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Intrathecal Hyperbaric Bupivacaine with Two Different Doses of Clonidine in Lower Limb Orthopaedic Surgery: A Comparative Study

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ABSTRACT

Introduction: *Spinal anaesthesia has long been known to be of benefit to patients undergoing major orthopaedic procedure. Numerous studies have investigated the effects of intrathecal clonidine co-administered with local anesthetics; very few studies have focused on small doses and a real dose-response in orthopedic patients. We assessed effectiveness and safety profile of two different combinations.*

Material and Method: *75 patients undergoing lower limb orthopaedic surgery were randomised into 3 groups of 25 each to receive 0.5% hyperbaric bupivacaine (B); clonidine 75 µg (0.5 ml) with 0.5% hyperbaric bupivacaine (BC-75); or clonidine 150 µg (1 ml) with 0.5% hyperbaric bupivacaine (BC-150). The onset and duration of sensory and motor blockade; and duration of post-operative analgesia were the primary outcome. Safety and hemodynamic changes were assessed as secondary outcomes.*

Results: *The onset and time to reach surgical anaesthesia at level L1 were significantly early with combinations (BC-150 < BC-75 < B). Total duration of analgesia and time to 2-segment regression were significantly longer (BC-150 > BC-75 > B). The response was dose dependant. No patients required supplemental analgesia intra-operatively. Onset of motor block was less in BC-75. Duration was significantly higher with combinations (BC-150 > BC-75 > B). The response was again dose dependant. Post-operative analgesia was also significantly longer (BC-150 > BC-75 > B). Minor haemodynamic changes were seen in all three groups. Few complications were reported with BC-150.*

Conclusion: *Small doses of clonidine (≤150 µg) when added to bupivacaine, significantly improves the sensory anaesthesia and post-operative analgesia in dose dependent manner; with relative haemodynamic stability and few adverse effects. The combinations are recommended when patients are scheduled for long orthopaedic procedures.*

Introduction

Spinal anaesthesia is a simple technique. It provides a deep and fast surgical block through the injection of small doses of local anesthetic solution into the subarachnoid space. Spinal anesthesia can be considered adequately safe, and severe complications are reasonably rare.

Clonidine, an imidazoline derivative with α2-adrenergic agonistic activity, is commonly used in intrathecal spinal anaesthesia. The action is

mediated through activation of post synaptic α-2 receptors in substantia gelatinosa of spinal cord. It blocks the conduction in C and Aδ fibers, increases potassium conductance and intensifies conduction block of local anesthetic.[1]

There are evidences in literature of the synergistic effects of clonidine and local anesthetics resulting in marked potentiation of the block induced by the local anesthetic agents. In contrast to opioids, clonidine does not cause pruritus or respiratory depression; however, it can cause dose dependent decrease of arterial blood pressure and heart rate, and sedation [2].

Numerous studies in orthopedic patients have investigated the effects of intrathecal clonidine co-administered with local anesthetics.[3-6] Though, the combination provide clinically significant prolongation of spinal anesthesia and post-operative pain relief, very few studies have focused on small doses and a real dose-response in orthopedic patients.[7-9]

Since the complex orthopaedic procedures often last for longer duration and require adequate post-operative anaesthesia, it is worth to assess onset and duration of sensory and motor blockade along with the hemodynamic stability and complications of different doses intrathecal hyperbaric clonidine in combination with long acting local anesthetic agent, bupivacaine.

Materials and Method

This prospective randomised study was initiated after the Institutional Ethics Committee approval. 75 patients undergoing lower limb orthopaedic surgery were recruited after written informed consent. Patients undergoing elective procedures with ASA-I and II grade, height > 150 cm**,** age 20-60 years, weight 50-90 kg were enrolled. Patients with psychiatric disorders, anti-hypertensive medication, who were unable to communicate, who had H/o hypersensitivity and drug allergy were excluded. Patients with conditions that precluded spinal anaesthesia and patients with chronic pain at puncture site were also excluded.

Enrolled patients were randomised into 3 groups of 25 each using computer generated randomisation scheme. The first group received 1 ml 0.9% normal saline added to 3 ml of 0.5% hyperbaric injection bupivacaine (control)(B). The second group received injection clonidine 75 µg (0.5 ml) and 0.5ml 0.9% normal saline added to 3 ml of 0.5% hyperbaric injection bupivacaine (BC-75) while third group received clonidine Injection 150 µg (1 ml) added to 3 ml 0.5% hyperbaric injection bupivacaine (BC-150).

