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# Efficacy of clonidine as an additive to levobupivacaine for epidural anesthesia and post-operative analgesia in infraumbilical surgeries – A randomized and double blind study

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## ABSTRACT

**Background:** Epidural anesthesia as a safe alternative to general anesthesia is commonly used for inducing anesthesia and post-operative analgesia in patients undergoing infraumbilical surgeries. The addition of an adjuvant not only increases the effectiveness of a local anesthetic by prolonging and intensifying the sensory blockade but also causes reduction in the dose of rescue analgesic agent in post-operative period. Clonidine is a potent and selective α-2-adrenoceptor agonist with analgesic potency. **Aims and Objectives:** This study was conducted to evaluate the efficacy of clonidine as an additive to levobupivacaine in infraumbilical surgeries. **Materials and Methods:** One hundred patients of American Society of Anesthesiologists Grade I or II who were undergoing infraumbilical surgery were randomly divided into two groups as levobupivacaine (L) and levobupivacaine with clonidine (LC). Patients were allocated to one of the two groups by computer generated random selection. Group L received 0.5% levobupivacaine (1.5 mg/kg) and Group LC received 0.5% levobupivacaine (1.5 mg/kg) with clonidine (2 μg/kg). The onset time for sensory, motor blockade, duration of anesthesia and duration of analgesia, and Visual Analog Scale (VAS) score were observed in both the groups. The hemodynamic variables such as heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation at various time intervals were measured. Any untoward side effects were noted in both groups. **Results:** The onset of sensory (7.8 ± 1.7 min) and motor blockade (10.9 ± 1.9 min) were significantly faster in clonidine group. Duration of anesthesia and duration of analgesia were prolonged in Group LC (234.5 ± 16.1 min, 412.8 ± 48.3 min) compared to Group L (173.56 ± 12.78 min, 269.2 ± 24.2 min) which was statistically significant ($P < 0.05$). Similarly, clonidine group had less VAS score compared to control group. There was no significant change in the hemodynamic variables between the two groups. Hypotension and bradycardia were found more in clonidine group compared to the control group. **Conclusion:** Clonidine as an adjuvant to levobupivacaine prolongs the post-operative analgesia and the duration of anesthesia for infraumbilical surgeries.

**Key words:** Anesthesia; Analgesia; Clonidine; Epidural; Infraumbilical surgeries; Levobupivacaine

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## INTRODUCTION

Pain management during surgery and post-operative period is an uphill task for an anesthesiologist and many breakthroughs have happened to alleviate pain. Epidural anesthesia remains the standard of care in many of the centers in our country. The advantages include early mobilization and a reduced risk of deep vein thrombosis and decreased post-operative pulmonary complication.[1]

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Various adjuvants such as epinephrine, fentanyl, morphine, neostigmine, midazolam, and clonidine have been used to reduce the dose of local anesthetic agents. However, the use of adjuvants brings their own side effects; hence, search for an adjuvant continues which would have best potentiating power; while having reasonable side effect profile. Levobupivacaine is preferred because of its less cardiotoxic effects.[2] Similarly, the susceptibility for seizure activity with levobupivacaine is 1.5–2.5 times less than that of racemic bupivacaine.[3] Alpha-2-agonist exerts their analgesic activity in the spinal cord by activating the post-ganglionic alpha 2 receptors in the substantia gelatinosa of the spinal cord. In our prospective, randomized, and double blind study, we aimed to evaluate clonidine, used as an adjuvant with levobupivacaine 0.5% for its analgesic efficacy and side-effects/safety profile in infraumbilical surgeries.

### Aims and objectives

The aim of the study was to evaluate the efficacy of clonidine as an adjuvant to levobupivacaine in terms of:

- Primary objectives
  1. Duration of sensory blockade
  2. Duration of postoperative analgesia.
- Secondary objectives
  1. Onset of sensory blockade
  2. Onset and duration of motor blockade.

