Original article:

COMPARATIVE STUDY OF DIFFERENT DOSES OF CLONIDINE (15µg, 30µg, 45µg) ADJUVANT TO BUPIVACAINE INTRATHECALLY IN LOWER LIMB SURGERIES.

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ABSTRACT:

BACKGROUND: Clonidine is added to intrathecal bupivacaine to improve intraoperative analgesia and to increase the duartion of sensory and motor block. **AIMS:** The aim of the study to evaluate and compare the effect of additon of three different doses of clonidine (15 µg, 30 µg and 45 µg) to 12.5mg hyperbaric bupivacaine in patients undergoing lower limb surgeries under spinal anesthesia. **STUDY DESIGN:** Randomized, prospective study was conducted at tertiary academic hospital. **MATERIALS AND METHOD:** 100 patients enrolled in the study were randomly divided into four groups of 25 each. Group-I received bupivacaine, whereas group-II, III and IV received 15µg, 30µg and 45µg clonidine respectively as an adjuvant to 12.5mg bupivacaine. The volume of solution was kept constant 3ml by adding normal saline whenever needed. **RESULT**: Highest level of sensory block, time to achieve this level and highest Bromage scale recorded were comparable among the groups. The regression of sensory block to S2 dermatome and mean duration of motor block were greatest in group IV followed by group III, II and I. There was significant fall in mean arterial pressure (MAP) in group IV as compared to other groups. Significant prolongation of sensory and motor blockade and duration of postoperative analgesia with group-IV as compared to other groups. **CONCLUSION**: Thus, addition of 30µg clonidine gives excellent analgesia with less adrehemodynamic instability and sedation.

KEYWORDS: Adjuvants to spinal anesthesia, intrathecal clonidine, α2 adrenoreceptors.

INTRODUCTION

Spinal anaesthesia was initially performed by Corning in 1885 and first used deliberately by Bier in 1898. Glucose containing solution for spinal anaesthesia was introduced by Barker in 1907. Since then, hyperbaric solution has been used for spinal anaesthesia. Spinal anaesthesia and post operative analgesia can be prolonged by using adjuvant to local anaesthetic agents like adrenaline, ketamine, midazolam, neostigmine and opioids.

Clonidine was first tried intrathecally by Gordh in 1983.[6] Clinical studies have suggested that intrathecal clonidine as an adjuvant to bupivacaine prolongs sensory aswell as motor block of spinal anesthesia. It decreases local anesthetic requirements and provides prolonged postoperative analgesia.Other effects of clonidine are antiemesis, reduced post- spinal shivering, anxiolysis, sedation, bradycardia and hypotension.

In this study, we have compared three different doses of clonidine as an adjuvant to intrathecal bupivacaine heavy for spinal anesthesia in patients undergoing lower limb surgeries aiming to

find out the lowest possible effective dose among them.

AIMS OF THE STUDY

The present study was designed to study intrathecal 0.5% heavy bupivacaine2.5ml (12.5mg) as a control and with different doses of preservative free clonidine 15, 30and 45micro grams (25 patients in each group) in lower limb surgeries.

- To compare the onset of sensory and motor block.
- To compare the duration of sensory and motor block.
- To assess the duration of post op analgesia.
- To compare perioperative hemodynamic changes.
- To compare the perioperative side-effects and complications.

MATERIAL AND METHODS

Study was conducted on 100 patients of age group between 20-60 years, ASA grade 1 or 2 and posted for lower limb surgeries in the or
department of V. S. Hospital.
All patients were randomly distributed into four groups of 25 patients each.

