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Original Article

# Comparative Study of Effects of Intrathecal Bupivacaine Plus Clonidine Versus Bupivacaine Plus Normal Saline for Hemodynamic Effects, Motor, and Sensory Blockade for Lower Abdominal Surgeries

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## Abstract

**Aim:** The aim of this study is to compare Effects of Intrathecal Bupivacaine Plus Clonidine Versus Bupivacaine Plus Normal Saline for Hemodynamic Effects,Motor, and Sensory Blockade for Lower Abdominal Surgeries.

**Methodology:** A prospective, randomized,and controlled study of the effect of intrathecal inj clonidine 75 mcg with hyperbaric bupivacaine 0.5% 15 mg (3 ml) for the lower abdominal surgeries was conducted. Group (b), 30 patients received 3 ml of 0.5% hyperbaric bupivacaine 15 mg with 0.5 ml of normal saline.Group (BC), 30 patients received 3 ml of 0.5% of hyperbaric bupivacaine with 75 mcg of inj clonidine. Time of injection to onset of analgesia to T10 level was detected by pin prick method for onset of sensory block.

**Results:** Onset of sensory blockade was rapid in group BC. Sensory block to T10 level at 1 min in Group BC was 100% ,in Group "B" was 56%. The degree of fall of blood pressure in both the groups was similar with P = 0.203 with no statistical significance. Hence, hypotension is not a significant side effect in the present study.The fall in heart rate <50 was 5 in Group BC and 4 in Group B. P = 0.128 is not statistically significant. There was no statistically significant difference in the motor blockade. Duration of analgesia was significantly prolonged in Group BC when compared to Group "B" ,"P" < 0.05 which is statistically significant.

**Conclusions:** It can be concluded that intrathecal clonidine in the dose of 75 mcg in adults along with bupivacaine 0.5% heavy 3 ml, significantly decreases the onset time for sensory blockade and prolongs the duration of post-operative analgesia. It is not associated with any significant side effects and hence can be used as an effective alternative for opioids for prolonging spinal anesthesia.

**Key words:** Bupivacaine, Clonidine, Intrathecal, Lower abdominal surgeries, Normal saline

## INTRODUCTION

Bupivacaine, amide linked local anesthetic with structural formulae 1-N butyle-piperidine; 2-Carboxylic acid 2, 6 dimethyl amide hydrochloride, is a highly lipid soluble substance. The pKa is 8.1 and pH is 3.5. It blocks nerve conduction by decreasing the entry of Na + ions during upstroke of action potential. A small percentage of given dose of Bupivacaine is excreted unchanged in urine. The remainder is metabolized in liver. The N-dealkylated metabolite, pipecolyroxylidine, is found in the urine. Bupivacaine like most local anesthetic agents is relatively free of side effects if it is administered in an appropriate dosage and in the appropriate anatomical location. Systemic toxic reactions to Bupivacaine usually only occur after unintentional intravascular injection or in excessive doses. The symptoms of Bupivacaine-induced

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CNS toxicity include tinnitus, light-headedness, confusion, circumoral numbness, metallic taste, and visual disturbance. If a sufficiently large dose of bupivacaine has been given, tonic clonic grand mal seizures may occur in some cases without premonitory signs. The initial signs of CNS excitement may be followed by generalized CNS depression, with cessation of seizure activity and respiratory arrest.

Clonidine is chemically 2[(2-6 dichlorophenyl) Imino] Imidozoline monohydrochloride. Clonidine is the only clinically available selective alpha-2 agonist with a selective ratio of 220: 1 for alpha-2 receptors. Clonidine is widely used during antihypertensive therapy and as a coanalgesic during chronic pain therapy. In addition, it has been given as adjuvant during spinal, epidural anesthesia and peripheral nerve blocks preferentially in combination with local anesthetics where clonidine amplifies and prolongs the local anesthetics effect. The analgesic effect of clonidine is more potent after neuraxial administration indicating a spinal site of action and favors neuraxial administration. Intrathecal injection of clonidine yields better analgesia accompanied by a 50% reduction in rescue morphine requirements. The clinically effective range intrathecally is 15–30 mcg dose of clonidine added to local anesthetic agent up to a maximum dose of 1 mcg/kg body weight.

