

Randomized clinical study comparing safety and efficacy of adjuvant intrathecal clonidine versus normal saline along with bupivacaine anaesthesia in lower limb surgery patients**Brijesh Kumar¹, Kiran Shetty², Vijaya Kiran Shetty³, Suresha K. R.^{4*}**

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ABSTRACT

Background: Various adjuvants have been used in intrathecal anesthesia to avoid intraoperative visceral and somatic pain and prolong postoperative analgesia. Clonidine, partially selective α_2 -agonist, is being evaluated as a neuraxial adjuvant with intrathecal bupivacaine. The objective of the study was to evaluate and compare safety and efficacy of intrathecal clonidine as adjuvant to bupivacaine with control normal saline.

Methods: American Society of Anesthesiologist grade 1 and 2 patients (60 patients) were randomly divided into two groups of 30 patients each for lower limb surgeries. Study group injected with intrathecal 3ml of 0.5% Bupivacaine heavy (15mg) + 1 μ g/kg of clonidine and control group injected with 3ml of 0.5% Bupivacaine heavy (15mg) + equivalent dose of normal saline. The onset and duration of sensory and motor block, duration of analgesia, and the incidence of side effects in both groups were observed and compared.

Results: Time for 2 segment regressions in study group was 186.17 \pm 25.92 minutes compared to control was 103.20 \pm 19.15 minutes (p value<0.001). Total duration of analgesia in control was 226.50 \pm 35.69 minutes and in the study group was 465.67 \pm 100.37 minutes (p value<0.001). The average duration of motor block in control group was 181.17 \pm 26.12 minutes compared to study group was 217.80 \pm 41.51 minutes (p value<0.001). The small dose of intrathecal clonidine is not significantly associated with systemic side effects such as bradycardia and hypotension.

Conclusions: Clonidine added to bupivacaine for intrathecal anesthesia effectively increases the duration of sensory block, duration of motor block and duration of analgesia and does not produce any significant hemodynamic changes. No significant side effects are associated with it.

Keywords: Bupivacaine, Clonidine, Intrathecal anesthesia, Lower limb surgeries

INTRODUCTION

Intrathecal anaesthesia commonly includes spinal and epidural anaesthesia. Spinal anaesthesia is defined as the temporary interruption of transmission of the nerve fibers

by injecting drug into the sub arachnoid space. It is safe and satisfactory if performed with the knowledge of its physiological consequences and in many instances, it is the method of choice in view of patient's condition and produces an ideal operating condition and post operative pain relief.¹

Local anaesthetics are used widely for the provision of anaesthesia and analgesia both intra- and post-operatively. They are used as the sole form of anesthesia, or in combination with general anesthesia. Development of local anesthetics, since the 1950s, has focused on amide local anesthetics (Lignocaine, Prilocaine, Bupivacaine) rather than ester local anesthetics because of number of limitations including instability in solution form, short shelf life, degradation when exposed to high temperatures, and an increased propensity to cause allergic reactions. The potency, duration, and onset of action for a local anesthetic are dependent upon lipophilic-hydrophobic balance and hydrogen ion concentration.²

For decades lignocaine has been the neuroaxial anesthetic of choice. Though it has many advantages in the form of rapid onset of action, good motor block manifested as good muscle relaxation. Nowadays its use is limited by increased incidences of neurological symptoms or transient radicular irritation.³ But bupivacaine is more potent than lignocaine and has longer duration of action. Its disadvantages are slow onset of action and decreased motor block.⁴ Hyperbaric bupivacaine 0.5% is extensively used local anaesthetic via intrathecal route. Though the duration of action of bupivacaine is prolonged, it will not produce prolonged post operative analgesia. So there is need for adjuvant for producing prolonged post operative analgesia. Several adjuvants have been used to prolong the duration of spinal anaesthesia. Vasoconstrictors like phenylephrine, opioids, dextran-40; carbonated local anaesthetics, proteins, potassium etc are some of well known agents. Morphine was the first and most commonly used opioid adjuvant for intrathecal administration with local anaesthetics producing intense, prolonged and segmental analgesic action without gross autonomic changes, loss of motor power or impairment of sensation other than pain when injected into subarachnoid or epidural space. However side effects such as potentially catastrophic, delayed respiratory depression, postoperative nausea and vomiting, pruritus, urinary retention etc have prompted further research to develop non- opioid analgesics with less worrisome side effects.⁵

Clonidine is of interest because it preserves cardiovascular reflexes, provides sedation, provides greater intra operative hemodynamic stability and a reduction in anaesthetic and postoperative analgesics requirements and also has a marked opioid sparing effect, further more intrathecal clonidine prolongs the duration of hyperbaric bupivacaine spinal block.^{6,7} Hence the present study was undertaken to evaluate the safety and efficacy of low dose intrathecal clonidine (1µg/kg) as an adjuvant to hyperbaric

bupivacaine for lower limb surgeries and compare with normal saline as control adjuvant.