Group B: 0.5% heavy bupivacaine 2.5ml (12.5mg) + inj. NS 0.9% 0.5 ml
Group BC15: 0.5% heavy bupivacaine 2.5ml (12.5mg) + clonidine 0.1 ml (15mcg) + inj. NS 0.9% 0.4 ml
Group BC30: 0.5% heavy bupivacaine 2.5ml (12.5mg) + clonidine 0.2 ml (30mcg) + inj. NS 0.9% 0.3 ml
Group BC45: 0.5% heavy bupivacaine 2.5ml (12.5mg) + clonidine 0.3 ml (45mcg) + inj. NS 0.9% 0.2 ml

Detailed preoperative history and physical examination was done on theprevious day of surgery.
Patients having history of allergy to any drug, pregnant patients, patientshaving psychiatric illness or having any contraindication to spinal anaesthesia were excluded from the study.
Patients using any drug that modifies pain perception were excluded from the study.
Procedure explained to the patient and patient was informed to communicate about the perception of any discomfort or pain.
Explained about VAS score.
Written informed consent was taken from the patients and his/her relatives.
All routine pre-operative investigations were done.
Patients were NBM for 6 hours prior to surgery.
Intravenous line taken by 18 gauge intravenous canula and preloaded with10ml/ kg of Ringer's lactate solution before procedure.
Pulse oximeter, non-invasive blood pressure monitoring and ECG were attached and base line reading was taken.
No narcotic or sedative premedication was given to any patient.

Technique:

Under all strict aseptic and antiseptic precaution, with patient in sittingposition, lumbar puncture was performed at L2-L3 inter-vertebral space with 23G Quincke needle and the selected drug was given slowly. After completion of procedure, patient was immediately turned to supine position and time of injection of drug was noted.
Pulse, BP and SpO_2 were recorded at 2, 4, 6, 10, 15, 20, 30, 45 and 60 minutes after giving spinal anaesthesia and then every 30 minutes till 240 minutes and then frequently upto 720 minutes.

Evaluation:

Onset of sensory blockade was noted as loss of pinprick sensation fromsubarachnoid injection.
Time to achieve sensory block at T10 dermatome and duration for regression of sensory block to S2 dermatome was noted.
Motor blockade was assessed by modified Bromage scale as used by Breen

Table 1: Modified Bromage score

Score	**Criteria**
1	Complete block (unable to move feet or knee)
2	Almost complete block (able to move feet only)
3	Partial block (just able to move knee)
4	Detectable weakness of hip flexion while supine (full flexion of knees)
5	No detectable weakness of hip flexion while supine
6	Able to perform partial knee bend

Following observations were made:

Onset of motor blockade, time to achieve full motor blockade and time to regression of motor blockade to score 6 was noted.
Patients were assessed for degree of sedation & scoring was done as follows.

Table 3: Campbell Sedation Score (Criteria)

Score	**Criteria**
1	Wide awake
2	Awake and comfortable
3	Drowsy and difficult to arouse
4	Not arousable

After establishment of adequate level of block, surgery was started and time of beginning and duration of surgery was noted.

·No sedative or analgesic medication was used during perioperative period.
·Patients were observed for any intraoperative complications like bradycardia,hypotension, sedation, shivering, nausea, vomiting, dryness of mouth andrespiratory depression and treated accordingly.
·Hypotension was defined as systolic blood pressure >20% decrease in baselinevalue and treated with an intravenous bolus of 6 mg of mephentermine andintravenous fluid.
·Bradycardia was defined as heart rate < 60/mins and treated with 0.6 mg of intravenous atropine.
·Patients were monitored for 12 hours after giving spinal anaesthesia.
·Patients were inquired frequently for the degree of pain they felt with the helpof visual analogue scale (VAS) and the time for the demand for analgesia wasnoted.
VAS involves use of a 10cm line on a piece of white paper and it representspatient's opinion of degree of pain. It was explained to all patientspreoperatively that one end of the line i.e. 'O' marks "no pain" at all, whileother end i.e. '10' represents "worst pain" patient ever felt. Patient was askedto rate the degree of Pain by making a mark on the scale. Thus the pain score was obtained by measuring the distance from the 'O' end to the indicatedmark.

Visual Analog Scale

10	9	8	7	6	5	4	3	2	1	0
Agonizing		Horrible		Uncomfortable			Annoying		None	

Time to first dose of post operative rescue analgesia and total duration ofanalgesia was noted.
·Inj Diclofenac 75mg i.v. was given when patients VAS score reached ≥ 4.

STATISTICAL ANALYSIS

Statistical analysis was done. Data was expressed as mean, mean + SD andpercentage.
Data were compared using Z test. The level of significance used was $p<0.05$.

