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EFFECT OF ORAL CLONIDINE PREMEDICATION ON THE DURATION OF ANALGESIA PRODUCED BY SPINAL BUPIVACAINE.

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ABSTRACT

The concept of "pre-emptive analgesia" is becoming popular and the use of clonidine along with regional techniques is one of the important milestones in post-operative pain management. The aim of our study is to assess the effects of oral clonidine premedication on the duration of analgesia by bupivacaine subarachnoid block. Its a randomized controlled trial involving one hundred American Society of Anesthesiologists (ASA) graded assessment of risk status I & II patients, aged 20 – 50 years undergoing various elective lower abdominal and lower limb surgeries in a tertiary medical care institute. The study group was divided into two groups of 50 patients each. Group A patients received no premedication and Group B received 100µcg of oral clonidine two hours prior to spinal anaesthesia. Both groups received 3ml of 0.5% Bupivacaine (heavy) for spinal anaesthesia using 25 gauge quincke spinal needles and sensory blockade attained was T_6. Hemodynamic parameters were monitored before, during and after the procedure. Time for onset of sensory and motor blockade, duration of maximum motor blockade, duration of postoperative analgesia and the incidence of complications were recorded and compared between the two groups. Clonidine prolonged the mean duration of motor blockade by 160.8 ± 29.88 min compared to 106.6 ± 9.11 min by control group ($P < 0.05$). The mean duration of analgesia was 183.30 ± 20.21 min in clonidine group compared to 115.9 ± 12.4 min in control group ($P < 0.05$) and the difference was found to be statistically significant. No significant difference was found on demographic data, hemodynamic parameters, and frequency of complications. 100µg oral Clonidine two hours prior to bupivacaine subarachnoid block prolongs the duration of post-operative analgesia.

KEY-WORDS: Bupivacaine, Clonidine, Motor blockade, Premedication, Sensory blockade, Spinal anaesthesia.

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INTRODUCTION

Subarachnoid block is a widely practiced technique and analgesia produced by spinal bupivacaine is well known. Extension of this analgesia into the postoperative period is an added advantage as the need for other analgesics are minimized.[1,2] Drugs like epinephrine,[3] fentanyl prolong bupivacaine spinal anaesthesia,[4] but have their own limitations. Clonidine, a non-opioid α_2 agonist[5] is administered sublingually,[6] intramuscularly,[7] intravenously[8] and by various other routes[9,10,11]. Given intrathecally[12] and epidurally provides post-operative analgesia. It also acts as a sedative and reduces post-operative shivering.[13] Hence we made an attempt to study the effect of oral clonidine on the duration of bupivacaine spinal analgesia.

MATERIALS AND METHODS

After approval from institutional ethics committee, a randomized controlled trial was undertaken on 100 patients of both sexes in the age group between 20-50 years belonging to ASA I & II, posted for elective general surgical, orthopaedic or gynaecological operations under spinal anaesthesia. Patients with spinal deformity, heart rate < 60/minute and patient on anticoagulant therapy were excluded from the study. Preanaesthetic evaluation was carried out in all the patients and written and informed consent for the procedure was obtained. Patients were randomly divided into two groups of 50 each. Group A received no premedication (control group) and group B (treatment group) received tab clonidine (100 µcg) orally given two hours before spinal anaesthesia.

Randomization was done using a lottery method with odd numbers going to group A (control) and even numbers to group B (treatment). The surgeon, patient and the anesthesiologist were blinded to the oral clonidine premedication. No other pre-medication or analgesics were given to the patient prior to surgery .On arrival into the operating room; an intravenous line was secured with 18 gauge cannula. The preoperative systolic and diastolic blood pressure (BP), pulse rate and saturated partial pressure of oxygen (SpO_2) were recorded using a standard hemodynamic monitor. All patients were preloaded with 10-15 ml/kg of ringer lactate solution before the intrathecal block. The patient was put in left lateral recumbent position and under all aseptic precautions; a lumbar puncture was performed at L_3-L_4 interspace with 25 gauge quincke spinal needle. Following free flow of CSF, analgesia was achieved with 0.5% bupivacaine (heavy). Immediately following intrathecal administration of the drug, patients were turned supine and heart rate , blood pressure and SpO_2 were recorded and noted. On achievement of appropriate level of anaesthesia, the surgery was allowed to commence and proceed.