METHODS

Study design

Randomized double-blinded clinical study, in which patients either injected with 3ml of 0.5% Bupivacaine heavy (15mg) + 1µg/kg of clonidine hydrochloride (Study Group) or injected with 3ml of 0.5% Bupivacaine heavy (15mg) + equivalent dose of normal saline (Control group). The simple randomization technique was used. This was double blinded using opaque sealed envelope; both patients and the anesthesiologists/nurses managing patients were blinded to knowledge of the group to which they belonged.

Study participants and eligibility criteria

This study was initiated after hospital research and ethics committee approval and written informed consent from the participants. 60 adult patients belonging to ASA Grade I and II aged between 20 and 50 years scheduled for various elective lower limb surgeries under spinal anaesthesia were included. A thorough preanaesthetic evaluation (PAE) was conducted on the day before surgery. PAE included history, clinical examination, and systemic examination was done. Investigations such as hemoglobin, total counts, differential count, erythrocyte sedimentation rate, urine routine, random blood sugar, electrocardiogram (ECG), chest X-ray, serum aminotransferases, bilirubin, serum creatinine, and blood urea were done before PAE. Patients with history of hypertension, ischemic heart disease, cerebrovascular accidents and endocrinal diseases like diabetes and pheochromocytoma and patients on chronic administration of α_2 agonist medication for hypertension were excluded from the study. Patients were pre-medicated with oral diazepam 0.1-0.2mg/kg and oral pantoprazole 40mg night before the surgery and were fasted for 8 hours preoperatively.

Interventions

In the operation theatre, an IV access was secured and started with Dextrose Normal Saline. Patients were connected to monitor that shows non invasive blood pressure (BP), ECG, heart rate (HR) and arterial oxygen saturation. Basal heart rate, systolic and diastolic BP, respiratory rate (RR) and arterial oxygen saturation were noted. Patients were preloaded with 15ml/kg RL over 15 minutes before subarachnoid block. Patients were placed in left lateral decubitus position for lumbar puncture. Under strict aseptic precautions a lumbar puncture was performed through a midline approach using either a 25G or 27G spinal needle at L3-L4 intervertebral space. Once a free flow of cerebrospinal fluid was obtained, the following test drugs were given to the patients as per the randomization list.

- Study Group - injected with 3ml of 0.5% Bupivacaine heavy (15mg) + 1µg/kg of clonidine hydrochloride.⁸
- Control group - injected with 3ml of 0.5% Bupivacaine heavy (15mg) + equivalent dose of normal saline.

After the injection the patient was returned to supine position and was retained in that position for 20 minutes before positioning for surgery.

Outcomes

The following parameters were recorded in all patients. Extent of sensory blockade- the highest level of sensory blockade was checked by pinprick sensation. Degree of motor blockade is checked according to Bromage scale.⁹ Duration of anaesthesia, duration of surgery, HR, NIBP (SBP, DBP), ECG, SPO₂ and RR are monitored at every 5 minutes for first half an hour and then at 15 minutes intervals. Adverse effects are monitored. Sedation scoring was done (0- No sedation; 1- Drowsiness; 2- Asleep but arousable; 3- Unarousable with loss of verbal contact)

Statistical analysis

Descriptive and inferential statistical analysis was used in our study. Results on continuous measurements were presented on Mean±standard deviation and results on categorical presented in Number (%). Student t test (two tailed, dependent) was used to find the significance of study parameters on continuous scale within each group. Chi square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups. Significance was assessed at 5% level of significance (P).

RESULTS

Table 1: Baseline demographic profile of the patients.