OBSERVATIONS AND RESULTS

Table 1: Demographic characteristics (Mean + SD)

	Group B	Group BC15	Group BC30	Group BC45
No of patients	25	25	25	25
Age(years)	35+/-8	34+/-9	35+/-8	35+/-12
Male/female	15/10	15/10	13/12	16/9
Asa grade 1	13	14	15	14
2	12	11	10	11

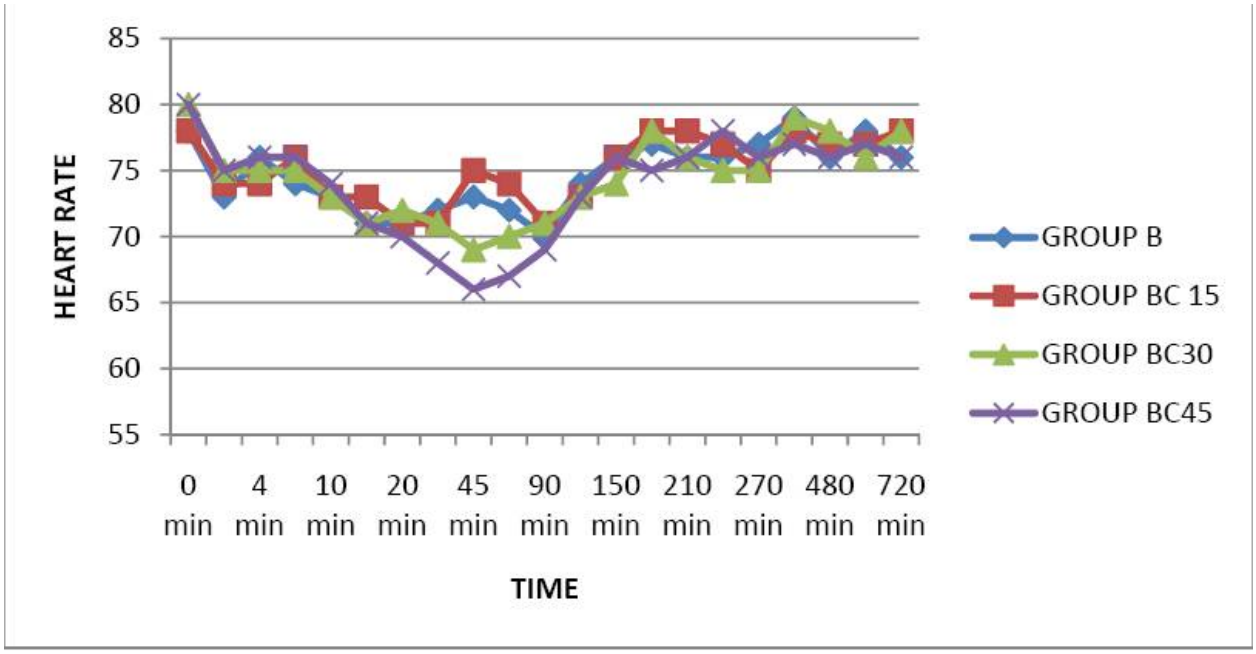
All data in different groups are comparable as $p>0.05$

Table 2: Characteristics of sensory and motor blockade (Mean±SD)

	Group B	Group BC15	Group BC30	Group BC45
Onset of sensory block (Mean ± SD) (min)	1.36±0.14	1.4±0.09	1.36±0.09	1.35±0.12
Time to achieve level of sensory block at T10 dermatome (Mean ± SD) (min)	5.42±0.34	5.44±0.44	5.38±0.39	5.42±0.4
Duration of regression of sensory block to S2 dermatome (Mean ± SD) (min)	120±5.77	133.24±8.18	147.48±9.78	170.3±7.10
Onset of motor block (Mean ± SD) (min)	1.8±0.16	1.80±0.1	1.63 ± 0.08	1.78 ± 0.016
Time to achieve motor block of score 1 (min)	3.7±0.29	3.54±0.45	3.58±0.31	3.6±0.35
Duration of regression of motor block to score 1(Mean ± SD) (min)	136±6.45	153±9.01	173.8±11.48	248.4±30.91

