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# A comparison of intrathecal clonidine and buprenorphine as spinal anesthesia adjuvant for abdominal and lower limb surgeries

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## ABSTRACT

**Background:** Many intrathecal adjuvants are being used with local anesthetics to prolong the intraoperative anesthesia and postoperative analgesia. Clonidine and buprenorphine are known to potentiate the effects of local anesthestics. **Aims and Objectives:** This study was designed to compare the duration of postoperative analgesia as well as duration of sensory and motor block onset, intraoperative hemodynamic changes, and perioperative complications between buprenorphine and clonidine when used as an adjuvant to intrathecal hyperbaric bupivacaine. **Materials and Methods:** A randomized double-blind study for 80 patients undergoing lower abdominal surgeries and lower limb surgeries was designed with Group B receiving 50 mcg of buprenorphine and Group C receiving 50 mcg of clonidine with 15 mg of hyperbaric bupivacaine 0.5%. Student's t-test and Chi-square were used for comparing the data. **Results:** The time of onset of duration of post-operative analgesia as well as sensory and motor block was significantly higher in buprenorphine group as compared to clonidine group. In present study, incidence of bradycardia as well as hypotension was significantly higher in group C as compared to group B ($P<0.05$). **Conclusion:** Addition of intrathecal buprenorphine and clonidine potentiates the duration of analgesia, sensory and motor block, with buprenorphine has a longer analgesic effect when compared to clonidine.

**Key words:** Buprenorphine; Clonidine; Bupivacaine; Spinal

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## INTRODUCTION

Karl August Bier[1] introduced spinal anesthesia in clinical practice in 1898. It is still the most popular technique for surgical procedures such as cesarean section, lower abdominal surgeries, orthopedic, and urological surgeries. Although it is easy to perform and provides fast onset and effective sensory and motor block, it has a limited duration of action. Many adjuvants have been tried to prolong the duration of surgeries and delay the onset of pain. Buprenorphine is a synthetic opioid which acts on the μ opioid receptors situated in the substantia gelatinosa of the dorsal horn of the spinal cord. Intrathecally, it improves both the duration and quality of postoperative analgesia. However, at higher doses, intrathecal buprenorphine has been associated with dose-related side effects such as pruritis, nausea, vomiting, and respiratory depression.[2-4]

Clonidine is an $\alpha 2$ agonist that has been extensively studied as an adjuvant to intrathecal bupivacaine for post-operative analgesia. Clonidine acts postsynaptically situated $\alpha 2$ adreno receptors in the dorsal horn of the spinal cord. However, intrathecal clonidine has again been known to cause dose-related side effects such as bradycardia, hypotension, dryness of mouth, and somnolence.[5]

This study was designed to compare the efficacy of doses of intrathecal buprenorphine and intrathecal clonidine as an adjuvant in spinal anesthesia. The duration of post-operative analgesia was the primary outcome of the study, along with these other measures like onset of motor and

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sensory block, duration of sensory block, motor block, the effect on heart rate (HR), blood pressure, respiratory rate, were evaluated as other outcomes. Also, any adverse effects were noted.

### Aims and objectives

To find and compare the safety and efficacy of clonidine and buprenorphine as spinal anaestheisa adjuvant for abdominal and lower limb surgeries.

## MATERIALS AND METHODS

After ethics committee approval of Subbaiah institute of medical sciences, Shimoga, a prospective randomized double-blind study was conducted over a period of 3 months on 80 patients to assess the duration of post-operative analgesia as well as the duration of sensory and motor blockage in patients receiving intrathecal buprenorphine and clonidine as adjuvant to bupivacaine. Along with these objectives the effect on onset of motor and sensory block and any associated side effects were also assessed. Patients under ASA 1 and 2 in the age bracket of 18–60 years of either gender, undergoing lower abdominal surgeries and lower limb surgeries like appendectomy, inguinal hernia repair, varicose veins surgeries, hysterectomy, femur and tibia fractures and knee arthroscopy were included in the study. Patients with severe systemic diseases, history of allergy to the medications used, patients on $\beta$ blockers, $\alpha 2$ agonists, basal HR $\leq$50/min, pregnant and lactating women, obesity- body mass index $\geq$30 were excluded from the study. All patients were evaluated preoperatively in the pre-anaesthetic clinic. The patients were familiarized with visual analogue scale (VAS) and its use in post-operative pain.