Parameters	Control group (Bupivacaine +Normal saline) (Mean±SD)	Study group (Bupivacaine + Clonidine) (Mean±SD)	p Value
Age (Yrs)	38.37±9.09	37.77±9.77	0.806
Weight (kgs)	61.40±9.80	61.50±9.59	0.968
Sex (M:F)	21:9	22:8	0.774
ASA I/ ASA II	22/8	21/9	0.774
Heart Rate	87.23±10.58	85.97±8.29	0.608
Systolic BP	130.97±9.80	130.40±11.38	0.835
Diastolic BP	84.47±4.49	84.13±8.08	0.844
Respiratory rate	16.07±0.87	16.03± 0.96	0.889
SPO ₂	99.63 ± 0.49	99.53 ±0.78	0.964
Sedation score (1-5)	1(awake)	1(awake)	

A total number of 71 patients were screened for the eligibility and 60 were enrolled. Excluded 11 patients (hemodynamic instability= 03, prior clonidine usage =02, contraindications to study drugs =05, refused consent =01) and 60 patients were randomized into the two groups (Study and control group). Baseline demographic profile of the patients is shown in Table 1.

Both the groups are comparable with respect to age, gender distribution, hemodynamic parameters, and sedation scores etc. The distribution of various surgical procedural indication among the both the groups is depicted in Table 2.

Table 2: Distribution of surgical procedures among both the groups.

Surgery	Control group (n=30)		Study group (n=30)	
	No	%	No	%
ACL repair	2	6.7	3	10.0
Arthroscopy	3	10.0	1	3.3
Bone grafting	0	0.0	1	3.3
Exchange nailing	0	0.0	2	6.7
Fissurectomy	1	3.3	0	0.0
Fistulectomy	1	3.3	0	0.0
Flap covering	1	3.3	0	0.0
Haemorrhoidectomy	2	6.7	1	3.3
Hernia repair	3	10.0	5	16.7
Hydrocelectomy	2	6.7	1	3.3
IL Nailing	1	3.3	2	6.7
IM nailing	2	6.7	0	0.0
Implant removal	0	0.0	2	6.7
ORIF	4	13.3	4	13.3
PFN	1	3.3	0	0.0
Sequestrectomy	1	3.3	0	0.0
Skin grafting	0	0.0	2	6.7
Stripping	0	0.0	2	6.7
TBW	2	6.7	1	3.3
Varicocelectomy	1	3.3	0	0.0
Others	3	10.0	3	10.0

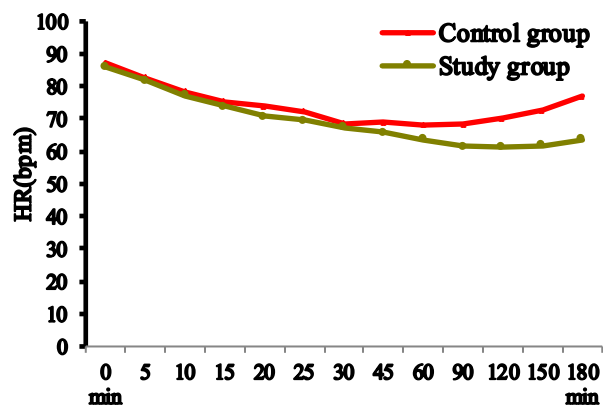


Figure 1: Comparison of mean heart rate at various time intervals.

The comparison of the mean heart rates between the groups is shown in Figure 1. The decrease in mean heart rate from 45 minutes until the end of 3 hours was greater in Clonidine group than in the Control group ($P<0.001$). In addition, the decrease from baseline value within the Clonidine group was also statistically significant at 45 minutes to the end of 3 hours. Only 2 patients in control group had bradycardia whereas 4 patients had bradycardia in clonidine group.

The comparison of mean systolic blood pressure at various time intervals is shown in Figure 2. The decrease in mean SBP after 120 minutes until the end of 3 hours was greater in clonidine group than in the control group ($P<0.001$).

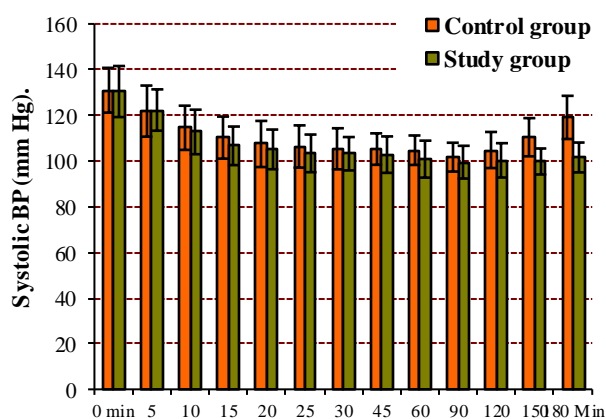


Figure 2: Comparison of mean systolic blood pressure at various time intervals.