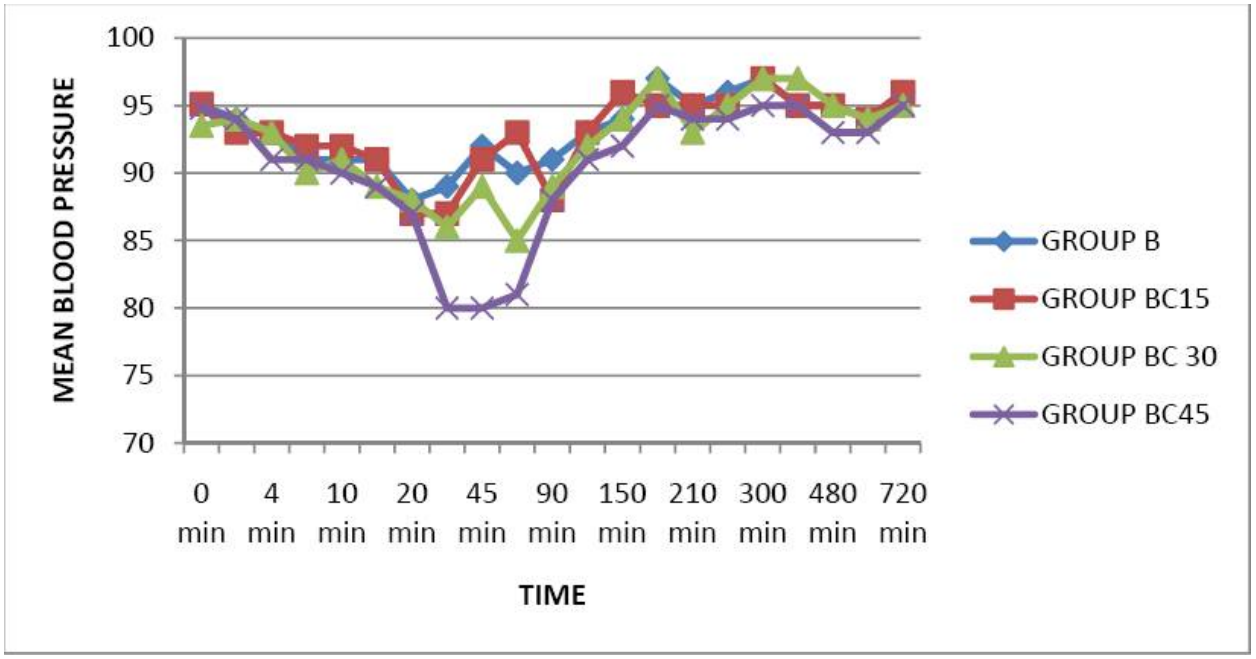
Table 6 compares onset, peak and duration of sensory and motor block. We could notappreciateany dose dependant variations in onset of sensory, peak sensory and onset ofmotor block($p>0.05$).
There is a statistically significant difference in regression ofsensory as well as motor blockade.
($p<0.05$)

Chart 1: Comparison of peri-operative heart rate versus time



There was statistically significant decrease in heart rate during 30-
60 minutes afterintrathecalinjection in group BC45 as compared to group BC30, group BC15 and groupB($p<0.05$).
But patients in Group BC30 also had bradycardia more than Group BC15 andGroup B.
After 60 minutes heart rate was comparable in all four groups ($p>0.05$).

