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# A comparative study of intrathecal clonidine and intrathecal tramadol for prolongation of neuraxial blockade analgesia with 0.5% bupivacaine in orthopaedic surgery

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## ABSTRACT

**Introduction:** Spinal anaesthesia is advantageous in that it uses a small dose of the anaesthetic, is simple to perform and offers a rapid onset of action, reliable surgical analgesia and good muscle relaxation.Effective postoperative analgesia can be provided by neuraxially applied local anaesthetics or opioids, which may be accompanied by unwanted side effects like motor block, hypotension or respiratory depression**. Aim:** A comparative study of Intrathecal Clonidine and Intrathecal tramadol along with 0.5% hyperbaric Bupivacaine for prolongation of Subarachnoid neuraxial blockade. **Materials and methods**: it is prospective randomized study which have 2 groups, each group of 25 patients randomly selected. Group A (N-25): Received Inj Clonidine hydrochloride (37.5 mcg) and 0.5% hyperbaric Bupivacaine hydrochloride (3.5 ml) + 0.75 ml Normal saline, Group B (N-25): Received inj Tramadol (25 mg) and 0.5% hyperbaric Bupivacaine hydrochloride (3.5 ml). **Results:** Intraoperatively significant differences in BP, pulse rate were noted, like hypotension and bradycardia more in the clonidine group.Time to full motor recovery was not delayed in any of the patients in both the groups.The mean duration of analgesia did differ in both groups. Mean duration of analgesia in Group A was 326.40 $\pm$ 30.39 mins and in Group B was 302.40 $\pm$ 12.00 mins. Time for two segment regression did differ in both the groups. The patients in both the groups showed minimal side effects, like nausea, vomiting and pruritis. The incidences of side effects were statistically insignificant. Both intrathecal clonidine and intrathecal tramadol act synergistically to potentiate bupivacaine induced sensory spinal block. Excellent surgical anesthesia and an extended analgesia was observed in post-operative period with minimum side effects were observed in both groups. **Conclusions:** Study has demonstrated that addition of Intrathecal Clonidine to bupivacaine, even in very small doses, significantly improves the onset and duration of sensory and motor block with relative hemodynamic stability. The 37.5 mcg dose provides maximum benefit and minimum side effects. It is recommended over Intrathecal Tramadol.

**Keywords:** Clonidine,analgesia,anaesthetic.

## Introduction

Spinal anaesthesia is one of the most frequently employed methods of regional anaesthesia. Temporary interruption of nerve transmission is easily produced by injecting local anaesthetic into the readily identifiable subarachnoid space. Spinal anaesthesia is advantageous in that it uses a small dose of the anaesthetic, is simple to perform and offers a rapid onset of action, reliable surgical analgesia and good muscle relaxation. Effective postoperative analgesia can be provided by neuraxially applied local anaesthetics1 or opioids[1-2], which may be accompanied by unwanted side effects like motor block, hypotension or respiratory depression[3].Spinal anaesthesia with hyperbaric Bupivacaine Hydrochloride is popular for longer procedures due to its prolonged duration. But there is a need to intensify and increase duration of sensory blockade without increasing the intensity and duration of motor blockade, and thus prolonging the duration of postoperative analgesia. Intrathecal and epidural clonidine provide effective analgesia in volunteers, in patients in labour and in those with postoperative pain

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without inducing repiratory depression or motor block. The addition of Alpha 2 agonists and opioids has been suggested as a method to accomplish these goals. This study is designed to quantitatively examine the effects of adding Clonidine and Tramadol to Hyperbaric Bupivacaine Hydrochloride in spinal anaesthesia on duration and recovery of sensory and motor blockade.

**Materials and methods**

It is prospective study done in Patients undergoing elective orthopaedic surgeries under spinal anaesthesia. Approval is obtained from ethical committee. A written informed consent from the patients consisting of 2 groups, each group of 25 patients randomly selected in this prospective randomized study as per the following criteria. Patients selected are in the age group of 18-60 years of either sex with ASA physical status I and II scheduled to undergo elective surgery.

Inclusion Criteria:

- Informed consent from all patients.
- Age 18 yrs-60 yrs, both male and female.
- Physical status ASA I and II.
- Patients undergoing elective orthopaedic surgeries under spinal anaesthesia.