## MATERIALS AND METHODS

This prospective, comparative, single-center, and clinical study was pre-approved by the Institutional Ethics Committee (IEC) for the final permission (vide letter no. 125-140/Bio/Ethical/MC/03/13). After obtaining the permission of IEC, the study was conducted in a medical college hospital of central India. Well informed written consent was obtained from the selected patients over the period of 1 year.

### Inclusion criteria

For the present study, 100 American Society of Anesthesiology physical status I-II patients between the age group 25–60, undergoing elective infraumbilical surgery were enrolled in this prospective, randomized, and double blinded study as described in Figure 1.

### Exclusion criteria

Patients with history of allergy to any of the study drugs, contraindications to neuraxial anesthesia, cardiovascular disease (NYHA Grade III and IV), psychiatric illness or mental retardation, renal or hepatic impairment, and pregnant patients were excluded from the study. Patients were randomly allocated to one of the two groups by computer generated random selection as below:

- Group levobupivacaine (L) – Levobupivacine 0.5% 1.5 mg/kg
- Group levobupivacaine with clonidine (LC) – Levobupivacine 0.5% 1.5 mg/kg + Clonidine 2 μg/kg.

The patients along with the primary investigator and recovery room nurse/observer involved in the treatment of the patients were blinded regarding the study group allocation throughout the study period using online randomization tool and allocation concealment method. Pre-anesthetic evaluation was done and the entire procedure along with Visual Analog Scale (VAS) was explained to the patient 1 day before the surgery and a fasting status of 8 h was ensured. Premedication consisted of oral alprazolam 0.25–0.5 mg night before and on the morning of surgery. Patient was shifted to the operation theater and routine monitors such as non-invasive blood pressure, electrocardiography, and pulse oximetry were attached. Baseline non-invasive blood pressure, heart rate (HR), respiratory rate, and oxygen saturation ($SpO_2$) on room air were recorded. An 18-gauge intravenous line was secured and ringer lactate infusion was started. Epidural catheter was threaded after loss of resistance (LOR) confirmation in sitting position. Appropriate drugs were given to patients epidurally.

The onset of sensory block was assessed using the ether-soaked gauze for every 2 min till complete loss of sensation at T8.

Motor blockade was assessed every 2 min using the modified Bromage Scale till score of 3 was achieved.[4]
0 – Bilateral sustained straightening of leg;
1 – Unable to straighten leg;
2 – Just able to flex knees;
3 – Foot movement only;
4 – Complete paralysis.

Time to two segment regression of analgesia to pin prick from the highest level achieved was considered as duration of anesthesia.

Sedation was evaluated by Ramsay Sedation Score.[5]
1 – Patient anxious and agitated or restless;
2 – Cooperative, oriented, and tranquil;
3 – Responds to commands only;
4 – Brisk response to glabellar tap or loud auditory stimulus;
5 – Sluggish response to light glabellar tap or loud auditory stimulus;
6 – No response.

Patients were monitored by systolic and diastolic blood pressure, HR, respiratory rate, and $SpO_2$ at 5 min, 15, 30, 45, 60, 90, 120, 180, 240, 300, and 360 min. Bradycardia