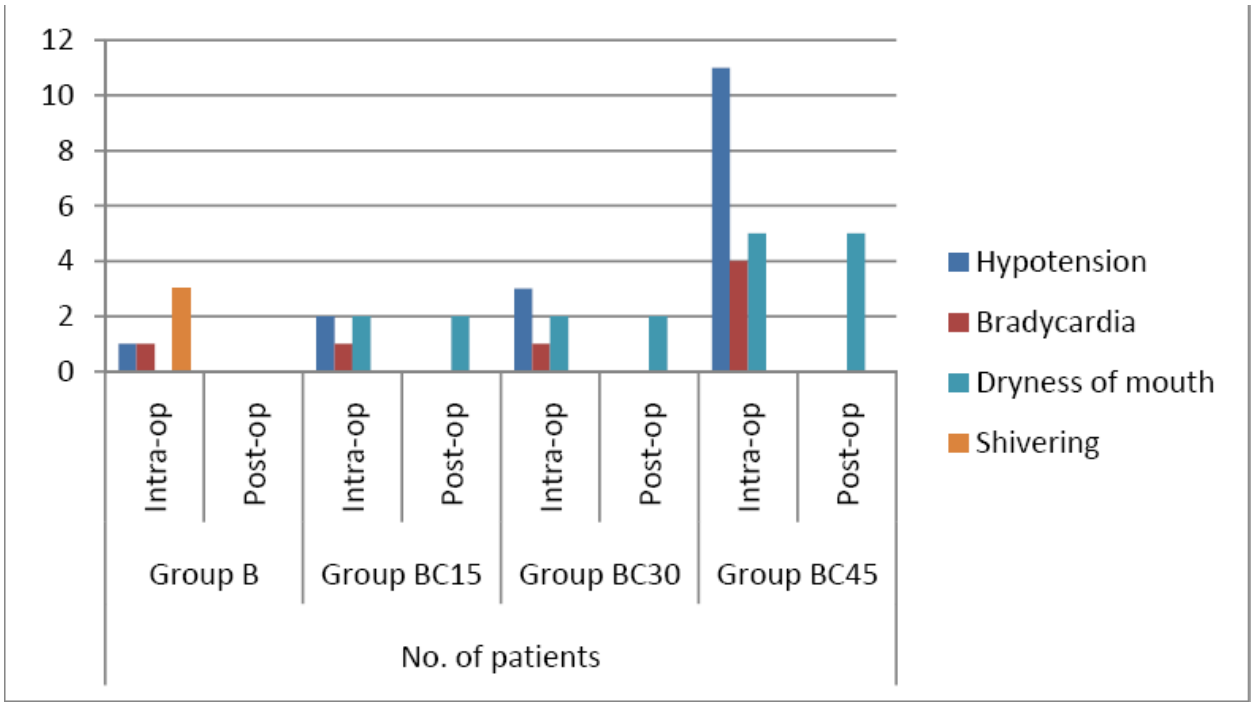
Chart 4: Comparison of peri-operative mean blood pressure versus Time



Mean blood pressure was decreased after 30-60 minutes in Group B, GroupBC15, Group BC30

and Group BC45 compared to Group B. ($p<0.05$) But patientsin Group BC30 also had fall in MB more than Group BC15 and Group B. Afterthat MBP was comparable in all four groups.

Chart 5: Comparison of peri-operative complications



Hypotension, bradycardia and dryness of mouth were seen more with Group BC45compared to other groups. Shivering was seen with Group B.