Exclusion Criteria:

- Emergency surgery cases
- Physical status ASA 3, 4, 5.
- Distortion of Spinal anatomy
- Superficial lumbar site infection.
- Pregnant women
- Patients with coagulopathy

Group A (N-25): Received Inj Clonidine hydrochloride (37.5 mcg) and 0.5% hyperbaric Bupivacaine hydrochloride (3.5 ml) + 0.75 ml Normal saline

Group B (N-25): Received inj Tramadol (25 mg) and 0.5% hyperbaric Bupivacaine hydrochloride (3.5 ml).

All the patients were advised to fast for a period of 6-8hours prior to the day of surgery.

All the patients were familiarized with visual analog scale of 10 cm for pain during the pre-anaesthetic checkup and informed the feeling of tingling, warmth or heaviness that may be felt after the intrathecal injection.

Each patient received 1 mg i.v midazolam in the pre operative room before shifting to O.T

Routine investigations viz., CBP, BT, CT, CUE, ECG, CXR-PA view, checked.

**Operation Theatre setup:** Anaesthesia machine with central oxygen pipeline and two full oxygen cylinders were kept in reserve. Appropriate sized endotracheal tubes with connections.

Two working laryngoscopes, tubings, circuit with properly fitting masks**.**

Pulse oximeter

Non invasive blood pressure monitor

Drugs for resuscitation – Atropine, Adrenaline, Mephenteremin, etc

Drugs for study – 0.5% heavy Bupivacaine, Clonidine, Tramadol

**Monitoring:**Continuous monitoring throughout the peri-operative and post-operative period done inside the operation theatre, viz., pulse rate, non-invasive blood pressure, Spo2 are recorded.

**Procedure:**Venous access is secured with a wide bore 18G intravenous canula and all the patients are preloaded with 15ml/kg of crystalloid solution (Ringer lactate) over 10-15 mins. Under strict aseptic precautions lumbar puncture is performed at the L3-L4 intervertebral space using a midline approach with a 23G Quincke spinal needle in the sitting position. After ensuring free flow of CSF, Patient in Group A received intrathecal Clonidine (37.5 mcg) along with 3.5 ml of 0.5% of hyperbaric Bupivacaine hydrochloride + 0.75 ml normal saline. Group B received intrathecal Tramadol (25 mg) along with 3.5 ml of 0.5% of hyperbaric Bupivacaine hydrochloride. All the patients received a coded intrathecal drug volume and the injection is given slowly. Time of onset of block was subjectively assessed by patient complaining of a feeling of warmth, heaviness of limbs, or a tingling sensation, objectively confirmed by decreased VAS scores to pinprick to 5 or less. The time of injection was recorded as zero hour and the level of anaesthesia, onset, duration of analgesia and in addition heart rate, blood pressure, and Spo2 are recorded every 5 minutes after the block for 30 mins, then every 15 mins thereafter till the end of the surgery, and then every 30 mins till the sensory and motor blockade is completely worn off.

The maximum ascent of sensory blockade, time to achieve sensory block upto T10, regression of block by 2 segments and duration of analgesia were also noted. Hemodynamic instability was defined as a 30% reduction in mean arterial BP from baseline value and was treated with 300 ml of additional fluids and i.v ephedrine 6 mg bolus if required.

**Intra and Post operative monitoring:** Patients are observed for any discomfort, nausea, vomiting, shivering, hypotension, pain, bradycardia and any other side effect. Pain assessment is done by Visual analog scale. Degree of motor block is assessed by the Bromage scale.

**Results**

**Table 1: Demographic characteristics of patients**

| Variable | Group A-Clonidine (n-25) | Group B- Tramadol (n-25) | p Value |
|---|---|---|---|
| Age (yrs) | 30.20 ± 11.48 | 31.68 ± 11.17 | 0.64 |
| Sex (M/ F) : (1/2) | 22/3 (1.12 ± 0.33) | 21/4 (1.16 ± 0.37) | 0.68 |
| Weight (Kg) | 67.80 ± 9.32 | 64.36±9.92 | 0.21 |
| HR (bpm) | 77.20 ± 9.52 | 76.64 ± 9.72 | 0.83 |
| SBP ( mm Hg) | 125.20 ± 11.38 | 120.76 ± 14.47 | 0.23 |
| DBP (mm Hg) | 78.80 ± 8.73 | 74.08 ± 10.07 | 0.08 |
| SpO2 | 99.72 ± 0.45 | 99.80 ± 0.40 | 0.50 |

There was no significant difference between the two groups.

