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Effects of Oral Clonidine Premedication on Spinal Subarachnoid Blockade with Hyperbaric Bupivacaine

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Abstract

Background: The prolongation of local anesthetic induced sensory and motor block after co-administration with intrathecal clonidine [1,2] is well documented, but with oral clonidine the effect remains controversial [1.3]. *Aim:* To assess the effects of oral clonidine premedication in bupivacaine spinal anaesthesia (SA). *Materials and Methods:* 40 patients of ASA I & II undergoing spinal anesthesia were randomly divided into two groups of 20 each. *Group* C: Oral clonidine 150µg premedication 90mins before SA with15 mg of 0.5% Bupivacaine heavy. *Group P:* SA with15 mg 0.5% bupivacaine heavy. *Result:* The time of onset of sensory blockade in group C was 2.95±0.68 min and in group P 6.75±0.71 min [p<0.0001], duration was 370.55±39.10 min in Group C and 253.50±43.95 min in Group P [p<0.0001]. The duration of motor block was 296.45±33.15 min in Group C and 196.3±32.7 min in Group P [p<0.0001]. No significant difference was found on demographic data, hemodynamic parameters and frequency of complications. *Conclusion:* Pre medication with 150 µg oral clonidine in bupivacaine spinal block, can be instituted to prolong the duration of both sensory and motor blockade in routine practice without the fear of added complications.

Keywords: Oral Clonidine; Bupivacaine; Spinal Anaesthesia; Sensory Blockade; Motor Blockade.

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Introduction

Several agents alone or in combination have been used to prolong the duration of spinal anesthesia for lengthened surgeries. Vasoconstrictors like epinephrine [4], opioid [5], dextran-40, carbonated local anesthetics, proteins, potassium etc. are some of the well-known agents. Clonidine, a non-opioid alpha2 adrenergic agonist [6] has been successfully used in the past and recent years and is administered sublingually [7], intramuscularly [8], intravenously [9] and by various other routes [10,11,12] as a premedication due to its sedation and anxiolytic properties and also as an agent for controlling shivering [13]. Regional anesthesia too was benefited by using clonidine, either by spinal [14] or epidural. Clonidine stimulates alpha 2 adrenergic inhibitory neurons in medullary vasomotor centre which decreases sympathetic outflow and is manifested as decreasesd systemic blood pressure, heart rate and cardiac output. Clonidine has also been used as an adjuvant in postoperative pain relief, alternative to opioid.

In view of wealth of literature supporting the potent analgesic properties of clonidine in central neuraxial blockade, we aimed to study the effect of oral clonidine premedication during bupivacaine spinal anesthesia.

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Aims and Objectives

Our primary aim is to study the effects of oral clonidine premedication with hyperbaric Bupivacaine on spinal anaesthesia. The objectives of this study are in reference to

- Onset and duration of sensory and motor blockade
- Haemodynamic status,
- Adverse effects

Materials and Methods

After obtaining approval from institutional ethics committee, our study, a randomized controlled prospective one, had been conducted during the period of August 2016 to July 2017 in a rural hospital medical college. Study design was an interventional one withcomputer generated randomly allocated patientsof sample size 40. Patients weredivided into two groups - clonidine (Group C) and control (Group P) of 20 patients each. All Patients were assessed on the previous day of the surgery. Patients satisfying the inclusion criteria were included in the study.

Inclusion Criteria

- Lower abdominal and lower limb surgeries under spinal anesthesia
- ASA grade I and II patients
- Age 20 to 60 yrs
- Weight 40-65kg
- Height 150-160cm

Exclusion Criteria

- Unwilling patient.
- Emergency Surgeries
- History of

  *known allergies to study drugs,

  *cardiovascular disorders,

  *on medications known to affect cardiovascular functions,

  *disorders known to affect autonomic function, *diabetes
- Pregnant patients
- ASA Grade III or higher.

Pre-anaesthetic evaluation:

Of detailed history, physical examination, systemic examination, routine investigations. After proper pre-anaesthetic counselling in the patient's own language a written and informed consent had been obtained.