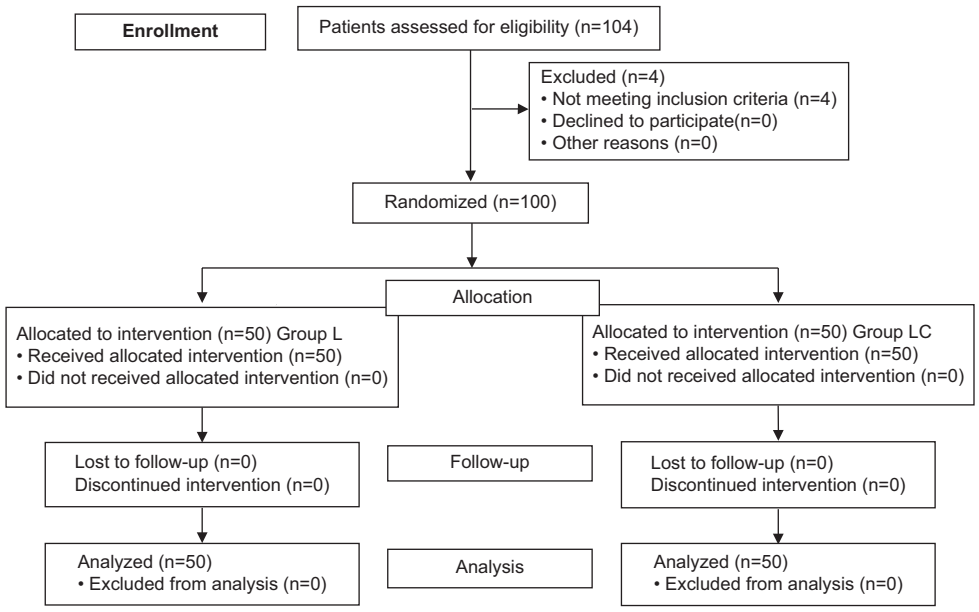


**Figure 1:** Consort flowchart

was defined as HR <50 beats/min and was treated with IV Atropine 0.6 mg.

A patient in whom there was inadequate sensory or motor blockade general anesthesia was to be administered and such cases were to be excluded. In this study, we did not have to administer general anesthesia to any of the patients as rescue anesthetic plan.

VAS was used to assess pain.[6] Patients were educated about the scale (0 being no pain and 100 being the worst possible pain). The time, when the patient first complained of pain, was considered as duration of analgesia and injection diclofenac sodium 75 mg was administered in 100 ml normal saline as rescue analgesia. Further analgesia was given as per the institutional acute post-operative pain service protocol.

Any side effects that occurred during the surgery or during the post-operative period were noted. After the surgery, the patients were shifted to the post-operative ward and the monitoring was continued. Episodes of nausea, vomiting, shivering, bradycardia, hypotension, and respiratory depression were observed.

The study parameters were defined as follows:

1. Onset of sensory block: Time interval from epidural drug administration time to achieve T8 blockade
2. Duration of analgesia: Time interval from onset of sensory block to requirement of first rescue analgesia
3. Onset of motor block: Time interval from epidural drug administration time to Bromage scale 3
4. Duration of motor block: Time interval from onset of motor block to attainment of complete movements (Bromage 0) in both lower limbs.

### Statistical analysis

The statistical analysis of the data was carried out using Statistical Package for the Social Sciences Inc., Chicago, IL, version 17.0 for Windows. All quantitative variables were estimated using mean and standard deviation; Scores or skewed data were presented as median or IQR. Normality of data was checked by measures Kolmogorov–Smirnov tests of normality. For normally distributed data, means of quantitative variables of two groups were compared using student t-test. For skewed data or scores, Mann–Whitney test was applied. $P<0.05$ was considered as statistically significant and $P>0.05$ was considered as statistically insignificant.

## RESULTS

### Demographic data

The age, weight, height, and duration of surgery were comparable in both groups (Table 1).

### Onset of sensory/motor blockade

The mean time for onset of sensory blockade in control and clonidine group was 15.9±2.3 min and 7.8±1.7 min (CI: 7.2–8.9, P=0.0001). Similarly, the mean time for onset of motor blockade in control group was 19.8±2.3 min whereas clonidine group was 10.9±1.9 min (CI: 8.6–9.7, P=0.0001) where clonidine group had a faster onset of action (Table 2).

### Duration of anesthesia/analgesia

The duration of anesthesia in Group L and Group LC was 173.5±12.7 min and 234.5±16.1 min (CI: 66.7–55.2). The difference in the total duration between the two groups

was significantly higher in clonidine group (P=0.0001). Similarly, the total duration of analgesia in the clonidine group (412.8±48.3 min) was significantly higher when compared to the control group (269.2±24.2 min) (CI: 158.7–128.4, P=0.0001) (Table 3).

The VAS score at the time of first analgesic request was 48.7±10.1 in control group and 41.5±7.3 in clonidine group. There was a significant lower VAS score in clonidine group compared to the control group (P=0.0001).