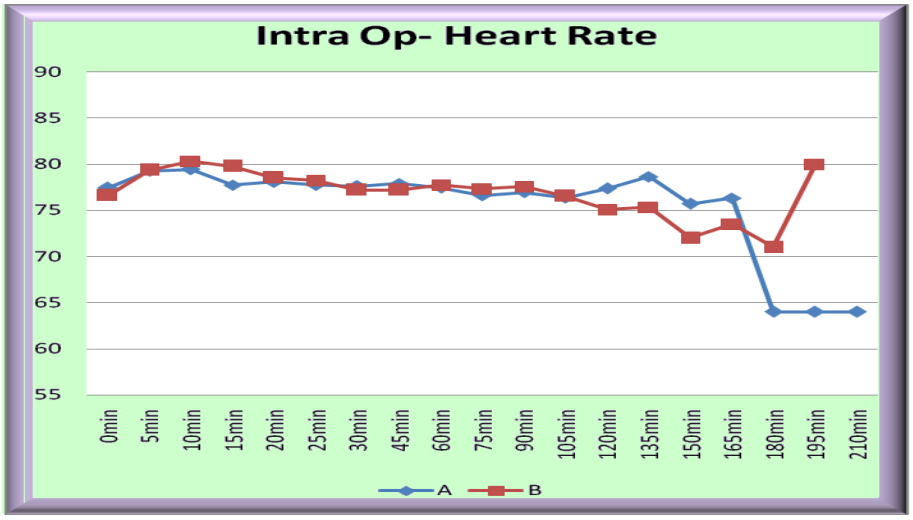


**Fig 1: Heart rate at different intervals Intra-operatively**

**A**- Clonidine (n-25) : **B**- Tramadol (n-25)

There was no significant difference between the two groups.

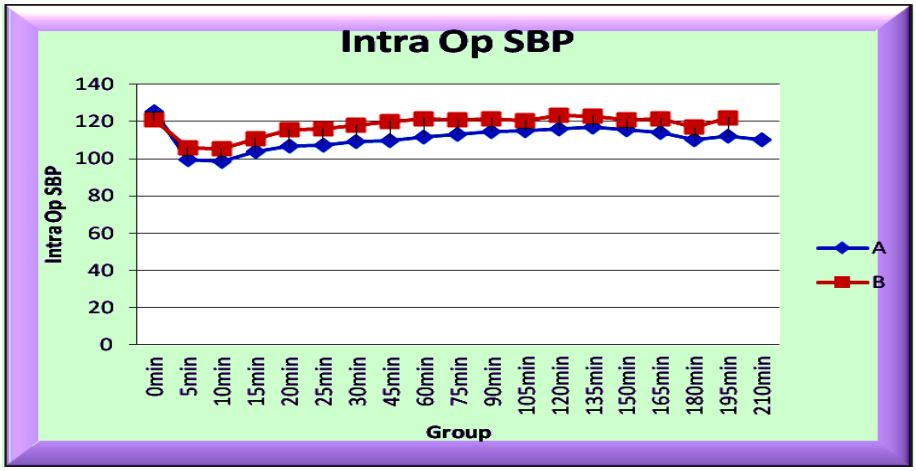


**Fig 2: Systolic Blood pressure at different intervals**

**A**- Clonidine (n-25) : **B**- Tramadol (n-25)

Systolic blood pressure on 5,10,15,20, 25, 30, 45, 60, 75, 90, 105 and120 min. **is** significant