Anaesthetic Protocol Followed

1. Premedications

Group C-1 tablet of clonidine 150µg in the morning of surgery orally, with a sip of water to the patients, 90 minutes before anesthesia.Group P-control group, no premedication of tablet of clonidine 150µg No oral gastric tube was used during surgery.

2. Preoperative Preparation

On arrival at the operation theatre, baseline heart rate, systolic, diastolic blood pressures ,Spo_2 (by pulse oximetry) were measured using an automated noninvasive monitor, an 18 gauge intravenous cannula was inserted under local anaesthesia ointment and lactated ringers solution of 15ml/kg was infused for co-loading. Scoring was done for sedation using a 5 point Ramsay scale. Score 1: Anxious, agitated, and restless. Score 2: Awake, cooperative, oriented, tranquil. Score 3: Semi asleep responds only to verbal commands. Score 4: Asleep with brisk response to glabellar tap or loud auditory stimulus. Score 5: Asleep with sluggish response to glabellar tap or loud auditory stimulus. Score 6: Non responsive.

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 per-operative analgesia and the incidence of complications were recorded and compared between the two groups.

3. Positioning and Technique of the Block

The patients were placed in the lateral decubitus for the anaesthetic procedure. Under strict aseptic precautions a lumbar puncture was performed through a midline approach using a 25 gauge quincke spinal needle at the L3-L4 inter vertebral space. Once a free flow of cerebrospinal fluid was obtained, 15 mg of 0.5% Bupivacaine heavy was injected.

4. Assessment of the level of the block

After the spinal injection ,the patient was retained in supine position till the Bromage scale 3 motor block was obtained. Dermatome levels of sensory anaesthesia were evaluated by pin prick. The levels

of pin prick analgesia were studied every 2 min until analgesia to pin prick recovered to the L1 segment.

a. Time of onset of sensory blockade was noted which is considered as the time interval between the completion of injection of local anaesthetic solution to the appearance of analgesia at L1 to pin prick.
b. Duration of sensory block was noted which is defined as the time interval between the onset of sensory block and the regression of block to L2 The time when patient asks for analgesia were monitored and noted.
c. Time for onset of motor blockade was noted which is 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).
d. Duration of motor blockade was noted which was the time interval between the establishment of inability to move the lower limbs both at the knee and ankle to the patient's ability to flex the feet.

Bromage Scale Grade: Scale 0 – Free movements of legs and feet, with ability to raise the extended leg.

Scales 1 – Inability to raise extended leg and knee flexion is decreased, but flexion of feet and ankles is present.

Scale 2 – Inability to raise leg or flex knees, flexion of ankle and feet Present.

Scale 3 – Inability to raise leg, flex knee or ankle, or move toes.

5. Intra-operative Monitoring

Intra operatively, the blood pressure and heart rate were monitored at 2 minutes interval for the first 10 minutes, later every 20 minutes for 1 hr and every 30 minutes for 2 hrs. Hypotension (defined as less than 20% of baseline blood pressure) was treated with intravenous fluid initially (250 ml boluses repeated twice) and intravenous mephentermine 6 mg, if required. Bradycardia (defined as heart rate of less than 50) was treated with intravenous 0.6 mg atropine sulfate.

6. Post-operative Monitoring

Assessed for side-effects like hypotension, bradycardia, pruritis, nausea, vomiting, shivering, respiratory depression.

7. Results

• *Statistical Method*

The parameters were expressed as mean± standard deviation and analyzed using chi square test or student 't' test as appropriate, with the p value reported at the 95% confidence interval. The results obtained in the study were analyzed using Microsoft Excel and SPSS for analyzing the collected data. Power of study was kept 80% (β=0.8).

'p' value >0.05 statistically not significant (NS)

'p' value of <0.05 as statistically significant (S)

'p' value of <0.01 as statistically highly significant (HS)

'p' value of <0.0001 as statistically very highly significant (VHS)

Result

The study groups C (Clonidine) and P (Control) of 20 patients each were comparable with respect to demographic profile. Non significant (NS) difference in the two groups with respect to age, weight and height (Table 1).

