Comparison between Epidural Ropivacaine versus Ropivacaine with Clonidine in Patients Undergoing Abdominal Hysterectomy: A Randomized Study

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Abstract

Context: Regional anesthesia has emerged as one of the preferred and convenient modes for intra- and post-operative management owing to its advantage of not interfering with the metabolic functions, better tolerability, and decrease in reflex activity. In recent years, ropivacaine has increasingly replaced bupivacaine as a preferred local anesthetic because of its similar analgesic properties, lesser motor blockade, and decreased propensity of cardiotoxicity. Neuraxial adjuvant such as clonidine used in epidural anesthesia offers advantage by augmenting the local anesthetic effect and reducing the anesthetic and analgesic requirement. Aims and Objectives: Comparison of onset, duration of sensory and motor block, and any adverse effects between 0.5% ropivacaine with normal saline versus 0.5% ropivacaine with clonidine (75 μg/kg).

Materials and Methods: This prospective randomized study was carried out in 50 patients (25 in each group) of American Society of Anesthesiologist Grade 1 and 2 scheduled for abdominal hysterectomy under epidural block. Group-1 (ropivacaine-clonidine [RC]): Epidural ropivacaine 20 ml (0.5%) with 0.75 μg/kg clonidine. Group-2 (ropivacaine [R]): Epidural ropivacaine 20 ml (0.5%) with normal saline. Onset, duration of sensory-motor block, heart rate, blood pressure, oxygen saturation, and respiratory rate were recorded.

Statistical Analysis: The statistical analysis was done using Statistical Package for Social Sciences version 15.0. Chi-square test, ANOVA, Student’s t-test, and paired t-test were used. Results: Groups were comparable with regard to demographic data and hemodynamic stability. Onset of sensory and motor blockade was faster in RC group as compared to R group. Duration of postoperative analgesia was significantly prolonged in RC group. No potential side effect was seen in either group. Conclusion: On account of faster onset, hemodynamic stability, and prolonged postoperative analgesia, ropivacaine with clonidine is a better option than ropivacaine alone.

Keywords: Abdominal hysterectomy, clonidine, epidural block, ropivacaine

Introduction

In recent years, regional blocks such as spinal, epidural, and a combination of spinal/epidural blocks have gained widespread popularity among the surgical fraternity and have been well accepted by both the patient as well as the surgeon. Regional blocks by lowering the side effects associated with general anesthesia contribute in reducing the postoperative duration of hospital stay.

Bupivacaine is one of the most common anesthetic agents used for gynecological surgeries; however, in recent years, ropivacaine has increasingly replaced bupivacaine for the said purpose because of its similar analgesic properties, lesser motor blockade, and decreased propensity of cardiotoxicity. Although ropivacaine is claimed to have lower cardiotoxicity, yet some researchers have concluded that it has a limited or no superiority in epidural analgesia. Although a slightly larger dose of ropivacaine is required as compared to bupivacaine to achieve the analgesic and anesthetic effect, the addition of adjuvant can decrease the dose of ropivacaine required thereby eliminating quite a few side effects associated with larger doses of ropivacaine.

Alpha 2-adrenergic agonists have both analgesic and sedative properties when used as an adjuvant in regional anesthesia.
Alpha 2-adrenergic agonists have shown prolonged postoperative analgesia when used as an adjuvant with epidural ropivacaine in spine surgeries.[9]

Clonidine, an alpha 2-adrenergic agonist that produces analgesia via a nonopioid mechanism, is used as an adjuvant in regional anesthesia in various settings.[9,10] The coadministration of clonidine and local anesthetic produces better analgesia than either drug alone.[11-13] The anesthetic and the analgesic requirement get reduced to a huge extent by the use of adjuvants because of their analgesic properties and augmentation of local anesthetic effects, as they cause hyperpolarization of nerve by altering transmembrane potential and ion conductance at locus coeruleus in the brainstem.[14]

Clonidine has been shown to improve analgesia when added to epidural ropivacaine.[2]

Addition of clonidine as an adjuvant helps in dose sparing of local anesthetic,[15] which consequently reduces the incidence of side effects associated with larger doses of these anesthetics. There have been numerous studies validating the dose sparing effect of adjuvant when used with local anesthetics; our study is an endeavor toward the same.

Keeping the pharmacologic effects of clonidine as an adjuvant in mind, a double-blind prospective randomized clinically controlled study was planned in our hospital (Integral Institute of Medical Sciences and Research, Lucknow, Uttar Pradesh, India), with an aim to compare the efficacy of clonidine with ropivacaine versus ropivacaine with normal saline when used for epidural block in patients undergoing abdominal hysterectomy.