Table 3: Sedation score

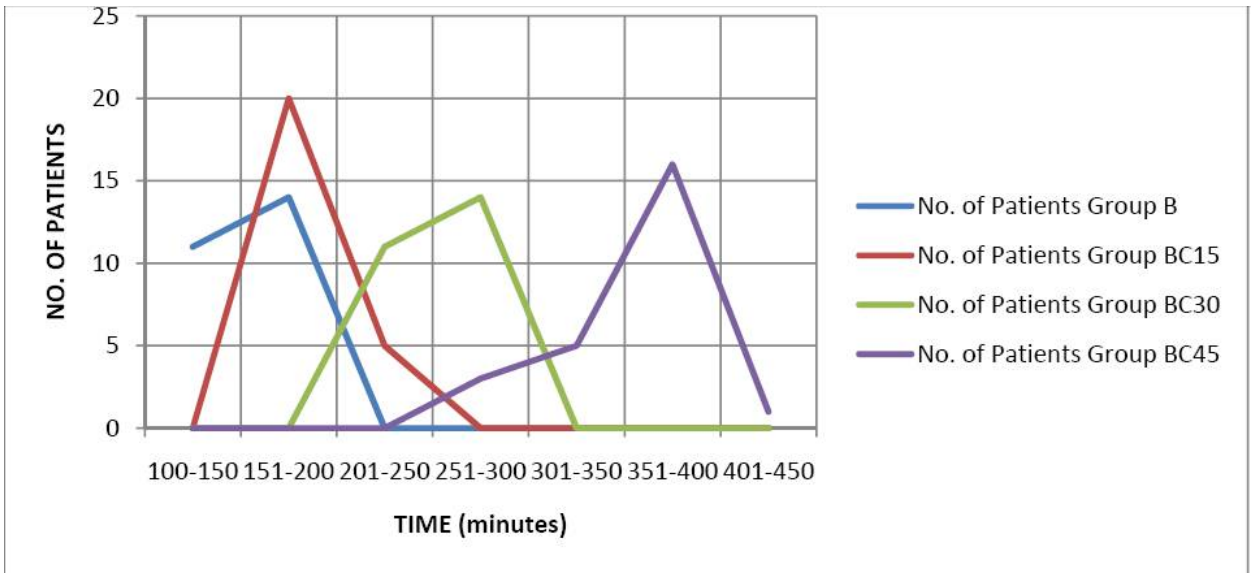
No. of patients				
Sedation score	GROUP B	GROUP BC15	GROUP BC30	GROUP BC45
1	0	15(60%)	10(40%)	5(20%)
2	0	10(40%)	15(60%)	20(80%)
3	0	0	0	0
4	0	0	0	0

Sedation was seen more in Group BC45 compared to other groups. ($p<0.05$)

Table 4: Total duration of analgesia in minute

Time in minutes	No. of Patients			
	Group B	Group BC15	Group BC30	Group BC45
100-150	11	0	0	0
151-200	14	20	0	0
201-250	0	5	11	0
251-300	0	0	14	3
301-350	0	0	0	5
351-400	0	0	0	16
401-450	0	0	0	1
Minimum time	145	165	210	290
Maximum time	165	210	300	420
Mean time ± SD	154±7.07	188.4±10.97	259.6±23.31	363.2±38.05

Duration of analgesia was prolonged as intrathecal dose of Clonidine was increased.($p<0.05$)



Duration of analgesia

DISCUSSION

Recently instead of only local anaesthetic,adjuvant drugs are added with the objective of prolonging the effect of subar achnoidblock with faster onset and improve the quality of analgesia in post operative period.In recent years clonidine, which is a selective partial agonist for alpha 2 adrenoreceptors, have been used to prolong the duration of spinal anaesthesia. Clonidineis known to increase both sensory and motor block of local anaesthetic..

Gordh et al[6] proved safety of parenteral preparation of clonidine for intrathecaluse in humans.

The primary objective of our study was to find out the effect of different doses ofintrathecal clonidine with hyperbaric bupivacaine for characteristics of sensory block,motor block, post-op analgesia, side effects and complications.
We selected 100 patients of ASA grade 1 & 2 and allocated in four groups.

- **Group B:** 0.5% heavy bupivacaine 2.5ml (12.5mg) + inj. NS 0.9% 0.5 ml
- **Group BC15:** 0.5% heavy bupivacaine 2.5ml (12.5mg) + clonidine 0.1 ml (15 mcg) + inj. NS 0.9% 0.4 ml
- **Group BC30:** 0.5% heavy bupivacaine 2.5ml (12.5mg) + clonidine 0.2 ml (30 mcg) + inj. NS 0.9% 0.3 ml
- **Group BC45:** 0.5% heavy bupivacaine 2.5ml (12.5mg) + clonidine 0.3 ml (45 mcg) + inj. NS 0.9% 0.2 ml

In our study, 100 patients of ASA grade 1 & 2 were selected and allocated in fourgroups. As shown in Table 4 age, sex and ASA grading of the patients were comparable in all four groups. (p>0.05).

Onset of sensory blockade:

Ghodki PS et al,[5] 2010 studied 30 mcg of clonidine intrathecally andconcluded that it has no effect on the onset of sensory and motor blockade.