Intergroup comparison of groups C (Clonidine) and P (Control) showed a statistically very highly significant (VHS) [p <0.0001] difference in the onset of sensory block, duration of sensory block [p <0.0001],

Table 1: Patients' demographic data

	Group	N	M±SD	p value
Age (yrs)	Clonidine (C)	20	30.6±8.20	p 0.25 (NS)
	Control (P)	20	33.7±8.8	
Weight (kg)	Clonidine (C)	20	51.95± 8.38	p 0.55 (NS)
	Control (P)	20	53.45±7.5	
Height (cm)	Clonidine (C)	20	155.4±3.48	p 0.85 (NS)
	Control (P)	20	155.6±3.5	

N= Number of patient

onset of motor block [p<0.0001], duration of motor blockade [p <0.0001]. Duration of surgery was non significant (NS) (Table 2).

Haemodynamic parameters

Systolic Blood Pressure

The mean systolic blood pressure before premedication (base line) was 119.7±8.92 mmHg in clonidine group and 121.9±6.4 mmHg in control group [p=0.45]. After 3 hours (pre-spinal) it was 104.5±8.75 mmHg in clonidine group and 108.50± 4.03 mmHg in control group [p=0.10]. Both were statistically insignificant.

Diastolic Blood Pressure

The mean diastolic blood pressure (base line) before premedication was 78.6±6.1 mmHg in clonidine group and 76.9±7.66 mmHg in control group [p=0.45]and after 3 hours of premedication (pre-spinal) it was 64.2 ± 6.95 mmHg in clonidine group and 65.9±5.90 mmHg in control group [p=0.40] (Graph 1,2). Both were statistically insignificant.

The mean pulse rate before pre-medication (base line) in the clonidine group (C) was 87±10.3 bpm and in control group(p), it was 85.7±9.69 bpm [p=0.06]. After 3h (pre-spinal),the pulse beat per minute became 70.48±11.67 in the clonidine group was and 69.1± 13.95 with the control group (p=0.73). No statistically significant difference was seen between the two groups .

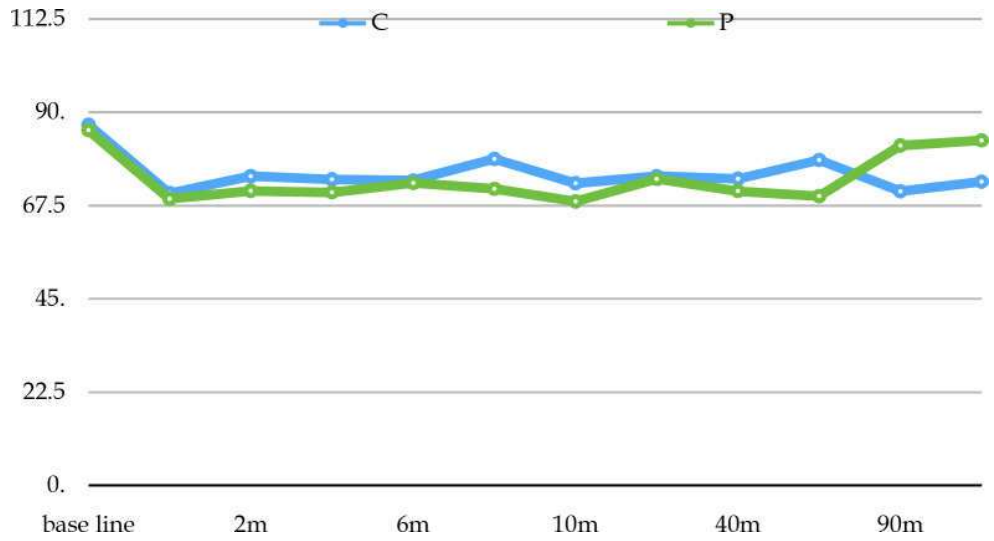
Per-operative complication

Although few incidences of hypotension, bradycardia, nausea, vomiting pruritus, shivering were noted with both the groups, the difference was not statistically significant.

