's t-test. Haemodynamic parameters comparison between groups was done again by Student's t-test. Intergroup comparison of requirement of Atropine and Mephenteramine was done by Contingency coefficient. Intergroup comparison of time of 1st analgesic request and the number of analgesics needed in 24 hours postoperatively was done by Student's t-test.

Significant figures: p>0.05 is not significant, p<0.05 is significant, p<0.01 is highly significant.

Results

The demographic profile of the patients comparing age, sex, height, weight, ASA class, needle used for SAB and also position for surgery show no statistically significant difference and were comparable in both groups in our study.

The mean sedation score at the time of premedication in clonidine group 1.53±0.51 and placebo group 1.70±0.53 was not significant (p < 0.221). However, the mean sedation score just before spinal, in the clonidine group was 2.67±0.71 compared to placebo group of 1.50±0.57 was found to be statistically significant (p < 0.000) (Table 1).

The clonidine group showed faster onset of sensory block at T10 and also for maximum sensory height achieved (Table 2). Mean time for onset of sensory block at T10 in clonidine group was 2.43±0.73 min, in placebo group was 4.63±1.50 min. this was statistically significant (p < 0.001).Mean time required to achieve the maximum sensory height in clonidine group was 6.67±2.50 min, in placebo group was 11.67±3.13 min. Both the above were statistically significant with p < 0.001. The mean time for onset of maximum motor block in clonidine group was 10.47±2.66 min and in placebo group was 11.40±4.30 min, which had no statistical significant difference (p < 0.317), (Table 2).

The mean time for 2 segment sensory regression and motor block regression to Bromage 2 was longer in clonidine group (Table 2). Mean time for 2 segment sensory regression from the highest level in the clonidine and placebo group was 129.67±30.68 min and 77.33±13.88 min respectively, which was statistically significant (p < 0.0001), (Table 2). Mean time for recovery of motor block to Bromage 2 in clonidine group 198.50±29.36 min, in placebo group153.00±31.08 min was statistically significant (p < 0.0001).

Table 1: Sedation Score

	Clonidine (Mean±SD)	Placebo (Mean±SD)	t	p
Before Pre-med	1.53±0.51	1.70±0.53	-1.238	0.221
Before Spinal	2.67±0.71	1.50±0.57	7.0000	0.000

Table 2: Intergroup Comparison of Sensory and Motor Block

	Clonidine (Mean SD)	Placebo (Mean±SD)	T	P
Time for sensory onset at T 10 (min)	2.43±0.73	4.63±1.50	-7.240	0.0001
Time for max sensory height (min)	6.67±2.50	11.67±3.13	-6.837	0.0001
Time for max motor block (min)	10.47±2.66	11. 40±4.30	-1.010	0.317
Time for 2 seg sensory regression (min)	129.67±30.68	77.33±13. 88	8.512	0.0001
Time for motor block reg to bromage 2 (min)	198.50±29.36	153.00±31.08	5.827	0.0001

Baseline haemodynamic parameters like heart rate, systolic and diastolic blood pressure were comparable in both the groups and were not statistically significant (p>0.05) (Table 3, 4 and 5).

The haemodynamic parameters before spinal and at 360 min from the time of premedication were statistically significant (p < 0.05) (Table 3, 4 and 5). Mean heart rate, mean systolic and mean diastolic pressures in clonidine group were 76.73 +10.74 beats/min, 119.63±9.65 mmHg and 74.00 ±7.17 mmHg in clonidine group compared to 92.76±15.04 beats/min, 130.76±8.97 mmHg and 79.10±7.90 mmHg in the placebo group.

Following spinal anaesthesia, the lowest mean heart, lowest mean systolic and mean diastolic pressure were comparable in both groups without any statistical significance (p>0.05) (Table 3, 4 and 5).

Comparison of haemodynamic changes from baseline to Prespinal showed statistical significance (p < 0.0001), (Table 3, 4 and 5). The change in the mean heart rate in clonidine and placebo group was 7.06±10.66 beats/min and -10.86±12.96 *beats/min* respectively. The changes in the mean systolic and mean diastolic pressure in clonidine group were 7.70±10.32 mmHg and 7.53±7.01 mmHg respectively, whereas in placebo group it was - 4.10 ±9.72 mmHg and 0.03±8.29 mmHg respectively.

Comparison of haemodynamic changes from baseline to 360 min showed statistical significance (Table 3, 4 and 5). The change in the mean heart rate in clonidine and placebo group was 6.06±9.13 beats/min and -1.13±7.37 *beats/min* respectively. The changes in the mean systolic and mean diastolic pressure in clonidine group were 8.60± 11.47 mmHg mmHg and 3.73±7.32 mmHgmmHg respectively, whereas in placebo group it was -0.20 ±8.40 mmHg and -2.20±6.56 mmHg respectively.

Intergroup comparison of number of atropine doses required to treat bradycardia (heart rate <60 beats/min) was compared between the two groups using contingency coefficient. One dose of atropine was required in 7 patients in clonidine group and 4 patients in placebo group. Second and third doses of atropine were required by 3 and 2 patients only in clonidine group. Intergroup comparison was found statistically nonsignificant (p < 0.064), (Table 6).