### Hemodynamic variables

Parameters such as HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, and $SpO_2$ showed no significant changes at various time intervals between the two groups. Although there was a greater fall in SBP and DBP in the clonidine group, the change was insignificant (Tables 4-6).

### Complications

In the present study, Ramsay sedation score of 2 was observed in 56% and 16% of the patients in Group LC and Group L, respectively. Sedation score of 1 was observed in 44% of patients in Group LC and 84% of patients in Group L.

This study also observed that the incidence of hypotension and bradycardia was more in clonidine group (8%, 4%) compared to the control group (2%, 0%). Shivering was more common in the control group (8%) compared to the clonidine group (2%).

## DISCUSSION

In the present study, both the groups were comparable with regard to demographic profile and duration of surgery

**Table 1: Demographic data**

| Variables | Group L (Mean±SD) | Group LC (Mean±SD) | P value | 95% confidence interval |
|---|---|---|---|---|
| Age (in years) | 37.4±11.8 | 37.7±13.0 | 0.90 (NS) | −5.2–4.6 |
| Weight (in kg) | 63.8±5.0 | 65.3±5.4 | 0.15 (NS) | −3.5–0.5 |
| Height (in cm) | 165.9±5.4 | 167.3±4.9 | 0.17 (NS) | −3.4–0.6 |

NS: Not Significant (P>0.05)

**Table 2: Onset time for sensory and motor blockade**

| Parameters | Group L (Mean±SD) | Group LC (Mean±SD) | P value | 95% confidence interval |
|---|---|---|---|---|
| Onset time of sensory blockade (min) | 15.9±2.3 | 7.8±1.7 | 0.0001 (S) | 7.2–8.9 |
| Onset time of motor blockade (min) | 19.8±2.3 | 10.9±1.9 | 0.0001 (S) | 8.0–9.7 |

S: Significant (P<0.05)

**Table 3: Duration of surgery, anesthesia, and analgesia**

| Variables | Group L (Mean±SD) | Group LC (Mean±SD) | P value | 95% confidence interval |
|---|---|---|---|---|
| Duration of surgery (min) | 80.2±19.9 | 80.0±22.0 | 0.96 (NS) | −8.1–8.5 |
| Duration of sensory blockade (min) | 173.5±12.7 | 234.5±16.1 | 0.0001 (S) | −66.7–−55.2 |
| Duration of analgesia (min) | 269.2±24.2 | 412.8±48.3 | 0.0001 (S) | −158.7–128.4 |

NS: Not Significant (P>0.05), S: Significant (P<0.05)

**Table 4: Differences in hemodynamic variables compared to the pre-operative variables (Heart Rate)**

| Time | Group L (Mean±SD) | Group LC (Mean±SD) | P value | 95% confidence interval |
|---|---|---|---|---|
| Pre-operative | 89.5±10.9 | 89.6±10.7 | 0.96 (NS) | −4.3–4.1 |
| 5 min | 87.7±10.9 | 87.1±10.1 | 0.77 (NS) | −3.5–4.7 |
| 15 min | 85.0±10.1 | 85.9±10.1 | 0.65 (NS) | −4.9–3.1 |
| 30 min | 83.0±10.1 | 84.5±9.5 | 0.44 (NS) | −5.3–2.3 |
| 45 min | 82.0±10.0 | 80.9±9.2 | 0.56 (NS) | −2.7–4.9 |
| 60 min | 79.7±9.2 | 77.6±9.1 | 0.25 (NS) | −1.5–5.7 |
| 90 min | 78.6±9.9 | 77.0±9.8 | 0.41 (NS) | −2.3–5.5 |
| 120 min | 77.1±9.9 | 75.2±11.3 | 0.37 (NS) | −2.3–6.1 |
| 180 min | 76.1±9.4 | 74.2±10.4 | 0.34 (NS) | −2.0–5.8 |
| 240 min | 78.4±8.6 | 77.2±9.0 | 0.49 (NS) | −2.2–4.6 |
| 300 min | 80.0±7.9 | 80.5±7.2 | 0.74 (NS) | −3.5–2.5 |
| 360 min | 83.04±7.5 | 85.96±8.5 | 0.07 (NS) | −6.0–0.2 |