## MATERIALS AND METHODS

A prospective, randomized, and control study of the effect of intrathecal inj clonidine 75 mcg with hyperbaric bupivacaine 0.5% 15 mg (3 ml) for the lower abdominal surgeries was conducted at Government general Hospital, Rangaraya Medical College after approval by the hospital ethics committee. The study period was August 2021–February 2022. After written informed consent, patients between ages of 18 and 60 years of ASA grade-1 were selected and divided into two groups of 30 each. Group (B) 30 patients, received 3 ml of 0.5% hyperbaric bupivacaine 15 mg along with 0.5 ml of normal saline to make total of 3.5 ml solution.

Group (BC) 30 patients received 3 ml of 0.5% of hyperbaric bupivacaine along with 75 mcg of inj clonidine to make total 3.5 ml solution.

### Inclusion Criteria

ASA Grade-1 and Age group 16–60 years of both sexes posted for elective lower abdominal operations were included in the study.

### Exclusion Criteria

Local sepsis, bleeding diathesis, raised intracranial tension, comorbid condition such as Valvular heart diseases, diabetes mellitus, obesity, and pregnancy were excluded from the study.

### Study Procedure

1. Written informed consent was obtained from all patients
2. Patients were premedicated on the night before surgery with tab ranitidine 150 mg and tab diazepam 10 mg
3. Before induction of spinal anesthesia, all patients received I.V infusion of Ringer lactate 1000 ml
4. Standard intraoperative monitoring was used (ECG, Pulse Oximetry, and Non-invasive blood pressure)
5. All Emergency drugs and equipment were kept ready.

Under strict aseptic precautions, lumbar puncture was performed using 25 g Quinkie Spinal needle with the patient in left lateral position in L3-L4 inter spinous space. After confirming free flow of CSF, either of the study drugs was injected into the subarachnoid space. Patients were turned supine immediately and were given supplemental oxygen and continued IV fluids.

### Observations Made Were:

Time of onset of analgesia: Time of onset of injection of local anesthetic intrathecally to onset of analgesia to T10 level. Sensory Blockade was detected by pin prick method.

Total duration of analgesia: Time taken from the onset of analgesia to the point of the time where patient complained of pain at operative site requiring rescue analgesics.

Motor blockade was assessed: Onset of motor blockade, complete blockade, and complete recovery of motor blockade, as per the Bromage Score [Table 1]. Total duration of motor blockade was defined as time taken from onset of motor blockade to complete recovery from motor blockade.

Hypertension is noted when the fall of BP >20% from base level, which was counteracted by rapid fluid administration and finally intravenous inj mephenteramine as demanded by the situation. Bradycardia was noted when the heart rate was <50 beats/min which was counteracted by inj atropine 0.5 mg.

## RESULTS

Of the 60 patients, 30 patients belong to Group BC were given, 3 ml of 0.5% bupivacaine with 75 mcg of clonidine

**Table 1: Bromage score (page 4 of topic)**

| | | |
|---|---|---|
| Grade I | Free movement of legs and feet | Nil |
| Grade II | Just able to flex knees with free movement of feet | 33% |
| Grade III | Unable to flex knees but with free movement of feet | 66% |
| Grade IV | Unable to move legs or feet | Complete 100% |

and patients belonging to Group B were given 3 ml of 0.5% bupivacaine + 0.5 ml of normal saline.

There was no significant difference in the demographic data [Table 2 and Figure 1] as for mean age, male and female ratio, body weight, and the type and duration of surgical procedures in two groups.

All the patients were tested for level of blockade before starting the procedure till deemed adequate for surgery. No patients in either groups required conversion to general anesthesia or additional analgesics during surgery. Sensory blockade at 1 min was statistically significant. Onset was rapid in group BC. Sensory block to T10 level at 1 min in Group BC was 100% where as in Group "B" was 56% [Table 3]. Hence, this is statistically significant. The duration of analgesia is significantly prolonged in Group BC when compared to Group "B," the "*P*" < 0.05 which is statistically significant [Tables 4 and 5, Figure 2].

There was no statistically significant difference in the motor blockade.

There was no significant statistical difference at 5 min interval in both groups for motor as well as sensory blockade [Figure 3].