Intergroup comparison of number of vasopressor doses (Mephenteramine 6 mg) required to treat hypotension (SBP <90 mmHg) was compared between the two groups using contingency coefficient scores. One dose of mephentermine was required in 3 patients in clonidine group and 4 patients in placebo group. Second dose of

Table 3: Intergroup Comparison of Heart rate (BPM)

	Clonidine (Mean±SD)	Placebo (Mean±SD)	t	P
Baseline	83.80±5.01	81.90±6.90	1.220	0.228
Pre-spinal	76.73±10.74	92.76±15.04	-4.749	0.0001
Lowest	63.90±7.98	67.40±8.91	-1.601	0.115
At 360 Mins	77.73±7.91	83.13±7.47	-2.67	0.01
Change (Baseline-Pre-spinal)	7.06±10.66	-10.86±12.96	5.852	0.0001
Change (Baseline to 360 Mins)	6.06 ±9.13	-1.13 ±17.37	3.359	0.001

Table 4: Intergroup Comparison of Systolic Blood pressure (mmHg)

	Clonidine (Mean±SD)	Placebo (Mean±SD)	T	P
Baseline	127.33±10.63	126.66±11.57	0.232	0.817
Pre-spinal	119.63±9.65	130.76±8.97	-4.625	0.0001
Lowest	100.00±9.11	101.80±9.79	-0.737	0.464
At 360 Mins	118.73±9.01	126.87±10.58	-3.205	0.002
Change (Baseline-Pre-spinal)	7.70±10.32	-4.10±9.72	4.556	0.0001
Change (Baseline to 360 Mins)	8.60±11.47	-0.20±8.40	3.388	0.001

Table 5: Intergroup Comparison of Diastolic Blood pressure (mmHg)

	Clonidine (Mean±SD)	Placebo (Mean±SD)	T	P
Baseline	81.53±7.53	79.13±6.67	1.306	0.197
Pre-spinal	74.00±7.17	79.10±7.90	-2.616	0.011
Lowest	56.93±7.14	56.90±6.89	0.018	0.985
At 360 Mins	77.80± 5.54	81.33±6.52	-2.261	0.028
Change (Baseline-Pre-spinal)	7.53±7.01	0.03±8.29	3.780	0.0001
Change (Baseline to 360 Mins)	3.73±7.32	-2.20±6.56	3.302	0.002

Table 6: Number of Atropine and Mephentermine doses required

	Atropine doses				Mephentermine doses		
	0	**1**	**2**	**3**	**0**	**1**	**2**
Clonidine	18	7	3	2	25	3	2
Placebo	26	4	0	0	26	4	0
CC		0.329				0.187	
p-Value		0.064				0.339	

Table 7: Post-operative Analgesic requirement

	Clonidine (Mean±SD)	**Placebo (Mean±SD)**	**t**	**P**
1st Analgesic Request	336.63±155.22	245.17±77.70	2.886	0.005
Rescue Analgesics Needed In 24 Hours	2.07±0.74	2.70±0.65	-3.520	0.001

mephentermine was required by 2 patients in clonidine group only. Intergroup comparison was found statistically nonsignificant ($p < 0.339$), (Table 6).

Intergroup comparison of the mean time for the first analgesic request and the mean number of rescue analgesics needed in first 24 hours done using student t-test was statistically significant. (Table 7). The mean time for the first analgesic request was 336.63±155.22 min and 245.17±77.70 min for clonidine and placebo groups respectively. The mean number of rescue analgesics needed in first 24 hours in clonidine and placebo group was 2.07±0.74 and 2.70±0.65 respectively.

Discussion

Spinal anaesthesia is the most commonly performed regional anaesthetic technique [1], for infraumbilical surgeries and several agents have been used to hasten the onset and prolong the duration of spinal anaesthesia. Vasoconstrictors like phenylephrine, opioids, dextran - 40, carbonated local anaesthetics, proteins, potassium, clonidine etc are some of the well-known agents [2]. Clonidine was introduced into clinical practice as an antihypertensive medication during early 1970. It has shown to be an effective premedicant, providing preoperative sedation, [3,4] perioperative haemodynamic stability, [5,6] and postoperative analgesia [9,10]. Clonidine, added to local anaesthetic for epidural, spinal, or peripheral block, prolongs and intensifies anaesthesia for surgery [11]. Orally or intrathecally administered clonidine in a dose ranging from 75 µg to 300 µg has shown to prolong duration of spinal anaesthesia. The purpose of our study was to investigate the effect of 150 µg oral clonidine premedication on bupivacaine spinal anaesthesia.

In our study, patients were more sedated in the clonidine group compared to placebo. Similar results were found in studies done by Liu et al. [17] and Niemi [18]. Sedative effect of clonidine may be mediated by postsynaptic α2A subtype adrenoceptors located in the locus coeruleus, causing a decrease in noradrenergic activity [19].