Randomization was achieved by a computer-generated random number table. Random groups assigned were enclosed in a sealed opaque envelope to ensure concealment of allocation sequence. After shifting the patient inside the operation theatre, the sealed envelope was opened by an anaesthesiologist not involved in the study, to prepare the drug solution according to randomization, in a sterile bowl. The observer who collected the perioperative data as well as the patients were blinded to the drug solution administered. The patients were divided into 2 groups, group B received 50 mcg of buprenorphine with 3 mL of 0.5% heavy bupivacaine and group C received 50 mcg of clonidine with 3 mL of 0.5% heavy bupivacaine. The patients were fasted for 6 h before the surgery. Electrocardiogram, pulse oximetry, and non-invasive blood pressure monitors were attached, and base line readings were noted. Intravenous cannulation was done with 18G cannula and Ringer lactate was started.

Lumbar puncture was performed with a standard technique at L2-L3 or L3-L4 interspinous space. After the subarachnoid injection, pulse rate, blood pressure and respiration rate were monitored immediately, at 5 min and then every 10 min for the rest of surgical procedure. Primary objective of Duration of post-operative analgesia was assessed along duration of sensory block and the motor blockade in both group B and group C along were assessed as secondary objectives. The sensory and motor onset was also assessed in both the groups. Pain was assessed by VAS. Sedation was assessed by Ramsay sedation score[6] (Table 1).

Incidence of side effects like nausea, vomiting, shivering, dryness of mouth, urinary retention and itching were monitored and recorded. Time of onset of block, i.e., from completion of spinal injection to achieving T10 block (in minutes) was recorded. Maximum height of block (sensory) by using pinprick (tooth prick) was recorded every 30 s. Haemodynamic parameters were recorded every 5 min during surgery and every 30 min during postoperative period. Time to attain highest motor blockade was recorded by using modified Bromage Scale[7] (Table 2).

Duration of sensory block was recorded as regression of block to L1, using pinprick method. Duration of motor blockade was recorded as time required attaining a Bromage Score (BS) of 1. Duration of postoperative analgesia was recorded by using[8] VAS (Table 3) during postoperative period every 30 min.

**Table 1: Ramsay sedation scale**

| Score | Definition |
|---|---|
| 1 | Anxious and agitated or restless or both |
| 2 | Cooperative, oriented, and tranquil |
| 3 | Responds to commands only |
| 4 | Brisk response to a light glabellar tap or loud auditory stimulus |
| 5 | Sluggish response to a light glabellar tap or loud auditory stimulus |
| 6 | No response to a light glabellar tap or loud auditory stimulus |

**Table 2: Modified Bromage scale**

| Grade | Criteria |
|---|---|
| 1 | Free movement of legs and feet |
| 2 | Just able to flex knees with free movement of feet |
| 3 | Unable to flex knees, but with free movement of feet |
| 4 | Unable to move legs or feet |

**Table 3: Visual analog scale**

| 0 | No pain |
|---|---|
| 1–3 | Mild pain |
| 4–6 | Moderate pain |
| >6 | Severe pain |

Bradycardia (HR <60/min) was treated with injection atropine 0.6 mg i.v., if accompanied with hypotension. Intraoperative hypotension was defined as a fall in mean arterial pressure (MAP) more than 20% from baseline. It was treated with i.v. fluid bolus of 200 mL Ringer lactate and injection mephentermine 6 mg i.v., if required.

Post-operatively, vital signs were monitored on every two hourly basis upto24 h. Rescue analgesic of inj. Tramadol 100 mg I V was given at VAS score of 4 and above.

## RESULTS

A total of 80 patients with comparable demographic features (Table 4) were divided into 2 groups, Group B and Group C.