A mid line lumbar puncture was performed with 25 gauge Quincks needle at L3/4 interspace with patients in sitting position and drug was injected after free flow of clear CSF. Patients were made to lie down on supine position immediately. After intrathecal drug administration, pulse, blood pressure (BP), SpO2, Respiratory rate (RR) and ECG were recorded at every 1 minute interval for initial 5 minutes; then every 5 minutes for another 25 minutes; then every 15 minutes till the procedure is completed. Blood pressure was measured using an automated oscillometer. Arterial oxygen saturation was registered continuously by pulse oximetry.

The level and duration of sensory anaesthesia, defined as the loss of sharp sensation by using a pinprick test (20 G hypodermic needle), were recorded bilaterally upto the mid-clavicular level. Time taken for sensory anaesthesia to reach L1 level was recorded every 15 seconds, then at every 1 minute for 15 minutes. Peak sensory level and time to achieve peak sensory level were recorded. Time to two segment regressions was recorded. Onset of motor block (time taken for complete motor blockade) was noted every 1 minute. Modified Bromage score was used for assessment of motor block. Duration (time to return of Bromage score to zero) was recorded.

Duration of pain relief i.e. time for first request for rescue analgesic was recorded. Visual analogue scale (VAS) was used for assessment of post-operative pain relief at 30, 60, 90, 120, 150, 180, 240, 360 and 480 minutes. At VAS score of 4 to 5, rescue analgesics were given in the form of

injection tramadol hydrochloride 100 mg I.V. + injection diclofenac sodium 75 mg IM. Sedation scores were recorded using four point scale where no sedation (score 0); drowsiness (score 1); asleep but easily arousable (score 2); and unarousable with loss of verbal contact (score 3). Any intra-operative and postoperative complications were recorded and treated accordingly. All patients were observed in the post anaesthesia care unit for next 24 hours.

Outcome

The primary outcomes were the onset and duration of sensory and motor blockade AND postoperative analgesia (time to first analgesic request). Secondary outcomes were hemodynamic changes and safety outcome.

Ethical Consideration

All the study documents were approved by the Institutional Ethics Committee. The study was conducted as per ethical principles of the Declaration of Helsinki, Good Clinical Practices guidelines, and Indian regulatory and ethical guidelines. Informed consent was obtained from the subjects. No change in the conduct of the study or planned analyses was instituted after the start of the study.

Statistical analysis

The sample size of 25 patients per group was based on the assumption that an increase of 60 minutes in the duration of spinal anaesthesia would be detected (α=0.05; β= 0.8), which was considered clinically meaningful.

The data are expressed as mean and standard deviation. Paired and unpaired *Student t-test* was used for each parameter for within and between group comparisons. Differences in hemodynamics between groups are analyzed using *Analysis of Variance (ANOVA)* with Dunnet test for *post-hoc* analysis. Nominal data were analyzed using the *Chi Square* test. $P < 0.05$ was considered to be statistically significant.

Results

All 75 patients completed the study as per the protocol. Demographic profile such as age, gender, weight and height and duration of surgery were comparable in all three-study groups. Majority of patients were male in all the three groups. (Table 1) The good to excellent surgical anaesthesia was recorded in 68%, 100% and 100% among B, BC-75 and BC-150 respectively. (Table 2)

Sensory Block

The onset and time to reach surgical anaesthesia at level L1 were significantly early in BC-150 and BC-75 as compared to B (BC-150 < BC-75 < B). Total duration of analgesia and time to 2-segment regression were significantly delayed in BC-150 and BC-75 (BC-150 > BC-75 > B). The response was dose dependant. The maximum sensory block of T4 was recorded in BC-150, T6 in BC-75 and T8 in B. (Table 2)

Motor Block

The onset (time to achieve complete motor block) was significantly less in group BC-75 as compared to B. Among combinations, the results were comparable. Bromage grade III motor block was achieved in all patients (100%) in BC-75 and BC-150 and 68% patients in B. Duration (Time to return of Bromage score to 0) was significantly higher in BC-75 and BC-150 as compared to B (BC-150 > BC-75 > B). The response was dose dependant. (Table 2)

Post Operative Analgesia

None of the patients required supplemental analgesia intraoperatively. Time to first analgesic requirement was significantly longer in BC-150 and BC-75 as compared to B (BC-150 > BC-75 > B). (Table 2) VAS score was significantly lesser in BC-75 and BC-150 as compared to B at all the time points (BC-150 < BC-75 < B) (Figure 1). Moreover, only one dose of rescue analgesic was required in BC-150 while 1-2 doses required in

BC-75 and 2-3 doses required in B in first 24 hours.