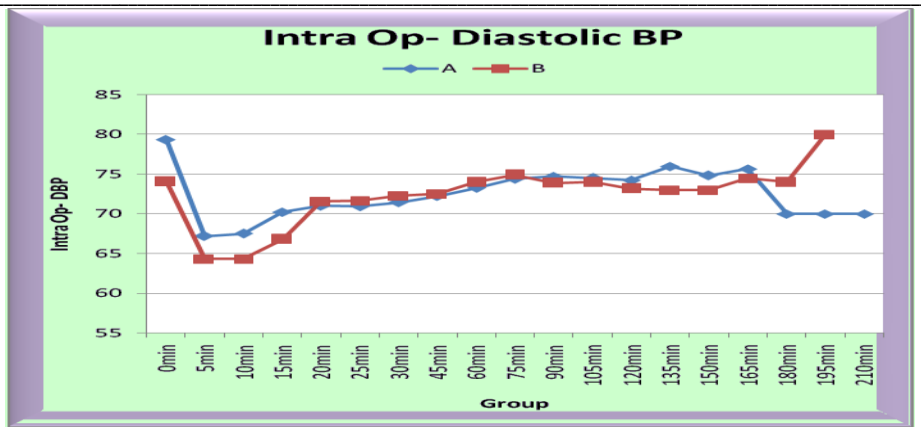


**Fig 3: Intra-operative Diastolic Blood pressure at different intervals**

**A**- Clonidine (n-25) : **B**- Tramadol (n-25)

Diastolic blood pressure on 5,10,15 min. **is** significant

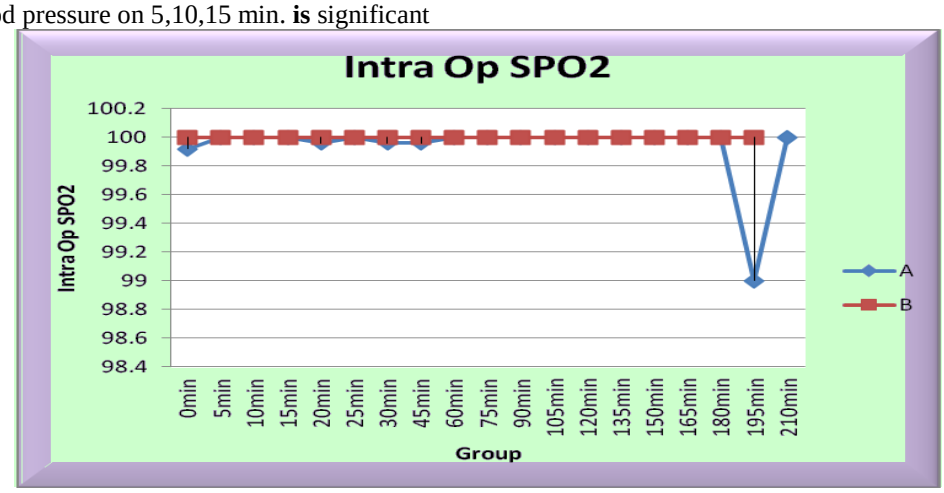


**Fig 4: Intraoperative oxygen saturation**

**A**- Clonidine (n-25) : **B**- Tramadol (n-25)

There was no significant difference between the two groups.

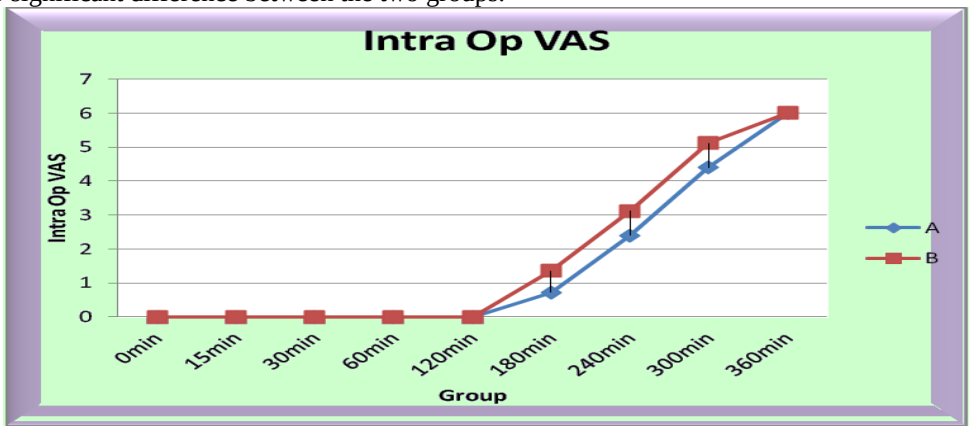


**Fig 5: Intra operative VAS score**

**A**- Clonidine (n-25) : **B**- Tramadol (n-25)

VAS score on180, 240, 300 min. is Significant.