During the procedure, no analgesic was administered; if any drug like pethidine needed to be administered for the patient, then these patients were excluded from the study. The following parameters were noted:-

1. **Time of onset of sensory blockade -** defined as the time interval between the completion of injection of local anaesthetic solution to the onset of complete loss of sensation to pin prick.
2. **Time for onset of maximum motor blockade -** defined as the time interval between the completion of the injection of local anaesthetic solution to the establishment of inability to move the lower limbs both at the knee and ankle (Bromage scale grade 3).[14]
3. **Duration of maximum motor blockade** - defined as the time interval between completion of the injection of local anaesthetic solution to the patient's ability to flex the feet.
4. **Duration of post-operative analgesia -** defined as the time interval between the onset of sensory block and the first dose of analgesic required.

Whenever patients developed hypotension (systolic BP <30% of baseline), preliminary

measures via increasing the rate of intravenous fluids, slight trendelenberg position and O_2 by mask were taken. If the fall in BP continued, intravenous ephedrine 5-10 mg was given. When the patients had bradycardia (pulse rate <50 per minute), atropine sulfate 0.5 mg intravenous bolus was given. Nausea and vomiting were also evaluated and were treated with 0.15 mg /kg IV metaclopramide. Post operative pain was evaluated by the time of requirement of the first dose of analgesic for grade 1 pain using the verbal rating score as follows: 0 – None,1 – Mild pain, 2 – Moderate pain, 3 – Severe pain.4 – Excruciating pain.[15]

Statistical Analysis

Statistical analysis was done using Microsoft Excel 2010. Mean ± SD was computed for continuous variables and percentages for categorical data. t-test was used to test the difference between quantitative variables and chi square test to test association between quantitative variables. P value < 0.05 was considered as statistically significant.