Hemodynamic characteristics: The fall in blood pressure of more than 20% of the pre-operative level was treated with mephentermine in both groups. In the present study, the fall of blood pressure was 8 in Group BC and 9 in Group B. The degree of fall in both groups was similar in both groups without any statistical significance. *P* = 0.203. Hence, the hypotension is not a significant side effect.

The fall in heart rate <50/min was treated with atropine. The fall in heart rate was 5 in Group BC and 4 in Group "B" [Table 6 and Figure 4].

Atropine users: patients in whom atropine was given for bradycardia.

Atropine non-users: patients in whom there was no bradycardia.

*P* = 0.128, it is statistically not significant.

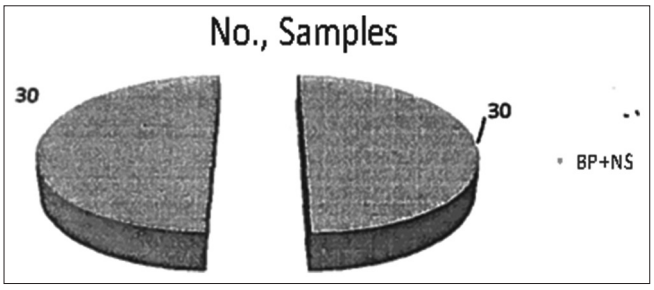


**Figure 1: Demographic variables (Page 5 of Topic)**

**Table 2: Demographic variables (page5 of Topic)**

| Intervention | No. Samples |
|---|---|
| BP+NS | 30 |
| BP+CL | 30 |
| Grand total | 60 |

**Table 3: Sensory level at 1 min (page 5 of Topic)**

| | <T10 | >T10 | Total |
|---|---|---|---|
| Group BC | 30 | 0 | 30 |
| Group B | 17 | 13 | 30 |
| Total | 47 | 13 | 60 |

## DISCUSSION

Clonidine, an alpha 2 receptor agonist, is widely used during antihypertensive therapy and as a coanalgesic during chronic pain therapy. Clonidine is also used preferentially in combination with local anesthetics where it amplifies and prolongs the local anesthetics effect.

Clonidine has been demonstrated repeatedly to prolong sensory and motor block along with intrathecal local anesthetics. For example, 178 patients from five studies,[1-5] randomized to receive spinal 13.75–15 mg bupivacaine alone or with clonidine (mean dose 146 mcg, range 75–225 micro g) experienced 31% longer sensory and

**Table 4: Duration of analgesia (page 5 of Topic)**

| | Group BC | Group B |
|---|---|---|
| Range | 3.1–5.5 h | 1.5–2.3 h |
| Mean | 3.907 h | 2.058 h |
| Variance | 0.233 | 0.072 |
| S.D | 0.054 | 0.005 |

**Table 5: Statistical analysis (page 5 of Topic)**

| | Variable 1 | Variable 2 |
|---|---|---|
| Mean | 3.907 | 2.058333333 |
| Variance | 0.233573448 | 0.072772989 |
| Observations | 30 | 30 |
| Pooled variance | 0.153173218 | |
| Hypothesized mean difference | O | |
| Df | 58 | |
| t Stat | 18.29417467 | |
| P (T≤t) one-tail | 4.60439E-26 | |
| tCritical one-tail | 1.671552763 | |
| P (T≤t) two-tail | 0.0000000000 | |
| t Critical two-tail | 2.001717468 | |

motor block when clonidine was added (mean duration of sensory/motor block with bupivacaine alone of 2.5/2.4 h compared with 3.7/3.3 h with clonidine). Similar results are reported with addition of clonidine to smaller doses of bupivacaine.[4,6-12]

Elia *et al.*[13] added clonidine to intrathecal local anesthetics such as bupivacaine, mepivacaine, prilocaine, and tetracaine; they assessed the harmful and beneficial effects of clonidine when used as an adjuvant to intrathecal local anesthetics to surgery and concluded the study which may serve as a rational basis to help clinician whether or not to continue clonidine with intrathecal local anesthetics.