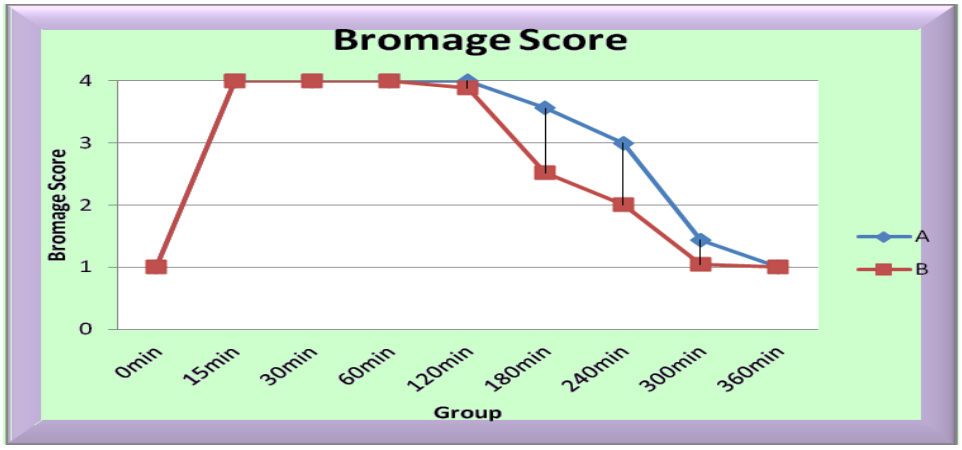


**Fig 6: Comparison between Intra-operative Bromage Score between two groups**

**A-** Clonidine (n-25) : **B**- Tramadol (n-25)

**Bromage** score on 120, 180, 240 , 300 min. is Significant.

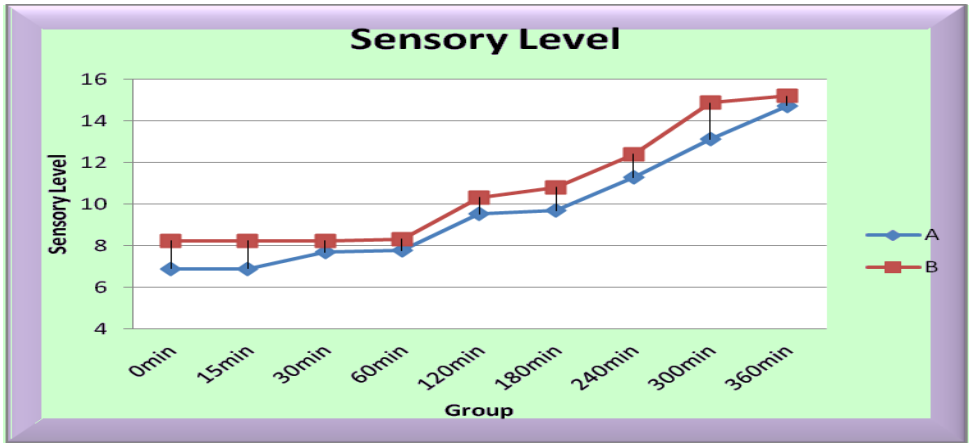


**Fig 7: Sensory Level between the two groups**

Sensory level 4 to 12 –Thoracic levels

Sensory level 12 & 14- Lumbar level 2, 4

**Sensory Level between the two group** on 0, 15, 180, 240, 300 min. is Significant.


**Fig 8: Time to full recovery**

Time of recovery is significant when compared in both groups.

**Table 2: Comparison of the Post- operative Heart rate, Systolic and Diastolic blood pressure and Spo2**

| **Variable** | **Group A**- Clonidine | **Group B**- Tramadol | **p Value** |
|---|---|---|---|
| HR (bpm) | 79.04 ± 6.43 | 78.56 ± 6.94 | 0.80 |
| SBP ( mm Hg) | 120.08 ± 5.72 | 124.56 ± 7.60 | 0.02* |
| DBP (mm Hg) | 75.20 ± 4.54 | 75.68 ± 5.82 | 0.74 |
| SpO2 | 100.00 ± 0.00 | 100.00 ± 0.00 | 1.000 |

SBP is significantly elevated in group –B i.e. tramadol group * Significant p value.