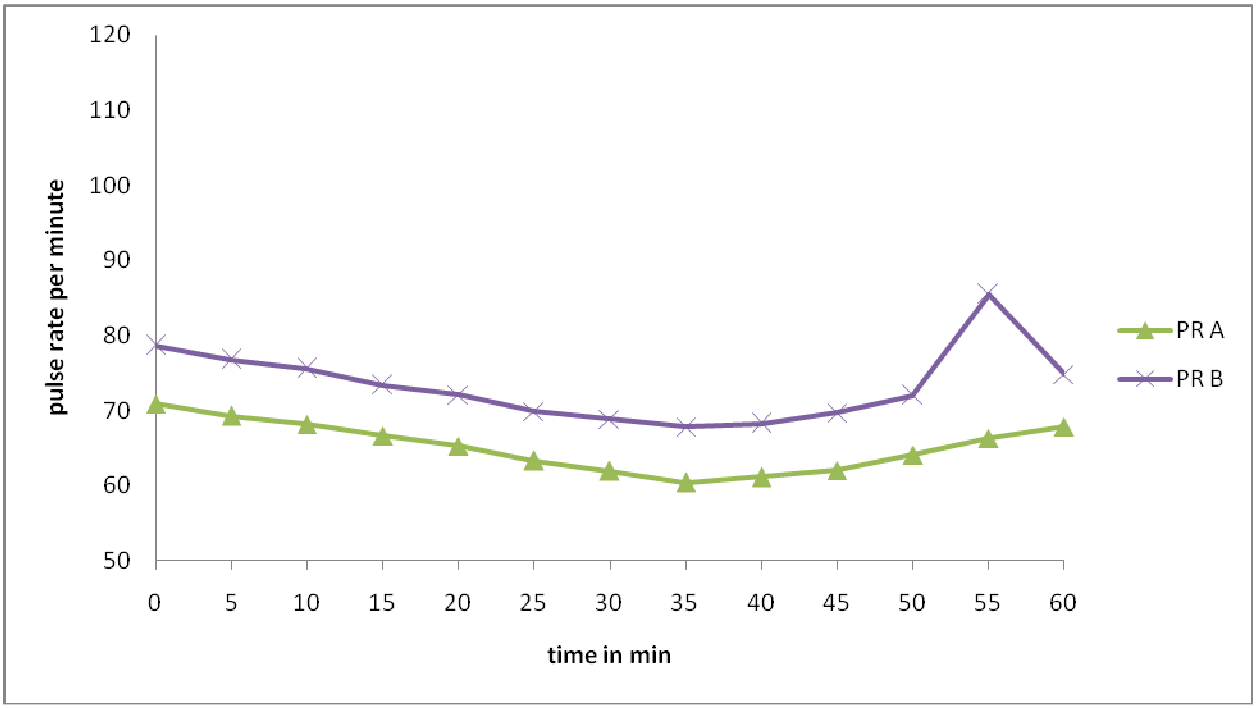
RESULTS

Demographic characteristics namely the age, weight showed no statistically significant differences.

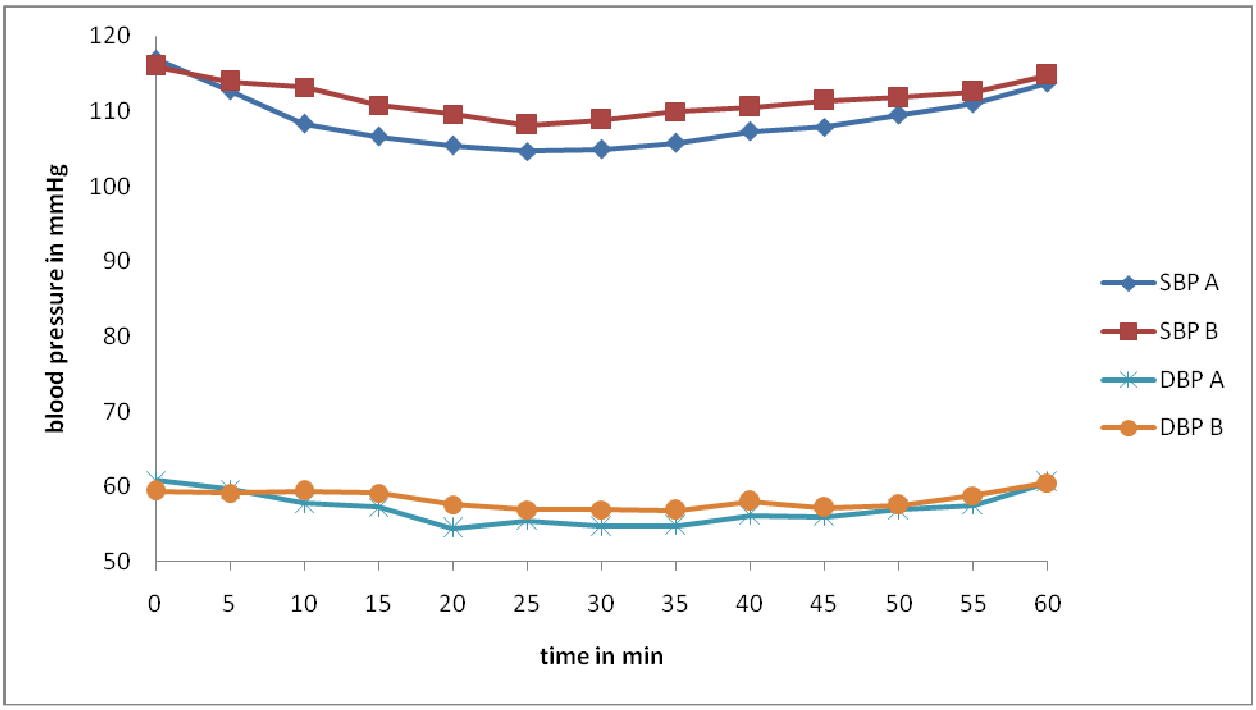
Hemodynamic Parameters

The hemodynamic parameters are depicted in the Graph 1 and 2 shown as pulse rate (PR in group A and B), systolic blood pressure (SBP in group A and B) and diastolic blood pressure (DBP in group A and B).