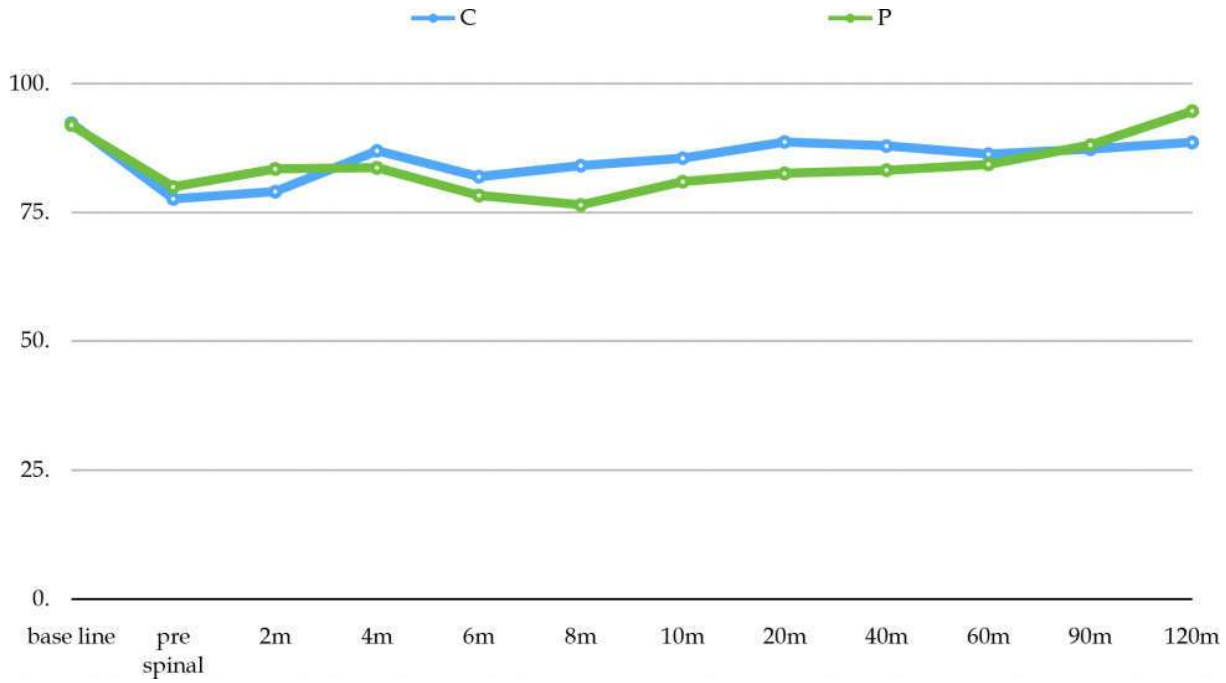
Table 2: Study parameters (Intraoperative)

Parameters	Group C M±SD	N 20	Group P M±SD	N 20	p value
Onset of Sensory block (min)	2.95 ± 0.68		6.75 ± 0.71		<0.0001 (VHS)
Duration of Sensory block (min)	370.55 ±39.10		253.50 ±43.95		< 0.0001(VHS)
Onset of Motor blockade at time (Bromage score 3) (min)	6.15 ± 0.93		11.55 ± 1.5		< 0.0001 (VHS)
Duration of Motor block(min)	296.45 ±33.15		196.3 ± 32.7		<0.0001 (VHS)
Duration of Surgery (min)	61.95 ± 3.72		60.04 ± 4.07		0.12 (NS)

N= Number of patient



Graph 1: Mean arterial pressure (MAP) at different time intervals: C (**Clonidine**) P (**Control**)



Graph 2 : Mean Pulse rate at different time intervals: C (Clonidine) P (Control)

Discussion

Administration of Clonidine through oral route is generally considered most suitable because it is convenient, effective, painless, non-invasive, relatively safe in recommended doses,therefore has the best patient compliance [15]. Clonidineresults in almost complete absorption after 1-2 hours and peak plasma concentration is observed between 1 and 3 hr [16] of oral ingestion.