Intrathecal injection of local anesthetics reduces blood pressure primarily by reducing sympathetic outflow. Because this effect is near maximal with doses of local anesthetics causing surgical anesthesia, one would not expect greater degrees of hypotension from clonidine-induced sympatholysis when it is added to local anesthetics. Indeed, maximal decreases in blood pressure and incidence of treatment with vasoconstrictors are only slightly increased from addition of 75–225 mcg clonidine to 15 mg bupivacaine (18% decrease in blood pressure and 24% incidence of ephedrine treatment with bupivacaine alone compared with an 18% decrease in blood pressure and 35% incidence of ephedrine treatment with bupivacaine plus clonidine [$n$ = 178]). In the present study with 15 mg bupivacaine and also with 75 mcg clonidine addition, the incidence of decrease in bp is comparable.

Dobrydnjov *et al.*[14] tried with low dose bupivacaine 6 mg, and low dose clonidine mcg, and 30 mcg for herniorrhaphy but the results when compared with the present study, there was insufficient sensory level for five cases of hernia surgery in their study.

van Tuijl *et al.*[15] demonstrated that the addition of 75 mcg clonidine to hyperbaric bupivacaine prolongs spinal analgesia and the motor block for cesarean section and improves early analgesia but did not improve the morphine requirements in the post-operative period.

Strebel *et al.* reported that[16] clonidine prolongs spinal anesthesia.[2,4,5]

Results of the present study are in agreement with these previous studies; however, these investigators used clonidine at doses of up to 450 mcg, the present study focused on smaller doses 75 mcg).

Clonidine is used many ways; it can be used oral, intra muscular, intravenous, epidural, and intrathecal for

**Table 6: Hemodynamic characteristics (page 6 of Topic)**

| | Patients with bradycardia | Patients without bradycardia | Total |
|---|---|---|---|
| Group BC | 5 | 25 | 30 |
| Group B | 4 | 26 | 30 |
| Total | 9 | 51 | 60 |