Graph 1: Pulse rate between the groups post spinal anaesthesia



Graph 2: Blood pressure between the groups post spinal anaesthesia



Pulse Rate

The mean pulse rate before pre-medication in the control group was 75.74 ± 7.78 bpm and 74.80 ± 8.82 bpm after two hours of premedication. Whereas in clonidine group, it was 69.86 ± 3.38 bpm before premedication and 67.82 ± 6.45 bpm after two hours of premedication. No statistically significant difference was seen between the two groups. (Graph 1)

Systolic Blood Pressure

The mean systolic blood pressure before premedication was 114.90 ± 7.61 mmHg in control group and 115.98 ± 8.46 mmHg in clonidine group. The mean systolic blood pressure after two hours of premedication was 114.80 ± 7.77 mmHg in control group and 113.74 ± 5.75 mmHg in clonidine group. No statistical significant difference in mean systolic blood pressure was seen between both the groups. (Graph 2)

Diastolic blood pressure

The mean diastolic blood pressure before premedication was 59.38 ± 6.73 mmHg in control group and 60.82 ± 7.34 mmHg in clonidine group. The mean diastolic blood pressure after two hours of premedication was 60.52 ± 5.58 mmHg in control group and 60.54 ± 6.05 mmHg in clonidine group and was statistically insignificant. (Graph 2)

Duration of motor blockade:

The time of onset of sensory blockade, time of onset of motor blockade is depicted in table 1 and revealed no statistically significant difference between the two groups. However, the mean duration of motor blockade was higher in the clonidine group (Group B) The mean duration of post operative analgesia was found to be 183.3 ± 29.4 min in the clonidine group (Group B) which was higher when compared to 115.9 ± 27.2 min in the control group (Group A) and was statistically significant with 160.8 ± 39.6 min compared to 106.6 ± 43.3 min in the control group and was statistically significant. (Table 1)

Table 1
Duration of motor blockade between the groups

Parameters	Control Group (Group A)	Clonidine Group (Group B)	t - value	p value
Mean time of onset of sensory blockade in min	1.81 ± 0.31	1.94 ± 0.33	1.907	0.059
Mean time of onset of motor blockade in min	4.79 ± 0.26	4.81 ± 0.29	0.269	0.788
Mean duration of motor blockade in min	106.6 ± 9.11	160.80 ± 29.88	12.265	0.000
Duration of post operative analgesia in min	115.90 ± 12.40	183.30 ± 20.21	20.93	0.000

Five patients had bradycardia and six patients had hypotension in the control group whereas, six patients had bradycardia and seven were hypotensive in the control group and the results were not statistically significant. Table 2 represents the incidence of side effects in both the groups. (Table 2)

Table 2
Side effects encountered between the groups

Side Effects	Number of patients in Group A(control group)	Number of patients in GroupB(treatment group)	Chi-square value	p value
Bradycardia	5	6	0.102	0.749
Hypotension	6	7	0.088	0.766
Vomiting	2	2	0.000	1.000
Sedation	2	2	0.000	1.000

DISCUSSION

The study was conducted on one hundred patients, fifty in each group receiving no premedication (Group A) and oral clonidine premedication (Group B) before spinal analgesia. The mean duration of motor and sensory blockade and the duration of analgesia was assessed and compared between the two groups. Our study revealed that 100 µcg of oral clonidine premedication two hours before spinal anaesthesia prolonged the duration of analgesia with spinal bupivacaine. The fall of pulse rate after clonidine premedication in clonidine group is due to the direct action of clonidine on the dorsal motor nucleus of vagus nerve. But this reduction in pulse rate and bradycardia in clonidine treatment group was not statistically significant. Similar study was conducted by Ota et al,[16] where in the mean pulse rate before premedication was 81 ± 10min and after 90 min of oral clonidine it was 69 ± 9 min similarly systolic blood pressure before premedication was 128 ± 21 mmHg and after premedication with tablet clonidine orally it was 121 ± 17 mmHg with no change in control group and found statistically insignificant. The time of onset of sensory and motor blockade between the two groups of our study was found to be statistically insignificant. However, in our study we took a standard sensory blockade level of T_6 and any patient greater or lesser than T_6 were excluded from the study. So we did not evaluate the two segment regression and thereby the duration of sensory blockade. The mean duration of maximum motor blockade in our study was 106.6 ± 9.11 min in the control group and 160.8 ± 29.85 min in the clonidine group which is statistically highly significant ($p < 0.05$). The exact mechanism whereby oral clonidine may affect motor blockade is unclear but both direct inhibition of Aα motor fibres and augmentation of intrathecal local anaesthetic

effects may play a role in the effects of oral clonidine.