Bhavini shah,[2] 2011 studied that with addition of clonidine (15 mcg, 30mcg, 60 mcg) to intrathecal bupivacaine did not affect the onset of sensoryblockade.

Bansal Sangeeta et al,[1] 2014 studied that addition of clonidine (45 mcg) tointrathecal bupivacaine had no effect on onset of sensory blockade.
As per Table 6 in our study there was no statistically significant differencefound regarding onset of sensory blockade, as it was 1.4±0.09 mins in GroupBC15 (p>0.05), 1.36±0.09 in Group BC30 (p>0.05) and 1.35±0.12 in GroupBC45 (p>0.05) as compared to 1.36±0.14 in Group B.

Time to achieve sensory level at T10 dermatome:

Thakur et al[15] studied that clonidine from 15 to 30 mcg did not result in anysignificant difference in peak dermatome level.

Van Tuijl et al[16] used clonidine (15 mcg, 30 mcg) with lower dose ofbupivacaine and find the same result as previous.

Bansal Sangeeta et al,[1] 2014 studied that addition of clonidine (45 mcg) tointrathecal bupivacaine had similar effects regarding time for peak sensorylevel.

Grandhe et al[7] used large dose of clonidine (1 mcg/kg) but showed similartrend.

In our study as per Table 6 we found no statistically significant differencein time to achieve sensory block at T10 dermatome, as it was 5.44±0.44 min inGroup BC15(p>0.05), 5.38±0.39 min in Group BC30 (p>0.05) and 5.42±0.4min in Group BC45 (p>0.05) as compared to 5.42±0.34 in Group B.

Duration of regression of sensory blockade to S2 dermatome:

B.S. Sethi et al[13] (2007) noted time for regression of sensory blockade bytwo segments was 150-240 min in clonidine (1 mcg/kg) group, which wassignificantly longer than duration of 90-130 min in control group.

Thakur etal[16] observed that mean time to two segment regression,regression to L3 dermatome, and time to first analgesic request wassignificantly more in clonidine groups (15 mcg, 30 mcg) than in control group,

Bansal Sangeeta et al,[1] 2014 observed that addition of clonidine (45 mcg)to intrathecal bupivacaine significantly increased duration of analgesia inclonidine group.

As shown in Table 6 in our study mean duration of sensory anaesthesia.

- **Onset of motor blockade:**

Ghodki PS et al[5] in 2010 studied 30mcg of clonidine intrathecally andconcluded that it has no effect on the onset of sensory and motor blockade.

Bhavini shah et al,[2] 2011 studied that with addition of clonidine (15 mcg,30 mcg, 60 mcg) to intrathecal bupivacaine did not affect the onset of motorblockade.

Bansal Sangeeta et al,[1] 2014 studied that addition of clonidine (45 mcg) tointrathecal bupivacaine had no effect on onset of motor blockade.

As per Table 6 in our study there was no statistically significant differenceregarding to time of onset of motor blockade as it was 1.80±0.1 in Group BC15(p>0.05), 1.63±0.08 in Group BC30 (p>0.05) and 1.78±0.16 in Group BC45(p>0.05) as compared to 1.8±0.16 in Group B.

- **Time to achieve motor block of score 1:**

Thakur et al[16] studied that clonidine from 15 to 30 mcg did not result in anysignificant difference for achieving motor block of score 1.

Bansal Sangeeta et al,[1] 2014 studied that addition of clonidine(45 mcg) tointrathecal bupivacaine had no effect to achieve motor blockade of score 1.

As shown in Table 6 in our study we observed that there was no statisticallysignificant Differenceregarding achieving motor block of modified bromagescore 1.

- **Regression of motor blockade:**

B.S. Sethi et al[13] (2007) observed that mean duration of motor block was205 min in clonidine group (1mcg/kg) compared to 161 min in the controlgroup.

Bhavini shah et al,[2] 2011 observed that addition of clonidine (15 mcg,30mcg, 60 mcg) significantyincrease the time o f motor blockade.

Bansal Sangeeta et al,[1] 2014 studied that intrathecal clonidine (45 mcg)increased the time for regression of motor blockade.