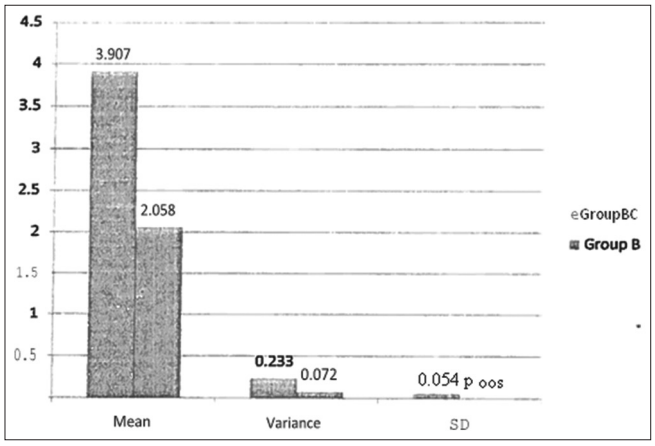


**Figure 2: Duration of analgesia (Page 5 of Topic)**

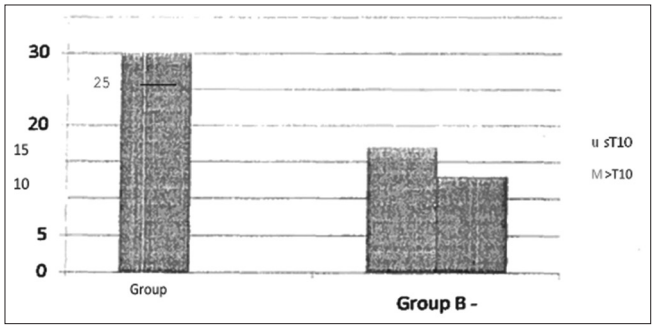


**Figure 3: Sensory block at 5 min was T4–T6 in both groups (Page 5 of Topic)**

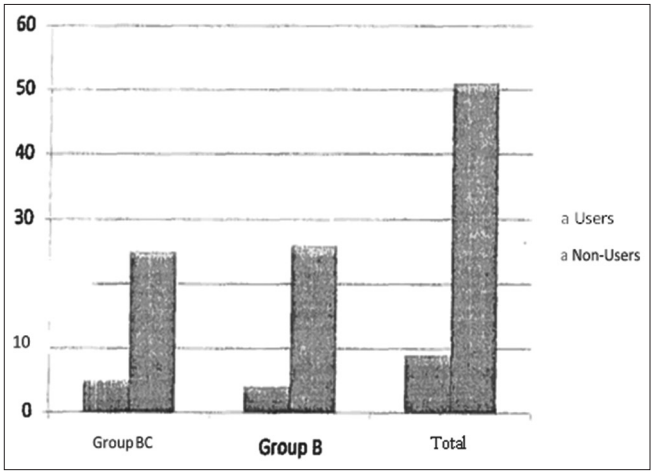


**Figure 4: Atropine non users in whom there was no bradycardia (Page 6 of Topic)**

obtaining the therapeutic results. However, the outcome of administration of the same drug by various routes yields different clinical results.

There were attempts to use the drug by Dobrydnjov *et al.*[17] by oral and intrathecal route for post-operative pain relief, following intrathecal Bupivacaine and they assessed the morphine requirements in the post-operative period. They concluded that addition of intrathecal clonidine prolonged analgesia and decreased morphine consumption postoperatively more than oral clonidine. Hypotension was more pronounced after oral than after intrathecal clonidine. Intrathecal clonidine is, therefore, recommended.

In clinical practice, intrathecal clonidine added to Bupivacaine is an interesting alternative to intrathecal opioids, due to a reduction of adverse effects such as respiratory depression nausea, vomiting, urinary retention, and pruritus. Further, clonidine does not potentiate opioid-induced respiratory depression, as clonidine and morphine act at different sites when mediating their analgesic effects.

Elsenach *et al.*,[18] compared the analgesic effects of intrathecal and IV clonidine with acute noxious stimulation. The data supported the value of intraspinal administration of clonidine for the treatment of acute pain and pain states associated with hyperalgesia. Analgesia from systemic administration of this drug is weak and they concluded that spinal rather than IV injection of clonidine is useful for analgesia. Hence, the present study proved the analgesic effect of intrathecal administered clonidine by prolonging the duration of analgesia of inj Bupivacaine.

Chiari *et al.*,[19] and FIIos *et al.*[20] observed the analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent during first stage of labor and concluded although duration and quality of analgesia were more pronounced the high incidence of hypotension limited its use and present study by supplementing the inj clonidine intrathecally along with the inj bupivacaine, balanced and offset the undue effects of inj clonidine if it was to be used alone intrathecally.

Merivirta *et al.*[21] conducted a study for unilateral analgesia after intrathecal inj bupivacaine 5 mg and intrathecal inj clonidine 15 mcg and concluded that unilateral spinal block can be achieved by combining l5 mcg of clonidine with 5 mg of hyperbaric bupivacaine. There was a small improvement in the quality of anesthesia, but, in contrast, clonidine prolonged the motor block and increased the need for vasopressors. In the present study, inj bupivacaine along with clonidine achieved sensory and motor block sufficient for the lower abdominal operations and 30% of patients required treatment for hypotension.

However, marked hemodynamic changes may limit the usefulness of intrathecal clonidine administered together with the local anesthetic, for post-operative pain relief.

The pharmacokinetic profile is consistent with rapid onset and limited distribution. Hence, 75 mcg of clonidine was selected in the present study. Intrathecal clonidine when combined with local anesthetics prolongs the sensory and motor blockade, produces analgesia for longer duration. In the present study, the analgesia achieved was for longer duration. The analgesia achieved in Group BC was 3.907 h and in Group "B" was 2.058 h. There is significant prolongation of the duration of analgesia which is beneficial, as it reduces the requirements of post-operative opioids and analgesics. Side effects with opioids are more like pruritis, respiratory depression, post-operative nausea and vomiting, constipation, and urinary retention.

Hence, there is definite advantage of clonidine which is devoid of above side effects.

It is suggested that 75 mcg clonidine may be an appropriate dose to combine with Bupivacaine as a single bolus.

## CONCLUSION

From the present study, intrathecal clonidine in the dose of 75 mcg in adults along with bupivacaine 0.5% heavy 3 ml, significantly decreases the onset time for sensory blockade and prolongs the duration of post-operative analgesia. It is not associated with any significant side effects and hence can be used as an effective alternative for opioids for prolonging spinal anesthesia.

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