The onset of sensory anaesthesia (Table 5) in group B was 3.66±1.002 min in comparison to group C which was 3.42±0.97 min. The onset of motor anaesthesia in group B was 4.32±1.2 min and in group C was 4.02±0.98 min. Mean time of regression to sensory level L1 in group B was 242.6±33 min whereas in group C was 226.2±36.8 min. Mean time to attain modified BS of 1 in group B was 282±46.7 min and in group C was 248.6±42.6 min. Mean time of first dose of rescue analgesic was 548±48 min in group B and 434±54 min in group C.

Incidences of side effects were comparable (Table 6) in both the groups. Four patients in group B and three patients in group C had sedation. Nausea was noted in 4 patients in group B and 3 patients in group C. Vomiting was noted in 1 patient in group B. 3 patients in group C had bradycardia and were treated with inj Atropine 0.6 mg. Hypotension was noted in 1 patient in group B and 2 patients in group C and were treated with inj mephentermine 6 mg IV bolus.

**Table 4: Comparison of demographic profile and duration of surgery**

| Demography and Sx duration | Group B | Group C |
|---|---|---|
| Age (years) | 50.64±10.2 | 49.6±7.8 |
| Height (cm) | 158±3.96 | 157±4.2 |
| Weight (kg) | 58.25±7.5 | 59.2±7.74 |
| Surgery duration (min) | 114.7±28.6 | 116.4±27.9 |
| Male/female | 26/24 | 27/23 |

## DISCUSSION

Spinal anesthesia is one of the most frequently used techniques for lower abdominal and lower limb surgeries with post-operative analgesia being a major advantage of spinal anesthesia. Adjuvants like ketamine, neostigmine, clonidine, benzodiazepines like midazolam, opioid like morphine, pethidine, and fentanyl have been used.[9] Side effects of each drug led to the search of newer and safer options.

Buprenorphine, a synthetic partial agonist opioid, acts on the μ opioid receptors situated in the substantia gelatinosa of the dorsal horn of the spinal cord. When used intrathecally, it has improved both the duration and quality of postoperative analgesia. However, the use of higher doses of intrathecal opioids has been associated with dose-related side effects like pruritis, nausea, vomiting and respiratory depression as reported in previous studies.[2-4] A lipid soluble non-ionised drug like buprenorphine passes rapidly via the arachnoid granulation into venous and lymphatic vessels, which allows a minimal increase of cerebrospinal fluid concentration with a minor risk of respiratory depression.

Clonidine, which is an alpha2-adrenergic agonist, has central brain stem action and peripheral action.[10] Hypothalamic alpha 2-adrenoceptors are inhibitory and cause decrease in outflow from the vasomotor centers and sympathetic centers. This explains the resultant decrease in peripheral vascular resistance, HR, blood pressure, and cardiac output. Extradural analgesic action is because of postsynaptic activation of descending inhibitory pathway that synapses into dorsal horn of spinal cord.[11] However, unlike spinal opioids, clonidine does not produce pruritus or respiratory depression. It also prolongs the sensory blockade.[12-14] It also reduces the amount or concentration of local anesthetic required to produce postoperative analgesia.[15]

In our study, mean duration of sensory block was observed to be 242.6±33 min in group B and it was statistically higher as compared to group C (226.2±36.8 min). Arora et al.,[16]

**Table 5: Comparison of study parameters**

| Study parameters | Group B | Group C | P-value |
|---|---|---|---|
| Onset of sensory anaesthesia (min) | 3.66±1.002 | 3.42±0.97 | >0.05 |
| Onset of motor anaeathesia (min) | 4.32±1.2 | 4.02±0.98 | >0.05 |
| Mean time to sensory level L1 (min) | 242.6±33 | 226.2±36.8 | <0.01 |
| Mean time to attain Bromage score of 1 (min) | 282±46.7 | 248.6±42.6 | <0.01 |
| Mean time of first rescue analgesic (min) | 548±48 | 434±54 | <0.05 |