H.saxena[8] et al found the same result after adding clonidine intrathecally.

As shown in Table 6 in our study we observed mean duration of motorblockade of modified bromage score 6 of 153±9.01 in Group BC15 ($p<0.05$),173.8±11.48 in Group BC30 ($p<0.05$) and 248.4±30.91 in Grou p BC45($p<0.05$) as compared to 136±6.45 in Group B.

- **Peri-operative hemodynamics**

1. **Heart rate:**

Grandhe et al[7] (clonidine 15 mcg, 30 mcg) and B. S. Sethi et al[13](clonidine 1mcg/kg) observed significantally lower heart rate in clonidinegroup compared to control group($p<0.05$).

As shown in Table 7 there was statistically significant decrease in heart rateduring 30-60 minutes after intrathecal injection in group BC45 as compared togroup BC30, group BC15 and group B($p<0.05$). There was no statistically

2. **Blood pressure:**

Thakur et al,[15] and Grandhe et al[7] observed significantfall in MAP in clonidine group

As shown in Table 8,9,10 after intrathecal injection, in all the patients thereis fall in blood pressure upto 30 min which was statistically insignificant in allfour groups ($p>0.05$). It was due to the effect of spinal anaesthesia leading tosympathetic blockade. There was statistically significant decrease in the SBP,DBP and MBP in group BC45 as compared to group BC30, group BC15 andgroup B ($p< 0.05$). 1 patient in group B (4%), 2 patients in group BC15 (8%), 3patients in group BC30 (12%) and 11 patients in group BC45 (44%) requiredthe treatment of hypotension.

- **Complications:**

B.S. Sethi et al,[13] 2007 observed fall in MAP and mean heart rate washigher in clonidine (1mcg/kg) group. But he observed no significant increase inother side effects like respiratory depression, nausea, vomiting, anddesaturation in clonidine (1mcg/kg) group.

Dryness of mouth was seen more with Group BC45 (20%) than GroupBC30 (8%), Group BC15 (8%) and Group B (0%).

Other side effects like nausea, vomiting, respiratory depression, shivering,urinary retention were not seen in any patient in Group BC15, Group BC30and Group BC45 in our study.3 patients from Group B had shiver ingintraoperatively.

- **Sedation:**

B.S. Sethi et al,[13] 2007 studied intrathecal clonidine and observed that 16out of 30 patients were sleeping comfortably and were easily arousable.

In our study as shown in Table 13 in Group BC15 15(60%) patients werewide awake, 10 (40%) patients were awake and comfortable. In Group BC30,10 (40%) patients were wide awake and 15 (60%) patients w ere awake andcomfortable. In Group BC45 5 (20%) patients were wide awake and 20 (80%)patients were awake and comfortable.

- **Duration of analgesia:**

Ghodki PS et al,[5] 2010 studied 30mcg of clonidine intrathecally andconcluded that it significantly prolongs the duration of spinal anaesthesia thusextending the analgesia as indicated by delayed demand for rescue analgesia inthe post operative period.

Sunil B. V et al,[14] 2014 observed that duration of analgesia is significantlyhigher in clonidine group (45 mcg) (260.71 ± 38.46) as compared to plainbupivacaine (164.42 ± 24.64)

In our study as per Table 14 mean time to first rescue analgesic wassignificantly higher in Group BC45 (363.2±38.05 min) compared to GroupBC30 (259.6±23.31 min) ($p<0.05$), in Group BC30 compared to G roup BC15(188.4±10.9 min) ($p<0.05$) and in Group BC15 compared to Group B(154±7.07 min) ($p<0.05$)

CONCLUSION

In conclusion, intrathecal addition of 45mcg clonidine to bupivacaine gives longerduration of postoperative analgesia than 30mcg or 15 mcg of clonidine but with moresedation and comparatively less hemodynamic stability. We got fairly good analgesiawith less sedation in 30mcg and l5mcg clonidine. However, duration of analgesia is morewith 30mcg clonidine than 15mcg clonidine. So, addition of 30mcg of clonidine givesexcellent analgesia with negligible hemodynamic instability and sedation is a betterchoice.

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