Dziudbziela et al[7] similarly studied the effects of oral and intramuscular clonidine in prolonging the duration of bupivacaine spinal analgesia and found no statistical difference in the onset of sensory and motor blockade between the two groups and the control group but the duration of maximum motor blockade was 185.9 ± 59.3 min compared to 141.9 ± 56.6 min in the control group and this was found to be statistically significant. Oral administration of clonidine[17] results in virtually complete absorption and peak plasma concentration occurs 1-3 hours after administration. Clonidine is highly lipid soluble, easily crosses the blood brain barrier and therefore may interact with α – adrenergic receptors [18] at spinal and supraspinal sites within the central nervous system. The mechanism of prolonging effect represents a direct analgesic action at spinal and supraspinal sites or constriction of spinal vasculature that delay vascular absorption of local anaesthetics. Clonidine inhibits neurotransmission in both 'Aδ' and 'C' nerve fibres which are theorized to mediate pinprick and surgical pain. It also potentiates the inhibitory effects of local anaesthetics on 'C' fiber activity. Therefore oral clonidine may exert its effects within the central nervous system, at peripheral nerve roots or by potentiation of effects of local anaesthetics.[19,20] The duration of post-operative analgesia[21,22] in control group was 115.90 ± 12.40 min and in clonidine group it was 183.30 ± 20.21 min which is statistically highly significant. This is due to the potent analgesic property of clonidine that acts at spinal and supraspinal sites. The most plausible non opioid mechanism for the analgesic action of α_2 agonists relates to the role of descending medullospinal noradrenergic pathway modulating spinal nociceptive processing. α_2 adrenergic receptor are strategically located on the dorsal horn neurons of the spinal cord where they can either inhibit the release of nociceptive neurotransmitters such as substance 'P' or calcitonin gene related peptide. Another mechanism of analgesia is by the synergistic interaction between α_2 adrenergic agonists and opiates in the spinal cord.

Dobrydnjov et al[23] did a similar study on 45 patients posted for osteosynthesis of femur fracture and found that oral clonidine premedication significantly prolonged the time required for the first dose of analgesic by 313 ± 29 min compared to 236 ± 27 min by placebo ($p < 0.05$). The common complications noticed in both the groups of our study were hypotension, bradycardia, nausea and vomiting. Even though there are no significant statistical differences in the incidence of complications in both the groups, the marginally higher incidence but of milder degree of bradycardia and hypotension in the clonidine group could be attributed to the inhibition of sympathetic overflow and the potentiation of parasympathetic nervous activity. Liu et al[19] did a similar study on oral clonidine and lignocaine spinal anaesthesia and reported no significant bradycardia or hypotension. The haemodynamic status was similar in both the groups post spinal anaesthesia. The sedation effect of clonidine was mainly due to its action on the locus coeruleus.

CONCLUSION

It is evident from the results of our study that Clonidine prolonged the mean duration of analgesia by 67.40 ± 7.81 min when compared to the control group ($P < 0.05$) and found statistically significant. No significant difference was found on demographic data, hemodynamic parameters, and frequency of complications. Hence, one can avoid addition of adrenaline and other narcotics to spinal bupivacaine to prolong the duration of analgesia in view of the limitations and complications using these drugs. Use of oral clonidine 100µcg two hours prior to spinal anaesthesia is safe and can be instituted into routine practice to prolong the duration of bupivacaine spinal analgesia with no fear of added complications. However, more studies have to be done on a larger population to conclude the evidence of our study.

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CONFLICT OF INTEREST: None declared.

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