Hemodynamic changes

The significant difference in the mean arterial pressure (MAP), systolic BP (SBP) and diastolic BP (DBP), RR and pulse were observed in BC-75 and BC-150 as compared to B at majority of time points. (Figure 2-6)

Intra and post-operative complications

Maximum sedation was seen with BC-150 followed by BC-75 (Table 2). Intra-operatively, hypotension and shivering were reported with B. Post operatively, vomiting, urinal retention, nausea and shivering were reported in < 10 % with B. Hypotension and dryness of mouth were reported in BC-150. No complications were reported in BC-75 (Table 3).

Table 1: Demographic characteristics of the patients

Complications	Control group (n=25)	BC-75 group (n=25)	BC-150 group (n=25)	P value
Weight (Kg)	55.6±7.9	58.2±6.4	55.1±5.2	**0.191**
Height (cm)	159.58±6.1	162.08±6.17	156.6±5.2	**0.106**
Male n (%)	16 (64)	21 (84)	15 (60)	**0.143**
Female n(%)	9 (36)	4 (16)	10 (40)	

Table 2: Characteristics of spinal anaesthesia

Parameters	Control group (B) (n=25)	BC-75 group (n=25)	BC-150 group (n=25)	P value
Quality of Surgical anaesthesia n (%)				
Excellent	5 (20%)	12 (48%)	18 (72 %)	0.001
Good	12 (48%)	13 (52%)	7 (28%)	
Average	8 (32 %)	0 (0%)	0 (0)	
Sensory Block				
Onset (minutes)	6.2 ± 0.6	4.9 ±1.0**	4.2 ±1.0**	**0.001**
Time to reach sensory block at L1 (min)	132.4 ±28.6	59.4 ±16.7 **	55.0 ±12.1**	**0.001**
Total duration of sensory block (min)	265 ± 14.3	416 ± 44.9**	666.0 ± 40.8** $	**0.001**
Peak sensory level achieved n (%)				
T4	0 (0)	0 (0)	2 (8)	0.01
T6	0 (0)	6 (24)	10 (40)	
T8	09 (36%)	11 (44)	13 (52)	
T10	16 (64%)	8 (32)	0 (0)	
2 segment regression (min)	62.6 ± 10.0	103.0 ± 15.1 **	174.0 ± 24.9** $	**0.001**
Motor Block				
Onset (Time to achieve motor block) (min)	11.9 ± 1.3	10.8 ± 1.3**	11.2 ±1.2	0.001
Duration (Return of Bromage score 0) (min)	3.4 ±.5	5.5 ± 1**	6.6 ± 1.1** $	**0.001**
Bromage Grade n (%)				
Grade I	0 (0)	0 (0)	0 (0)	**0.001**
Grade II	8 (32)	0 (0)	0 (0)	
Grade III	17 (68)	25 (100)	25 (100)	
Analgesia				
Time for first rescue analgesia (min)	275.6 ±11.2	444.8 ±44.6**	684 ± 36.4** $	**0.001**
Sedation Score				
Grade 0	25 (100%)	0 (0%)	0 (0%)	
Grade I	0 (0%)	12 (48%)	0 (0%)	
Grade II	0 (0%)	13 (52%)	25 (100%)	
Grade III	0 (0%)	0 (0%)	0 (0%)	

Note: ** p value is significant (P < 0.001) when compared to control group. $ p value is significant (P < 0.001) when compared to BC-75 group.

Table 3: Intra and post-operative adverse event

Complications	Control group n (%)	BC-75 group n (%)	BC-150 group n (%)
Intra-operative			
Hypotension	4 (16%)	0 (0)	0 (0)
Shivering	4 (16%)	0 (0)	0 (0)
Post-operative			
Vomiting	1 (4.0)	0 (0)	0 (0)
Urine retention	2 (8.0)	0 (0)	0 (0)
Nausea	2 (8.0)	0 (0)	0 (0)
Shivering	1 (4.0)	0 (0)	0 (0)
Hypotension	0 (0)	0 (0)	5 (20)
Dryness of mouth	0 (0)	0 (0)	3 (12)