**Materials and Methods**

After approval from the Institutional Ethical Committee, a total of 50 female patients aged between 40 and 60 years of American Society of Anesthesiologist (ASA) physical status 1 and 2, scheduled for elective abdominal hysterectomy under epidural block were enrolled in this randomized double-blind study.

Patients with significant cardiovascular disease, renal failure, hepatic dysfunction and chronic pulmonary disease, neuromuscular disorder, morbid obesity, bleeding disorders, infections, history of allergy, or sensitivity to any of the studied local anesthetics were excluded from the study.

**Study groups**

After obtaining written informed consent, the enrolled patients were randomly assigned in a double-blinded fashion to one of the two groups of 25 patients each (n = 25) with computer-generated codes.

- **Group-1 (ropivacaine-clonidine [RC]):** Epidural ropivacaine 20 ml (0.5%) with 0.75 μg/kg clonidine
- **Group-2 (R):** Epidural ropivacaine 20 ml (0.5%) with normal saline.

Patients were asked to nil per oral for solid food 8 h before surgery and nil per oral for clear liquid for 2 h before surgery.

All the patients were administered premedication with tablet ranitidine 150 mg a night before surgery.

On the day of surgery, the patients were wheeled into the operation theater and connected to all noninvasive monitors. Baseline hemodynamic parameters, heart rate (HR), noninvasive blood pressure (NIBP), electrocardiogram, and oxygen saturation (SpO₂) were recorded.

Patients were placed in the sitting position and under strict aseptic precautions; local infiltration of lignocaine hydrochloride 2 ml was performed at lumbar level L2–3. Epidural space was localized and confirmed by the loss of resistance to saline technique using an 18-gauge Tuohy needle. An epidural catheter was then inserted into the space in a cephalic direction and aspirated for detection of cerebrospinal fluid or blood and secured to skin.

After 5 min of institution of test dose (3 ml of 2% lignocaine with 1 in 2 lakh adrenaline solution), Group R received epidural ropivacaine 20 ml (0.5%) with normal saline, whereas group RC received epidural ropivacaine 20 ml (0.5%) with 0.75 μg/kg clonidine.

The anesthesiologist performing the block recorded the baseline value of vital signs (BP, HR, and SpO₂) before performing the procedure, and once in every 5 min inside the OT, then after every 15 min in the postanesthesia care unit till the recovery of sensory and motor function.

The sensory level was checked and confirmed with pinprick method bilaterally for onset. Motor block was assessed using a modified Bromage scale (0 = no motor block, 1 = unable to raise extended legs, 2 = unable to flex knees, 3 = unable to flex ankle and foot).

**Times for recordings**

HR, NIBP, respiratory rate, and peripheral SpO₂ were recorded at:
- T0 - before administration of drug
- T1–5 min - after administration of the drug
- T3–10 min - after administration of drug
- T4–15 min - after administration of drug
- T5–30 min - after administration of drug
- T6–60 min - after administration of drug
- T7–T9 - every hour till 240 min.

Pain was assessed using 10 point visual analog scale in which a score of “0” indicated “no pain” and a score of “10” “worst pain imaginable.”

Motor block duration was the time for return to Bromage scale 1. Adverse effects such as nausea, vomiting, and shivering were also documented and managed symptomatically.

Hypotension was defined by a decrease in mean arterial pressure (MAP) below 20% of baseline or systolic
BP (SBP) <90 mm Hg and was treated with injection mephentermine 6 mg/ml.

**Statistical tools employed**

**Statistical analysis**

Student’s t-test (paired and unpaired).

Sample size:

\[
n = \frac{(Z\alpha + Z\beta)^2 (\sigma_1^2 + \sigma_2^2)}{d^2}
\]

Taking \(\sigma_1 = 1.28\), \(\sigma_2 = 1.46\), \(d = 1.28\)

Significant level

\(\alpha = 5\%
\)

\(\beta = 10\%
\)

Power = 90%

Sample size comes out to be \(n = 25\) per group

\(\sigma_1\) = Standard deviation of Group 1

\(\sigma_2\) = Standard deviation of Group 2

\(d\) = Mean standard deviation

\(\alpha\) = Type I error (5%)

\(\beta\) = Type II error (10%)

Power = \((100-\beta)\) i.e., 90%.

The values were represented in number (%) and mean ± standard deviation. To compare the change in a parameter at two different time intervals paired t-test was used.

**Observations and Results**

The enrolled patients were randomized into two groups of 25 patients each \((n = 25)\) using random number table as given in Table 1.

At baseline, both the groups were matched for age, body weight, and ASA grade showing no statistically significant intergroup difference \((P > 0.05)\) [Table 2].