We found in our study that the time taken for onset of sensory block at T 10 and the attainment of highest level of sensory block was significantly shorter in the clonidine group compared to placebo. The time for 2-segment regression was prolonged in clonidine group compared to placebo. The results of this study match well with the studies done by Ota et al. [15,16,20]. However our study was in contrast with study done by Bonnett et al. [21] who showed that subarachnoid clonidine but not oral clonidine prolonged the duration of sensory block. In our study we found no difference in the time of onset of complete motor block between the two groups and the duration of motor block was prolonged in clonidine group, in accordance with the studies by Singh et al. [22,23]. Thus, we confirm that oral clonidine (0.15 µg) premedication prolongs the sensory and motor blockade during bupivacaine spinal anaesthesia. Studies using intrathecal clonidine have demonstrated prolongation of sensory and motor block indicating antinociceptive action of clonidine in the dorsal horn of the spinal cord [18]. 150 µg oral clonidine used in our study seems too small to increase the concentration of clonidine in cerebrospinal fluid. Clonidine is highly lipid soluble and crosses tissue barriers rapidly and therefore may interact with a- adrenergic receptors at spinal and supraspinal sites within the central nervous system [17].

In our study, the mean systolic pressures were comparable before premedication. However, prespinal mean systolic blood pressure showed

significant difference between the two groups. The lowest mean systolic pressure recorded after spinal anaesthesia were comparable in both groups. The number of patients requiring intravenous Mephentermine to treat hypotension were 5/30 in clonidine group and 4/30 in placebo group ($p < 0.339$). Our study coincided with the study done by Ota et al. [15] showing no significant difference in SBP before premedication and also the lowest SBP after spinal anaesthesia. However, it differed from Ota et al. [15] by being statistically significant between the two groups. Thus, we conclude that oral clonidine (150 μg) premedication though lowers the mean SBP for prolonged period, the incidence of intervention to treat hypotension is minimal and comparable to that of placebo.

In our study, the heart rates were comparable at baseline between the groups. Even the lowest heart rate recorded following spinal anaesthesia were comparable. However, prespinal heart rates were significantly lower in the clonidine group compared to placebo. The results of this study match well with the studies done by Ota et al. [15]. The number of patients requiring intravenous Atropine to treat bradycardia were 12/30 in clonidine group and 4/30 in placebo group. The heart rates recorded at 360 min from the time of premedication was significantly lower in clonidine group compared to placebo.

Singh et al. [23] used 200 μg oral clonidine 90 minutes before spinal anaesthesia. They found that incidence of bradycardia (HR <50 beats/min) was higher in clonidine group (40%) compared to placebo (10%). Ota et al. [20] in their study of dose related prolongation of tetracaine spinal anaesthesia used 75 μg, 150 μg and 300 μg oral clonidine 60 minutes before anaesthesia. They found that frequency of bradycardia (HR<45 beats/min) was significantly greater with 300 μg than with 150 μg of oral clonidine. Though the incidence of bradycardia was higher in the above studies, the dose of clonidine used by them was more than 150 ug. In our study there was a higher incidence of bradycardia in clonidine group (12/30) as compared to placebo (4/30). The definition of bradycardia in our study was a heart rate < 60 beats/min, whereas in other studies bradycardia was defined as either heart rate < 50 beats/min [29] or < 45 beats/min [15,20]. This might explain the higher incidence of bradycardia for 150 μg clonidine in our study. However, the lowest heart rate seen in our study was 52 beats/min. Thus, we confirm that 150 μg oral clonidine, though lowers the heart rate, the requirement of intervention is minimal and comparable to that of placebo, and this dosage may be safely used as a premedicant.

In our study, we found a significant difference in the time of 1st analgesic request and the number of rescue analgesics needed in first 24 hours between the two groups. The analgesic effect of clonidine has been demonstrated by many studies. Our study results were in accordance with the results by Niemi, [18] Bernard et al. [11] and Bonnet et al. [24] in which clonidine group showed delayed onset of pain and decreased opioid dose requirement during the 24-hour postoperative period. The analgesic property of clonidine administered intrathecally or epidurally has been attributed to its action on an adrenoceptor of the dorsal horn of the spinal cord [18]. Oral clonidine used in the present study also showed reduction in the analgesic requirement in the early postoperative period. The mechanism of action of oral clonidine may be same as that of systemically administered clonidine and needs further evaluation.

Several limitations of our study need to be discussed, though they may not have significant influence in our study. Lack of dose-response or time-response design. We used a standard dose of 150 μg oral clonidine irrespective of the weight of the patients, volume of distribution, gastric emptying, metabolism etc which may affect the plasma levels of clonidine and we did not measure the plasma level of clonidine in each patient during the study. Higher incidence of sedation after clonidine premedication may have resulted in unblinding of the subjects and biased our results. The type of surgery might have influence on recorded lowest blood pressures and heart rate values.

Conclusion

we conclude that oral clonidine at a dose of 0.15 mg given 90 min before bupivacaine anaesthesia produces higher incidence of sedation, hastens the onset of sensory block without any effect on the onset of motor block, prolongs the duration of both sensory and motor block. Although produces a reduction in blood pressure and heart rate, the haemodynamic interventions required is minimal. It also reduces the analgesic requirement in the early postoperative period.

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