Figure 1: Post-operative Visual Analogue Scale

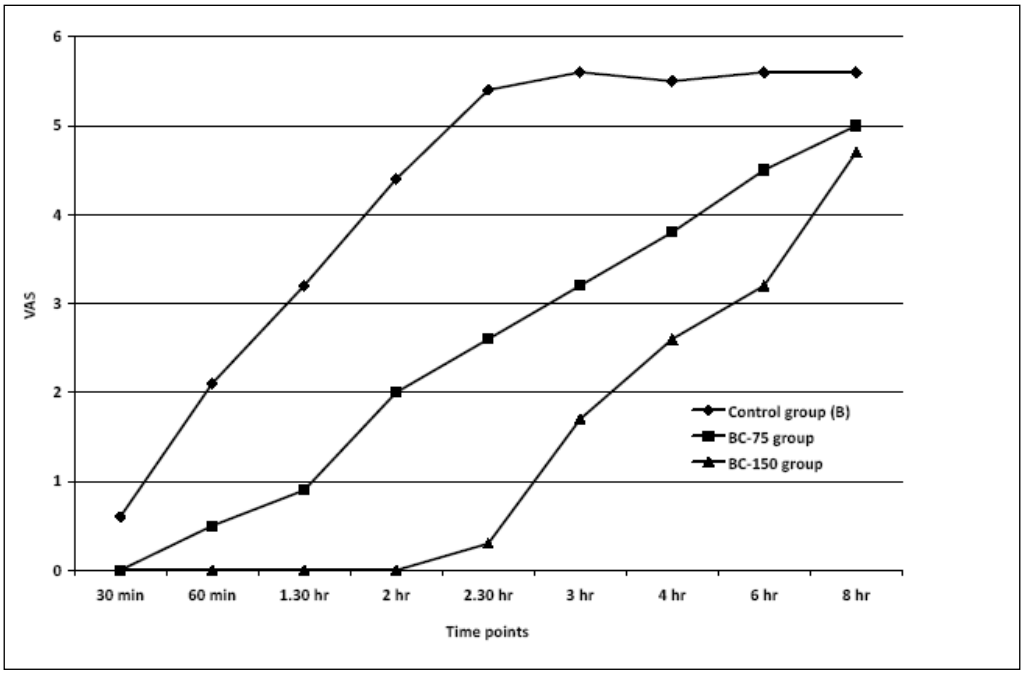


Figure 2: Change in mean arterial pressure

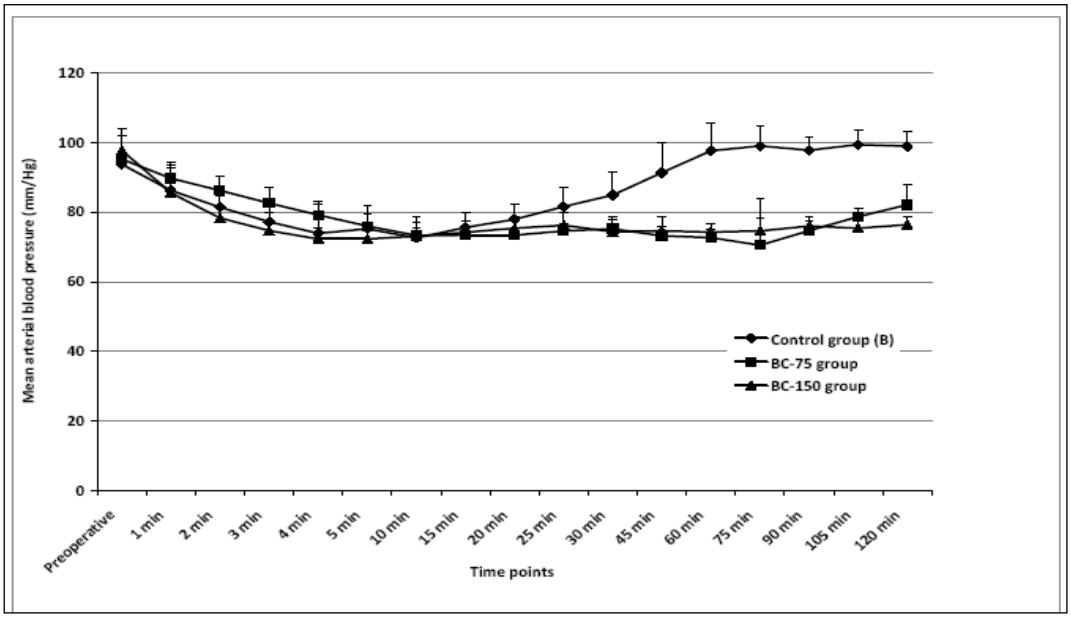


Figure 3: Change in mean pulse

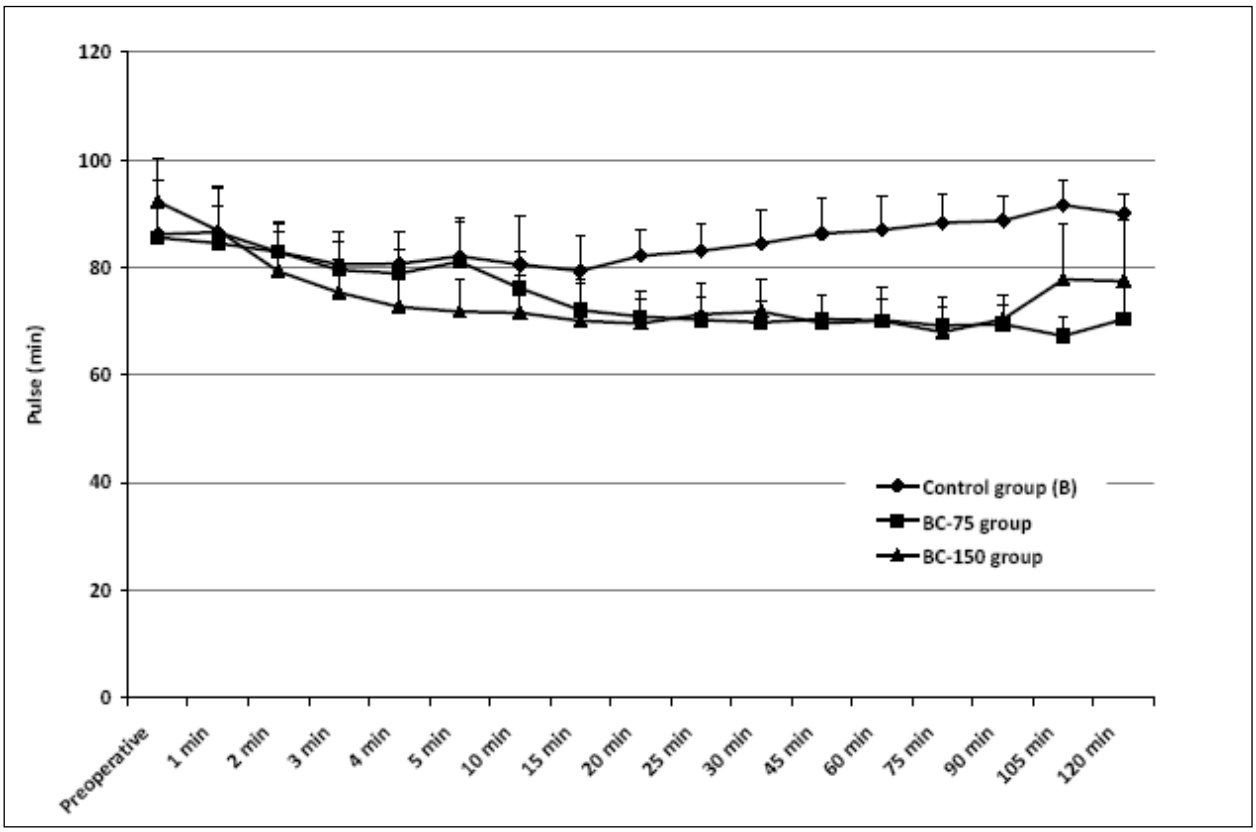