The Comparison of mean DBP at various time intervals is shown in Figure 3. The decrease in mean diastolic blood pressure from 30 minutes until the end of 3 hours was greater in clonidine group than in the control group ($P<0.001$).

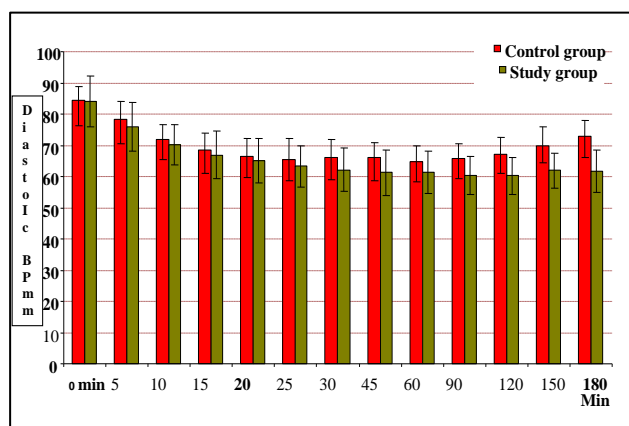


Figure 3: Comparison of mean diastolic blood pressure at various time intervals.

In addition, the decrease from baseline value within the study group was also statistically significant at 45 minutes to the end of 3 hours. 7 patients had hypotension in control group whereas 9 patients had hypotension in study group.

The comparison of mean SpO₂ at various time intervals shown in Figure 4.

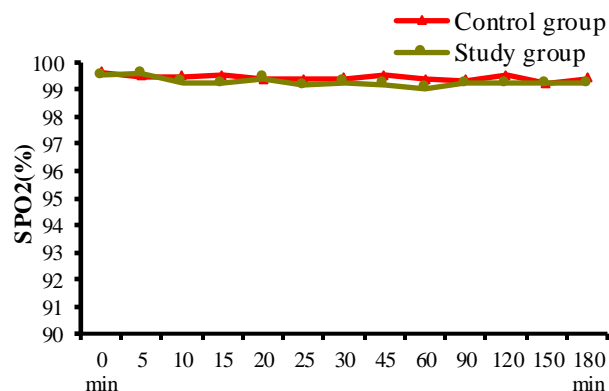


Figure 4: Comparison of mean SpO₂ at various time intervals.

There was no significant change in SpO₂ from the baseline in both the groups ($P>0.05$). The comparison of study parameters (duration of surgery, regression of sensory analgesia by two segments, duration of motor blockade and time for rescue analgesia) between two groups is shown Table 3.

Table 3: Comparison of study parameters between two groups.

Study parameters	Control group(n=30)	Study group (n=30)	P value
Duration of Surgery	117.83±29.23	121.67±34.85	t=0.462; p=0.646
Time for 2 segment regressions of sensory block	103.20±19.15	186.17±25.92	t=14.007; p<0.001**
Duration of motor blockade	181.17±26.12	217.80±41.51	t=4.091; p<0.001**
Time for first rescue analgesia	226.50±35.69	465.67±100.37	t=12.297; p<0.001**

There was no statistically significant difference in the duration of surgery between both the groups ($P>0.05$). The time taken for regression of sensory analgesia by two segments was significantly more in study group (186.17±25.92min) when compared to control group (103.20±19.15min) (P value <0.001). The duration of motor blockade was significantly longer in study group (217.80±41.51min) when compared to control group (181.17±26.12min) (P value <0.001). The time for first rescue analgesia in clonidine group was significantly more (465.67±100.37min) when compared to control group (226.50±35.69min) (P value <0.001). Comparison of extent of sensory blockade achieved in both the groups is

depicted in Figure 5. The Comparison of Sedation score is shown in Table 4.

Table 4: Comparison of Sedation score.

Sedation score	Control group (n=30)	Study group (n=30)
0	26(86.7%)	5(16.7%)
1	4(13.3%)	9(30.0%)
2	0	16(53.3%)
Mean±SD	0.13±0.35	1.37±0.77
Inference	Study group had significantly higher sedation score with P<0.001**	

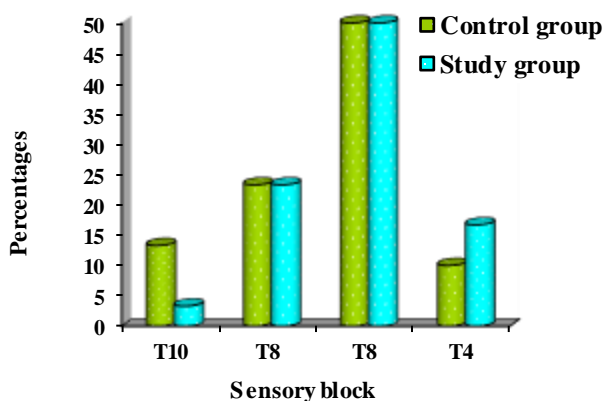


Figure 5: Comparison of extent of sensory blockade achieved in both the groups.