**Discussion**

Clonidine is a selective partial agonist for alpha2-adrenoreceptors. It is known to increase the density of both sensory and motor block of local anaesthetic .The analgesic effect following its intrathecal administration is mediated spinally through activation of post synaptic alpha 2-receptors in substantia gelatinosa of spinal cord[4,5] and it works by blocking the conduction of C and A delta fibres, increases potassium in isolated neurons invitro and intensifies conductance block of local anaesthetic. Paqueron et al [6] recently suggested that one of the mechanisms for the enhanced potency of intrathecal clonidine administration in a rat model of neuropathic pain is its ability to modulate spinal cord NMDAR activation via suppression of NR1 phosphorylation.Tramadol is a centrally acting analgesic agent with elimination half life of 5.5 hrs and provides clinical analgesia by stimulation of μ receptors and to a lesser extent the delta and kappa receptors. It also activates spinal inhibition of pain by decreasing the reuptake of norepinephrine and serotonin. It causes less repiratory depression and pruritis. It was suggested by other studies that tramadol may have local anaesthetic effects on peripheral nerves. Intrathecal opiod administration has been demonstrated to provide effective postoperative analgesia after a variety of surgical procedures, at the cost of increased risk of respiratory depression. Tramadol, in contrast to a centrally acting opiod analgesic, has minimal respiratory effect, because it has 6000 fold less affinity for μ receptors compared to morphine. It also inhibits serotonin and norepinephrine reuptake in the spinal cord and has no reported neural toxicity over a period of 1 year. For this prospective randomized trial, we studied fifty ASA 1 and 2 physical status patients with lower limb orthopaedic surgeries over a period of 18 months. Patients with physical status [3,4,5] infection over lumbar site area, allergy to the trial drugs, bleeding and clotting disorders, pregnant women were excluded from the study.I have observed that addition of clonidine improved the onset time, speed of spread, and duration of block in a dose dependant manner. I valued the subjective sensation of feeling of warmth in lower limbs in all the patients receiving clonidine, which corresponded with decreased VAS score at the calf level. A similar correlation of subjective sensation of swelling after regional blocks has been reported by paqueron et al [14].As shown in table 1 and 2 there was no significant difference between the groups with regard to demographic data such as age, weight and sex.The mean age of the patients was 30.20 ± 11.48 in group A and 31.68 ± 11.17 in group B.

The mean weight was 67.80 ± 9.32 in group A and 64.36 ± 9.92 in group B which were comparable.

The sex ratio was 1.12 ± 0.33 in group A and 1.16 ± 0.37 in group B. Hence it is found that there was no significant difference between both the groups. Hemodynamic variables such as heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation were monitored preoperatively and there was no significant differences observed between the two groups. As shown in table 3 and 4, the mean heart rate was 77.20 ± 9.52 in group A and 76.64 ± 9.72 in group B, systolic blood pressure was 125.20 ± 11.38 in group A and 120.76 ± 14.47 in group B, diastolic blood pressure was 78.80 ± 8.73 in group A and 74.08 ± 10.07 ingroup B and Spo2 was 99.72 ± 0.45 in group A and 99.80 ± 0.40 in group B.There was no significant difference in the intraoperative heart rate between the two groups. A small dose of intrathecal clonidine is not usually associated with systemic side effects such as bradycardia, hypotension, or sedation. Accordingly studies using very low doses intrathecal clonidine such as 15 to 30 mcg found no hemodynamic instability. Mean intraoperative systolic blood pressure was significantly lower in Group A throughout with $p < 0.05$. Animal studies have provided evidence of a biphasic effect on blood pressure after intrathecal clonidine6. Since clonidine is a mixed α1-α2 adrenargic agonist, high clonidine doses causes' peripheral vasoconstriction, which results in a U shaped hemodynamic dose response curve. There was no significant difference in the intraoperative diastolic blood pressure among the two groups. These findings agree with other investigations demonstrating a decrease in arterial BP with such doses and relative hemodynamic stability with administration of larger