Figure 4: Change in respiration rate

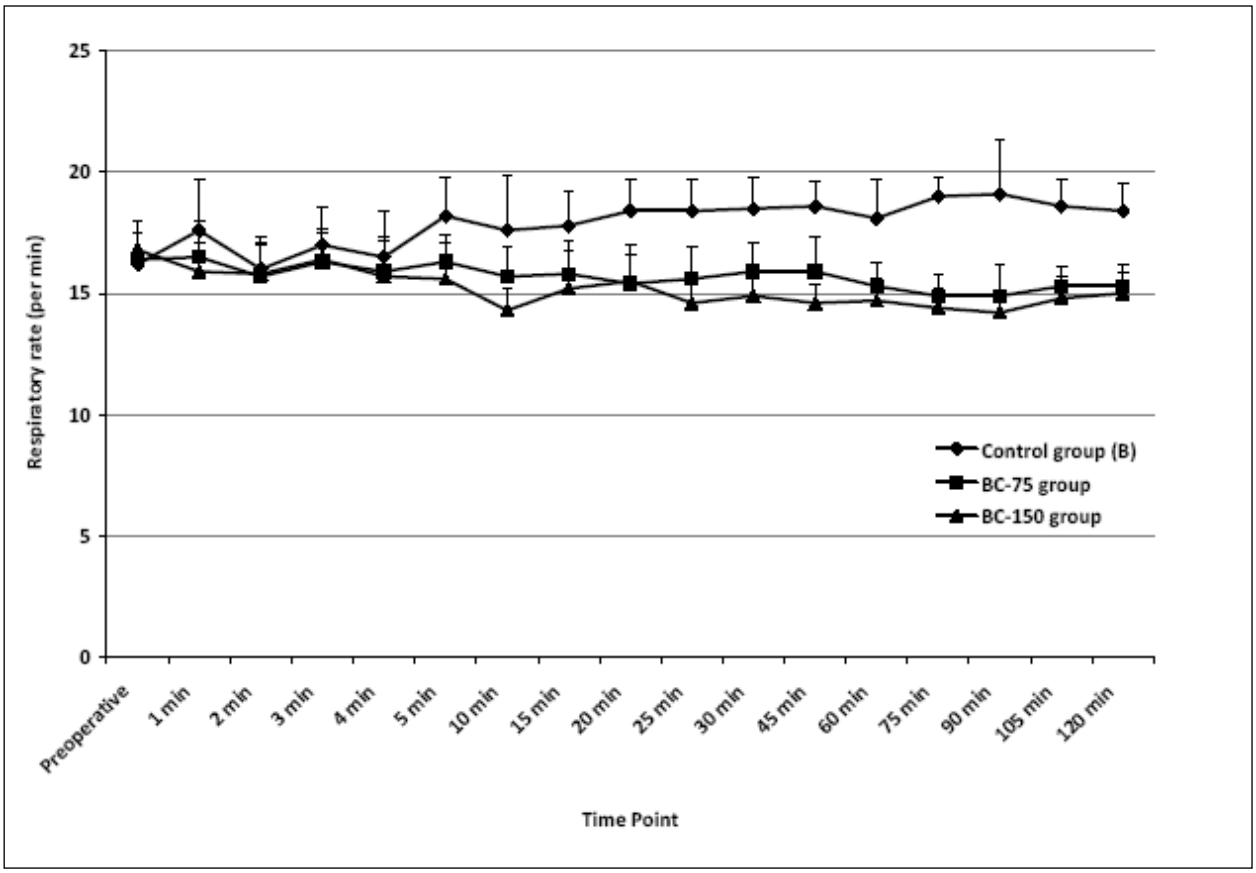


Figure 5: Change in systolic blood pressure

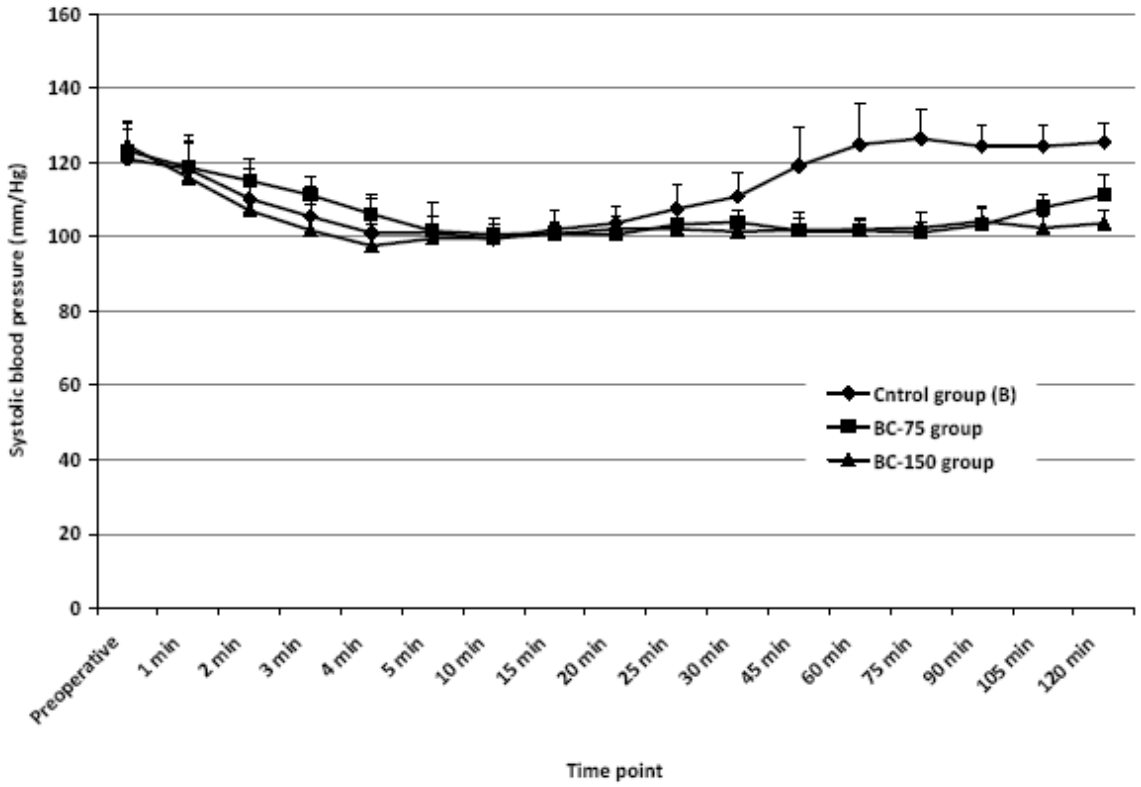
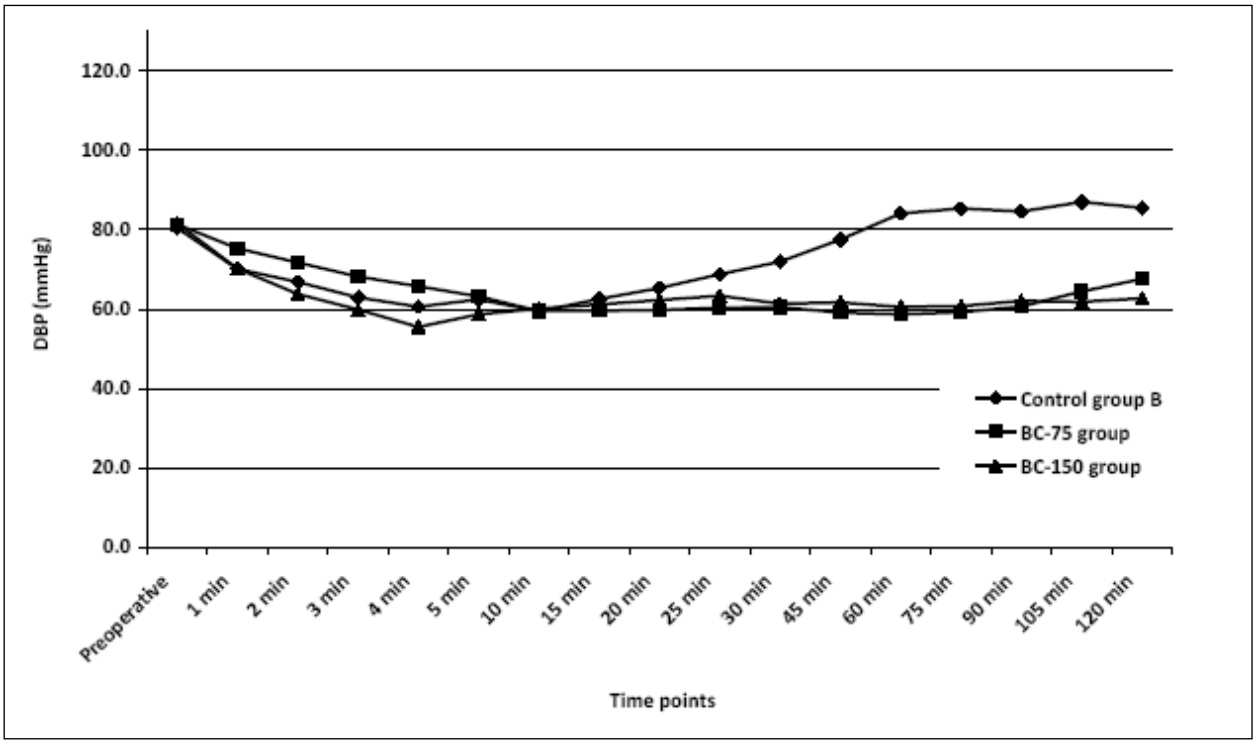


Figure 6: Change in diastolic blood pressure



Discussion

Complex orthopedic procedures demand longer motor and sensory blockade; and the post-operative pain relief. Because of these reasons, several additives (epinephrine, opioids, clonidine and neostigmine) are often used with intrathecal injection of long acting local anesthetic agents. This helps in improving the quality, duration of spinal block and postoperative analgesia especially in the surgeries which last for > 2-2.5 hours.