The incidence of sedation was significantly higher in clonidine group (1.37±0.77) compared to control group (0.13±0.35) (P<0.001). The Comparison of various adverse effects between both the groups is depicted in Figure 6. There was statistically no significant difference in the incidence of nausea, vomiting, dry mouth, desaturation, bradycardia and hypotension between both the groups whereas the incidence of shivering was significantly less in study group (6.7%) than the control group (26.7%) (P<0.05).

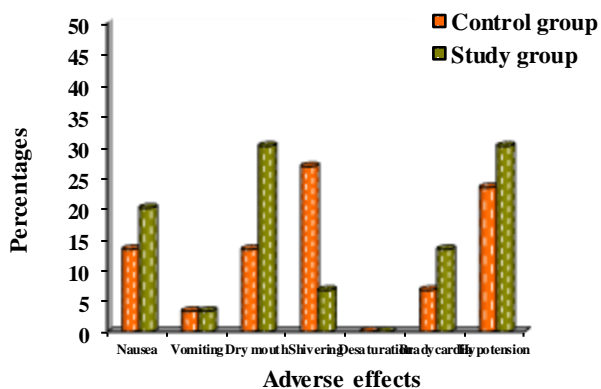


Figure 6: Comparison of various adverse effects between both the groups.

DISCUSSION

The spinal anesthesia is preferred for lower limb surgeries as it is simple, easy to perform, and economical with rapid onset of anesthesia and complete muscle relaxation. In our study, we used 0.5% hyperbaric bupivacaine to create subarachnoid block.¹⁰

In the present study, results showed that the addition of clonidine in the dose of 1µg/kg to 0.5% bupivacaine increased the duration of sensory block, motor block and duration of analgesia in patients undergoing lower limb surgeries. Clonidine is a selective partial agonist for α2 receptor, moderately lipid soluble and easily penetrates the blood-brain barrier, leading to spinal and supraspinal receptor binding and thus provides effective and long-lasting postoperative analgesia. They act by binding to presynaptic C-fibers and postsynaptic dorsal horn neurons.¹¹

Their analgesic action is a result of depression of the release of C-fiber transmitters and hyperpolarization of postsynaptic dorsal horn neurons. The prolongation of effect may result from synergism between local anesthetics and α2-adrenergic agonists to motor neurons in the dorsal horn.¹²

Sensory characteristics and analgesia

Clonidine produces spinal cholinergic activation with cholinergic interaction in spinal α2 adrenoceptors and produces noradrenaline release in the descending noradrenergic pathways which causes analgesia. In addition it stimulates release of acetylcholine which enhances analgesia.¹³ The analgesic action of clonidine may be at peripheral, spinal and brainstem sites. It does produce a minor degree of nerve conduction blockade at very high concentration with some preference for C fibres.¹⁴ This conduction blockade may underlie, in part, the enhancement of peripheral nerve block when this agent is added to bupivacaine. Spinal action of clonidine through release of acetylcholine and noradrenaline has also been proposed as the mechanism of action of prolonging spinal.¹⁵

In our study it was noticed that the maximum level of sensory blockade achieved both the groups were similar at T6 segment. The time for 2 segmental regression of sensory blockade was compared, it was seen that the time for 2 segment regressions in study group was 186.17±25.92 minutes and in control group it was 103.20±19.15 minutes (p value <0.001). The total duration of analgesia in control group was 226.50±35.69 minutes and in the study group it was 465.67±100.37 minutes (p value <0.001). This shows that clonidine prolongs the duration of postoperative analgesia. Our study is consistent with that of BS. Sethi et al, and Strebel, et al.^{16,17}