Because clonidine is highly lipid soluble, it easily crosses the blood brain barrier, therefore may interact with á adrenergic receptors [17], which are strategically located on the dorsal horn neurons of the spinal cord where they can inhibit the release of nociceptive neurotransmitters such as calcitonin gene related peptide or substance 'P'. This may be the most probable reason for non opioid mechanism of the analgesic action of α2 agonists which relates to the role of descending medullospinal noradrenergic pathway modulating spinal nociceptive processing.

The exact mechanism of clonidine for prolongation of sensory block with spinal anaesthesia is unclear.It may due to (1) spread of drug into the spinal cord via systemic circulation causing direct spinal activation which represents an analgesic action at spinal and supraspinal sites or (2) constriction of spinal vasculature which delays vascular absorption of local anaesthetics. Another mechanism of analgesia is by the synergistic interaction between α, α2 adrenergic agonists and opiates in the spinal cord. Clonidine inhibits neurotransmission in both 'C and 'Aδ' nerve fibres [18] which mediate surgical pain and pinprick. It also potentiates the inhibitory effects of local anaesthetics on 'C' fiber activity [19]. Therefore oral clonidine may exert its effects within the central nervous system, at peripheral nerve roots or by potentiating the effects of local anaesthetics [1,20]. The time of onset of sensory block between the two groups of our study was found to be statistically very highly insignificant ($p<0.0001$). The duration of analgesiain our study was 370.55±39.10 min in clonidine group and 253.50±43.95 min in control group which was statistically very highly significant ($p < 0.0001$). This is due to the potent analgesic property of clonidine that acts at spinal and supraspinal sites. Dobrydnjov et al. [21]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. Bonnet et. al. [1] failed to demonstrate significant prologation of bupivacaine induced sensory and motor blockade following clonidine 150µg or 0.3 mg orally and claimed that subarachnoid clonidine but not oral clonidine prolonged the duration of sensory block at spinal

and supraspinal sites within the central nervous system. Our study but did not go in accordance with them.

The mechanism by which oral clonidine affect motor blockade is not known - may be both by direct inhibition of Aα motor fibres and augmentation of intrathecal local anaesthetic. In our study, we found a significant difference ($p < 0.0001$) in the time of onset of complete motor block between the two groups - group C: 2.95±0.68 and group P: 6.75 ±0.71. The duration of motor block was prolonged in clonidine group (296.45±33.15) than the control group (196.23±32.7), $p < 0.0001$. Thus, we confirm the prolongation of sensory and motor blockade by oral clonidine during spinal Bupivacaine anaesthesia. Since clonidine is an antihypertensive due to its central effect or its direct action on peripheral α2 adrenoreceptors ,we anticipated a fall of prespinal blood pressures after oral ingestion of clodine [22,23]. Dodd JM et al. [24] presented that patients were able to generate a sympathetic response to surgery and hypotension despite the presence of the α2 agonist agent. In our study, both the groups showed decrease in MAP from baslinein systolic and diastolic blood pressures with or without premedication but the comparison was non-sigcant. It was thus clear from our study that fall in blood pressure was insignificant with a premedication of single oral dose of 150µg of clonidine.

The heart rate in clonidine treated groups in the present study, did not differ from the control group either in baseline or in pre spinal values and the comparison was insignificant,indicating our pre-medication did not have any effect on heart rate [25], though following spinal anaesthesia, there was a fall in heart rates in both the groups due to sympatholysis and the potentiation of parasympathetic nervous activity [26].

The complications noticed in our study were hypotension, bradycardia, nausea and vomiting but no significant statistical differences was there.

Conclusion

In view of the limitations of adding narcotics to spinal bupivacaine for prolonging the duration of analgesia, we conclude that pre medication with 150 µg oral clonidine can be instituted into bupivacaine spinal analgesia to prolong the duration of both sensory and motor blockage in routine practice without the fear of added complications. It is safe, do not prevent increase in serum catecholamine in response to modulation of efferent sympathetic nerve traffic [25].

Limitation of our study is that to conclude the evidence, more observations have to be done on a larger population because the type of surgery might have influence on recorded lowest blood pressures, heart rate values and also on requirement of rescue analgesics.Changes in volume of distribution, gastric emptying, metabolism etc. may cause varying actions with different plasma levels of clonidine, in patients.

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