Our results showed that addition of clonidine to bupivacaine provides an effective, fast onset and long duration of spinal anesthesia. Onset and time for sensory anesthesia to reach at L1 was almost 2 - 2.5 times lesser with the combination (BC-150<BC-75<B) Dose dependant effect was seen in total duration of anaesthesia and 2-segment regression time (BC-150>BC-75>B).

Our findings are in the line with published literature which demonstrated that addition of intrathecal clonidine to bupivacaine, even in very small doses, significantly improves the onset and prolongs spinal anaesthesia.[1,10,11] These effects could be because of potentiation of sensory block by presynaptic (inhibition of transmitter release) [12] and postsynaptic (enhancing hyperpolar-ization) [13] effects of clonidine. The role of vasoconstriction in prolonging sensory block is minor.[14]

We also found highest cephalad extent of anesthesia with BC-150 (T4) followed by BC-75 (T6) and then B (T8). This could be one reason of more intense anesthetic blockade and fewer requirements of supplemental analgesics with BC as compared to B. This was in accordance with Dobrydnjov et al, who had reported a higher block of 2 to 4 segments with BC-30 μg as compared to B. However, Grandhe [15] found maximum sensory level of T_5 with BC which could be because of smaller dose of local anaesthetic used by them.

Quality and duration of motor block again confirmed that the combination is doing better. The finding is in the line with published literature[1][15] [4][18] [10]. This is significant finding, as intrathecal clonidine alone, even in doses of up to 450 μg, does not induce motor block [17] and could be because of action of clonidine on α_2-adrenoceptor of spinal cord and also potentiating the intensity and motor blockade action of local anesthetic. Prolongation of motor block will helps in performing orthopedic surgeries in better way.

Perhaps the greatest benefit of spinal anaesthesia is its role in providing adequate pain control, which is the key to the post-operative recovery of patients undergoing orthopaedic surgery. In our study, total duration of analgesia was significantly higher in BC as compared to B. The action was dose dependant (BC-150>BC-75>B). VAS scores were significantly lesser with combination (BC-150<BC-75< B). Our study results were similar to Baker [19], Strebel et al [20], Grandhe [15], Sethi et al [1], Filos KS (1994) [21], Mercier F J (1998) [22] and Chiari et al (1999) [23].

We observed reduction in arterial BP with combination. No active intervention was given as the B.P. readings remained above the critical value of 65 mmHg at majority of times. These findings agree with other investigators demonstrating a decrease in arterial BP even with lower doses (15-150 μg) of clonidine and relative hemodynamic stability with administration of larger doses [5, 6, 8, 20, 24]. Some authors argued that the hypotensive effects of clonidine at lower dose can be because of low dose of Bupivacaine used in those studies. They hypothesized that in case of larger doses of local anaesthetics, the hypotensive effect of clonidine is masked by dense axonal blocked produced by local anaesthetic [25].

Counteraction of sympatholysis and hypotensive action of α_2-adrenergic agonists on brainstem nuclei and on sympathetic pre-ganglionic neurons in the spinal cord by direct vasoconstriction action of the α_2-adrenergic agonists on the peripheral vasculature is also proposed.[26]

Further, all patients in our study were preloaded with crystalloid 500ml (Ringers lactate) and wedge was provided immediately after spinal

block. This could be the reason why decreased in heart rate and blood pressure was not significant.

As expected [1][19], sedation because of action of α-2-adrenergic agonists on the locus caeruleus, was higher with combination; however there was no respiratory depression or fall in SpO2. Unlike in control group, shivering was not observed with combination because of inhibition of central thermoregulatory centres by Clonidine. Dryness of mouth was reported with combination and was because of inhibition of saliva secretion by Clonidine.

Limitation of our study design was setting the lower limit of the tested dose range at 75 μg of clonidine. Therefore, we cannot exclude the possibility of effectiveness and dose dependent effect of smaller clonidine doses. The study was underpowered to detect potentially significant differences in secondary outcome variables, the data generated gives us fair idea about the safety and haemodynamic stability of the combination.

To conclude, small doses of clonidine (≤150 μg) when added to bupivacaine, significantly improves the sensory anaesthesia and post-operative analgesia in dose dependent manner; with relative haemodynamic stability and few adverse effects. The combinations are recommended when patients are scheduled for long orthopaedic procedures.

Conflict of interest

No author has any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations.

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