**Table 6: Comparison of side effects in the two groups**

| Side effects | Group B (%) | Group C (%) |
|---|---|---|
| Sedation | 4 (10) | 3 (7.5) |
| Nausea/vomiting | 5 (12.5) | 3 (7.5) |
| Bradycardia | 0 | 3 (7.5) |
| Hypotension | 1 (2.5) | 2 (5) |

also documented similar findings and duration of sensory blockade was significantly higher (P<0.05) with addition of buprenorphine as compared to clonidine to bupivacaine. The longer duration of action of buprenorphine can be attributed to its high affinity for opioid receptor and high lipid solubility.[17]

Mean duration of motor block was significantly prolonged (P<0.05) with addition of buprenorphine (282±33 min) than that with clonidine-bupivacaine (248.6±42.6 min). This observation in the present study supported by observation of Arora et al.,[16] who also compared buprenorphine and clonidine and observed statistically significant prolonged duration of motor block with buprenorphine (262±46.7) than clonidine (228.6±46.7)[12] We found delay in onset of sensory block in buprenorphine bupivacaine group (3.66±1.002 min) than in clonidine-bupivacaine (3.42±0.97 min). Arora et al., also observed similar delayed onset of sensory block with addition of buprenorphine to bupivacaine as compared to bupivacaine alone. Benhamou et al.,[18] also demonstrated that clonidine increased the spread of the sensory block, intraoperatively. Nicol and Holdcroft[19] tried to explain this in their study on parturient, postulating that because clonidine becomes slightly hypobaric at body temperature, rostral spread might have occurred with the patient in the sitting position for several minutes after the intrathecal injection. Singh et al.,[20] observed statistically significant (P<0.05) difference i.e., addition of buprenorphine to bupivacaine delayed onset of sensory block significantly as compared with addition of clonidine.

We also observed delay in onset of motor block in buprenorphine group (4.32±1.2 min) as compared to clonidine group (4.02±0.98 min). We observed incidences of bradycardia (about 7.5%) which required treatment and hypotension requiring treatment in group C as compared to group B. Similar findings were noted by Manuraj et al.,[21] where sustained decrease in the pulse rate with the addition of clonidine. This finding correlates with the observations of Sonya et al.,[17] who also observed fall in HR and MAP more with clonidine than that with buprenorphine added to bupivacaine. The action of clonidine on α2 adrenoceptors which are inhibitory and causes decrease in outflow from vasomotor centers and sympathetic center explains this finding as this effect is lacking with the buprenorphine.[22] However, the incidence of significant hypotension and bradycardia was significantly higher (50%) with clonidine as an adjuvant to bupivacaine (P<0.05) when compared with buprenorphine. This higher incidence of hypotension and bradycardia in present study with clonidine is clearly attributable to α1 agonistic action of clonidine. This finding was similar to the findings of Negi et al.[20] Incidence of nausea and vomiting was higher in Group B when compared to group C, which is due to the activation of mu receptors. Mean duration of post-operative analgesia in group B was 548±48 min whereas in group C (434±54 min) the observed difference was statistically highly significant (P<0.001). Similar findings were found in the study conducted by Bakshi et al.,[23] and Ramya et al.[24]

### Limitations and study

The major limitation of the study is that investigator cannot objectively quantify the post operative pain.

## CONCLUSION

Intrathecal buprenorphine as well as intrathecal clonidine as adjuvants to hyperbaric bupivacaine provide prolonged duration of anesthesia and post-operative analgesia. A low dose of buprenorphine has better efficacy in terms of longer analgesic effect and decreased requirement of supplemental analgesics in comparison to low dose of clonidine. Also, buprenorphine provides significantly stable intraoperative hemodynamic and more prolonged duration of block and post-operative analgesia as compared to clonidine with lesser incidence of side effects. Delayed onset and prolonged fixation time when compared to clonidine can be considered as a limiting factor. The results show a definitive prolongation of both sensory and motor blockade of spinal anesthesia in buprenorphine group when compared to clonidine group.

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**Author's Contribution:**
**NPL** and **CK**- Concept and design of the study; **MBN**- Interpreted the results; reviewed the literature; **KM**- Concept, coordination, statistical analysis and interpretation, preparation of manuscript and revision of the manuscript.

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