doses. Although neuraxial clonidine may be systematically absorbed leading to reduced sympathetic activity by actions in the brainstem and periphery[7-9], neuraxial clonidine also directly decreases MAP by inhibition of preganglionic sympathetic neurons in the spinal cord. Most of the studies using 37.5 mcg to 150 mcg reported significant hypotension and bradycardia while with higher doses of 300 and 450 mcg, relative hemodynamic stability is observed, suggesting a pressor effect on peripheral sites6 .Maximum benefit was seen with the dose of 37.5 mcg, but 20% of patients had fall in pulse and BP and 90% patients were sedated. Regarding onset time, our findings were similar to Filos Ks[10] who compared 150, 300, and 450 mcg of clonidine for postop analgesia after elective caesarian section performed in GA and found immediate reduction of pain scores with 300 and 450 mcg of clonidine, namely 3rd and 6th min after injection. Mean intraoperative Visual analog scale was comparable at 0 hrs, 15 mins, 30 mins, 60 mins and every 1hr till 6hrs was found to be significantly lower in group A at 180 mins to be 0.72 $\pm$ 0.98 as compared to group B with 1.36 $\pm$ 0.95 and p value 0.023 and P value at 240 mins and 300 mins , shows group A VAS scores significantly lower than the group B.I have observed decreased VAS scores to pin prick almost instantly with 37.5 mcg dose in all orthopaedic patients and instant reduction of pain observed. A possible explanation could be from the results of the study by Nishiyama et al[11] showing that intrathecally administered combination of bupivacaine and clonidine produce synergistic analgesic effects on both acute thermal and inflammation induced pain with decreased side effects. After a dose of 1 mcg/kg intrathecally clonidine in humans, the peak CSF level was about 6 mcM. These concentrations are within range required to partially block voltage gated Na+ and K currents and to shift the steady state inactivation curve to more negative potentials. Heo and young et al[12] had found no difference in the onset time using 150 mcg clonidine. The mean Bromage score was significantly higher in group A at 180 mins to be 3.56 $\pm$ 0.57 as compared to group B with 2.36 $\pm$ 0.49 and p value 0.0001 and P value at 240 mins and 300 mins show significantly higher group A Bromage scores compared to group B.The spread of block to T10 and higher in our study was quicker in clonidine group when compared to intrathecal tramadol administration. The duration of sensory block was prolonged in comparison to intrathecal tramadol. Mean sensory level was significantly prolonged in group A at 180 mins to be 9.68 $\pm$ 1.10 as compared to group B with 10.80 $\pm$ 1.29 and p value 0.0018 and P value at 240 mins and 300 mins show significant prolongation of sensory level in group A compared to group B. Two segment regressions were prolonged in clonidine group compared to tramadol group. The duration of motor block in our study was comparable to studies of Strebel[13], and grandhe [14] in spite of higher volume or higher dose of clonidine used by them. Full recovery from subarachnoid blockade was significantly higher in group A, with time of 326.40 $\pm$ 30.39 mins as compared to group B time of 302.40 $\pm$ 12.00 mins with p value of 0.0001.Total analgesia time was prolonged in our study similar to strebel et al1[3]. I found a better quality of block in the clonidine group compared to tramadol group. This was comparable to the results of Dobrydnjoy et al[15] who reported the surgeon rating the operating conditions as excellent or good in 95-100% of patients receiving 15 and 30 mcg clonidine with bupivacaine. Brijesh Jain et al[16] in 2000 found that intrathecal tramadol 25 mg added to hyperbaric bupivacaine provided a mean duration of post-operative painrelief of about eight hours, which is similar to our finding.

The incidence of hemodynamic side effects like decreased blood pressure, bradycardia, and other side effects like somnolence, dryness of mouth were minimum and well tolerated by patients in the tramadol group. Alsheshmi J.A et al[17] in 2003 found that intrathecal tramadol did not seem to influence the intra operative hemodynamic profile.

In conclusion, my study has demonstrated that addition of intrathecal clonidine to hyperbaric bupivacaine, even in very small doses, significantly improves the onset and duration of sensory and motor block with relative hemodynamic stability. The 37.5 mcg dose provides maximum benefit and minimum side effects. It is recommended when prolongation of spinal anaesthesia is desired as, for example in patients scheduled for long, lower extremity orthopaedic surgeries, lower abdominal surgeries. The two groups did differ significantly with regard to the mean duration of subarachnoid block.

The comparative result of the study showed that the duration of subarachnoid block by intrathecal administration of 25 mg of tramadol with 0.5% of hyperbaric bupivacaine was significantly shorter in duration than the 37.5 mcg clonidine with 0.5% of hyperbaric bupivacaine group.

## Conclusion

My study has demonstrated that addition of Intrathecal Clonidine to bupivacaine, even in very small doses,

significantly improves the onset and duration of sensory and motor block with relative hemodynamic stability. The 37.5 mcg dose provides maximum benefit and minimum side effects. It is recommended over Intrathecal Tramadol when prolongation of spinal anaesthesia is desired as, for example in patients scheduled for long, lower abdominal and lower extremity orthopaedic procedures.

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