Motor characteristics

Dobrydnjov et al, 76 noted that intrathecal clonidine alone even in doses of 450µg does not induce motor block or weakness. In contrast, intrathecal clonidine combined with local anaesthetics significantly potentiates the intensity and duration of motor blockade. The explanation for this could be that α2 agonist induce cellular modification in the ventral horn of spinal cord (motoneuron hyperpolarisation) and facilitate local anaesthetic action.^{18,19} Clonidine may cause local vasoconstriction, thereby reducing vascular removal of local anaesthetics surrounding the neural structures. This may also partly explain increased duration of motor blockade associated with clonidine administration.¹⁷

In present study the average duration of motor block in control group was 181.17±26.12 minutes compared to study group 217.80±41.51 minutes (p value<0.001). Our results are consistent with BS Sethi et al.^{16,18}

Stephan Strebel employing 37.5µg, 75µg and 150µg clonidine in addition to bupivacaine noted that complete motor blockade of lower extremities was observed in all the patients. After 4, 5, 6 and 7 hours the Bromage score was significantly higher in patients who received clonidine compared to control group.¹⁷ The results of the present study concur with the studies of BS Sethi et al, Dobrydnjov et al, and Stephan Strebel et al.

Sedation

Sedation commonly accompanies the use of clonidine for regional anaesthesia, consistent with the known sedative/ anaesthetic sparing properties of α2 agonists by its action on locus coeruleus.²⁰ This brainstem nucleus is associated with a wide variety of physiological regulatory responses, including regulation of sleep and wakefulness. This centre is inhibited by clonidine via a G-protein mediated mechanism that involves inhibition of adenylyl cyclase. Several studies have demonstrated the reduced need for other sedatives and anxiolytic medications when clonidine is administered intraoperatively.²¹ In the present study number of patients with grade 2 sedation was 16 and number of patients with grade 1 sedation was 9. All could be easily arousable and SPO₂ was well maintained. Our results are in similar with BS Sethi et al, and Stephan Strebel.^{16,17}

Hemodynamic changes: Clonidine affects BP in a complex fashion after neuraxial administration because of opposing actions at multiple sites.²²

In nucleus tractus solitarius and locus coeruleus of brain stem, activation of postsynaptic α2 receptors reduces sympathetic drive. In addition, clonidine is not a pure α2 agonist. It also activates non adrenergic imidazoline preferring binding sites in the lateral reticular nucleus thereby producing hypotension and antiarrhythmic action. In the periphery activation of presynaptic α2

adrenoreceptors at sympathetic terminals reduces the release of epinephrine, which could cause vasorelaxation and reduced chronotropic drive. These brainstem and peripheral effects of α2 stimulation are counterbalanced by direct peripheral vasoconstriction from clonidine. As a result, the dose response for clonidine by neuraxial administration is U shaped with peripheral vasoconstriction from circulating drug concentration at high doses opposing central sympatholysis.¹⁹

In addition, clonidine directly inhibits sympathetic preganglionic neurons in the spinal cord. The degree of clonidine induced hypotension is related to the spinal level of injection. Clonidine reduces heart rate, partly by a presynaptically mediated inhibition of nor adrenaline release at the neural receptor junction and partly by a vagomimetic effect. Hemodynamic effects begin within 30 minutes and reach maximum within 1-2 hours and lasts approximately 6-8 hours.

Dobrydnjov et al, 76 employing different doses of clonidine noted that mean arterial pressure was significantly lower during first 45-120 minutes in patients who received 15µg-30µg of clonidine. The maximal fall in mean arterial pressure was 11-19mmHg in patients who received 15µg of clonidine whereas the fall was 15-20mmHg in patients who received 30µg of clonidine. In control group the fall in mean arterial pressure was only 5-14mmHg.¹⁸

In our study, we have observed small dose of intrathecal clonidine is not significantly associated with systemic side effects such as bradycardia and hypotension.

Benhamou et al, 84 also noted that hemodynamic changes in blood pressure and heart rate were not significant when bupivacaine in combination with clonidine was employed.

Chiari et al, noted that blood pressure and heart rate changes are seen usually with higher doses of clonidine (>200µg).^{23,24} In the present study only low dose clonidine (1µg/kg) was employed and all the patients were preloaded with RL and hemodynamic changes were minimal in both the groups. The results of the present study concur with the results of Benhamou et al and Chiari et al.

CONCLUSION

The addition of clonidine (1µg/kg) to bupivacaine for intrathecal anesthesia effectively increases the duration of sensory block, duration of motor block and duration of analgesia and does not produce any significant hemodynamic changes. No significant side effects are associated with addition of 1µg/kg clonidine to 3ml of 0.5% Bupivacaine.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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