NS: Not Significant (P>0.05)

**Table 5: Differences in hemodynamic variables compared to the pre-operative variables (Systolic Blood Pressure)**

| Time | Group L (Mean±SD) | Group LC (Mean±SD) | P value | 95% confidence interval |
|---|---|---|---|---|
| Pre-operative | 124.4±9.1 | 127.4±9.8 | 0.11 (NS) | −6.7–0.7 |
| 5 min | 123.5±9.1 | 125.2±9.8 | 0.37 (NS) | −5.4–2.0 |
| 15 min | 121.2±7.9 | 122.7±8.5 | 0.36 (NS) | −4.7–1.7 |
| 30 min | 119.5±8.3 | 117.7±9.1 | 0.30 (NS) | −1.6–5.2 |
| 45 min | 117.7±7.8 | 115.0±10.8 | 0.15 (NS) | −1.0–6.4 |
| 60 min | 116.5±9.5 | 112.4±11.2 | 0.05 (NS) | 0–8.2 |
| 90 min | 115.9±8.4 | 113.2±8.5 | 0.11 (NS) | −0.6–6.0 |
| 120 min | 114.0±8.4 | 112.3±7.8 | 0.29 (NS) | −1.5–4.9 |
| 180 min | 113.6±7.6 | 112.6±6.1 | 0.46 (NS) | −1.7–3.7 |
| 240 min | 114.6±6.5 | 114.8±5.3 | 0.86 (NS) | −2.5–2.1 |
| 300 min | 116.5±6.9 | 116.3±5.1 | 0.86 (NS) | −2.2–2.6 |
| 360 min | 118.9±6.3 | 120.8±6.0 | 0.12 (NS) | −4.3–0.5 |

NS: Not Significant (P>0.05)

**Table 6: Differences in hemodynamic variables compared to the pre-operative variables (Diastolic Blood Pressure)**

| Time | Group L (Mean±SD) | Group LC (Mean±SD) | P value | 95% confidence interval |
|---|---|---|---|---|
| Pre-operative | 81.0±6.2 | 82.9±5.0 | 0.09 (NS) | −4.1–0.3 |
| 5 min | 79.0±6.7 | 81.2±7.6 | 0.12 (NS) | −5.0–0.6 |
| 15 min | 77.6±5.4 | 80.0±6.8 | 0.05 (NS) | −4.8–0 |
| 30 min | 75.2±6.4 | 76.4±8.3 | 0.42 (NS) | −4.1–1.7 |
| 45 min | 73.5±6.8 | 74.4±9.6 | 0.58 (NS) | −4.2–2.4 |
| 60 min | 73.4±6.8 | 72.4±8.6 | 0.52 (NS) | −2.0–4.0 |
| 90 min | 71.7±5.8 | 72.2±8.6 | 0.73 (NS) | −3.4–2.4 |
| 120 min | 69.7±6.8 | 72.1±6.5 | 0.07 (NS) | −5.0–0.2 |
| 180 min | 71.3±6.9 | 70.9±7.0 | 0.77 (NS) | −2.3–3.1 |
| 240 min | 71.6±6.3 | 73.2±6.5 | 0.21 (NS) | −4.1–0.9 |
| 300 min | 73.3±4.8 | 74.7±5.8 | 0.19 (NS) | −3.5–0.7 |
| 360 min | 77.3±6.7 | 79.4±5.5 | 0.08 (NS) | −4.5–0.3 |

NS: Not Significant (P>0.05)

and it was found that duration of sensory blockade was prolonged significantly in clonidine group as compared to the control group. Similarly, clonidine prolonged the duration of post-operative analgesia (412.8±48.33 min) when compared to the control group (269.2±24.23 min) which was statistically significant.

Alves and Braz[7] in their study demonstrated that the duration of sensory blockade was significantly prolonged when clonidine was added to ropivacaine epidurally.

Milligan et al.,[8] found in their study that the time to rescue analgesia was significantly delayed in Group LC compared to Group L and Group C (clonidine). Other studies by Gupta et al.,[9] Ghatak et al.,[10] Alves and Braz[7] also showed a significant prolongation of duration of analgesia in their respective studies when clonidine was used as an adjuvant to local anesthetics in epidural administration. Disma et al.,[11] showed that a dose of 2 μg/kg of clonidine increases the duration of post-operative analgesia in caudal anesthesia for the lower abdominal surgery.

It was observed that clonidine combined with levobupivacaine has a faster onset of sensory and motor block which was in accordance with Milligan et al.,[8] Gupta et al.,[9] and Jain et al.[12]

Chalkiadis et al.,[13] in their study demonstrated the absorption characteristics of epidural levobupivacaine with clonidine and adrenaline through caudal epidural route and showed that clonidine mixed with levobupivacaine had a faster absorption compared to adrenaline mixed with levobupivacaine. Clonidine being a lipophilic drug is rapidly absorbed into the spinal compartment and blocks the conduction of C and Aδ fibres.[14]

The VAS score was lower in clonidine Group LC compared to the control Group L which was statistically significant (P<0.05). Alves and Braz[7] also showed a significant lower VAS score compared to the control group. However, Milligan et al.,[8] demonstrated a lower VAS score in levobupivacaine with clonidine group but it was not statistically significant compared to the levobupivacaine only group.

In the present study, the hemodynamic parameters such as systolic blood pressure and diastolic blood pressure

that were recorded showed a decreasing trend after the administration of epidural anesthesia in both groups. While the clonidine group showed a greater fall in systolic and diastolic blood pressure compared to the control group, this change was statistically insignificant. Similarly, the studies conducted by Ghatak et al.,[10] and Alves and Braz[7] showed no significant decrease in blood pressure between the clonidine and the control groups in their respective studies.

Gupta et al.,[9] Alves and Braz[7] in their studies showed the sedative effect of clonidine after epidural administration in more than 50% of patients when compared to the control group which was in accordance with our study too. The sedative effect of clonidine can be explained by the agonistic action of clonidine on locus coeruleus.

Hypotension and bradycardia were the major side effects that we observed in our study which was also reported by the studies conducted by Gupta et al.,[9] Alves and Braz.[7]

Regional anesthesia is a safe alternative to general anesthesia with an advantage of post-operative pain relief. Clonidine in epidural administration along with local anesthetics produces sedation, analgesia, anxiolysis, hypnosis, and sympatholysis.[15,16]

Clonidine produces analgesia by blocking the conduction of C and Aδ fibers and increasing potassium conductance in isolated neurons *in vitro* and thereby intensifying conduction block of local anesthetics. Because systemic pharmacokinetics is not a factor in these *in vitro* experiments, these data support a direct effect of clonidine on neural transmission in high local concentrations, such as may occur after local injection. Second, clonidine may cause local vasoconstriction in the clinical setting, thereby reducing vascular removal of local anesthetic surrounding neural structures. Although clonidine and other α2 adrenergic agonists can vasoconstrict in high concentrations, there is little evidence for this mechanism with clinically used concentrations.[17] The faster onset of action of local anesthetics, rapid establishment of both sensory and motor blockade, prolonged duration of analgesia into the post-operative period, and stable cardiovascular parameters make alpha-2 agonists a very effective adjuvant in regional anesthesia.[18,19]

### Limitations of the study

The limitations of the study include a small sample size and a single centric study. Furthermore, we did not compare epidural with more recent peripheral nerve blocks such as adductor canal or femoral nerve block.

## CONCLUSION

This study concluded that levobupivacaine and clonidine when administered together epidurally can provide a prolonged duration of anesthesia and analgesia with a faster onset of action and reduced requirement of rescue analgesics in post-operative period.

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**Authors Contribution:**
**AA-** Concept and prepared first draft of manuscript; **BB-** Design of the study; **PS-** Reviewed the literature; and **ST-** Concept, coordination, interpreted the results, preparation of manuscript, and revision of the manuscript

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