At baseline, both the groups were matched for all the hemodynamic parameters (HR, diastolic BP (DBP), SBP, and mean arterial BP) and did not show a significant intergroup difference \((P > 0.05)\) [Table 3].

While comparing SBP between both the groups, statistically no significant difference was observed at baseline, after 5 min, and 60 min intervals. At all the other intervals, the difference among the groups was statistically significant \((P < 0.05)\). Throughout the study period, Group 2 had higher mean values as compared to Group 1 [Table 4].

With respect to mean DBP of patients, statistically no significant intergroup differences were observed at baseline, 5 min, 180 min, and 240 min intervals. However, at all the other time intervals, Group 2 had higher mean value as compared to Group 1 and the difference was statistically significant too \((P < 0.05)\) [Table 5].

Statistically significant intergroup differences in MAP were observed throughout the study period except at baseline and after 5 min. At all other time intervals, mean value

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**Table 1: Group-wise distribution of subjects**

| Group          | Number of patients | Description                                    |
|----------------|-------------------|-----------------------------------------------|
| Group 1 (RC)   | 25                | Patients who received epidural 0.75 μg/kg clonidine with 20 ml (0.5%) ropivacaine |
| Group 2 (R)    | 25                | Patients who received epidural 20 ml (0.5%) ropivacaine with normal saline |

**Table 2: Baseline demographic, anthropometric, and surgical complexity**

| Characteristic | Mean±SD (n=25) | Significance of difference (ANOVA) (P) |
|----------------|----------------|---------------------------------------|
| Age            | 50.2±5.2       | 48.2±5.1                              | 0.416          |
| Body weight    | 49.4±6.7       | 49.2±5.8                              | 0.674          |
| ASA I: II      | 14:11          | 13:12                                 | 0.683          |

**Table 3: Baseline hemodynamic variables in the study population**

| Hemodynamic variables | Mean±SD | Statistical significance (ANOVA) (P) |
|-----------------------|---------|-------------------------------------|
| Heart rate (l/min)    | 82.80±8.25 | 83.28±6.02                                 | 0.576          |
| Diastolic blood pressure (mm Hg) | 82.32±3.45 | 80.80±6.71                                 | 0.589          |
| Systolic blood pressure (mm Hg) | 126.72±5.56 | 128.56±3.72                                 | 0.304          |
| Mean arterial pressure (mm Hg) | 97.12±3.09  | 96.72±4.30                                  | 0.855          |

**Table 4: Systolic blood pressure in the study population at different time intervals**

| Time intervals | Mean±SD | Statistical significance (ANOVA) (P) |
|----------------|---------|-------------------------------------|
| Baseline       | 126.72±5.56 | 128.56±5.72                                 | 0.304          |
| After 5 min    | 125.4±6.21  | 127.36±4.07                                 | 0.103          |
| After 10 min   | 123.12±6.58 | 126.64±3.86                                 | 0.007          |
| After 15 min   | 116.64±4.64 | 121.12±2.89                                 | <0.001         |
| After 30 min   | 118.48±6.64 | 123.76±4.41                                 | 0.002          |
| After 60 min   | 118.00±6.73 | 120.00±4.58                                 | 0.306          |
| After 120 min  | 118.64±4.50 | 125.28±2.76                                 | <0.001         |
| After 180 min  | 119.28±4.96 | 128.48±3.97                                 | <0.001         |
| After 240 min  | 122.72±5.83 | 128.64±4.61                                 | <0.001         |

SD=Standard deviation, RC=Ropivacaine-clonidine, R=Ropivacaine

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of Group 2 was found to be higher as compared to that of Group 1 [Table 6].

Mean time taken for onset of motor as well as sensory block was less in Group 2 (RC) as compared to Group 1 (R), thus showing early onset of sensory and motor block in ropivacaine with clonidine group as compared to ropivacaine with normal saline group. Mean duration of motor as well as sensory block was more in Group 1 as compared to Group 2. For the block characteristic, the difference between both the groups was statistically significant ($P < 0.05$). Mean duration of analgesia was higher in Group 1 (RC). The demand for rescue analgesic was early in R group as compared to RC group. The difference between two groups was statistically significant ($P < 0.001$) [Table 7].

The two groups were almost comparable as far as side effects were concerned. Dry mouth and Nausea/vomiting were the most common side effects observed in RC group. Sedation was the next most common side effect. None of the patient had respiratory depression. There was no significant difference among the groups with respect to different side effects ($P > 0.05$) [Table 8].

### Discussion

During a regional anesthetic procedure, the target of the anesthetic team is to provide a good quality of block that ensures hemodynamic stability, has a short onset time, is long enough to allow the successful completion of the operative procedure and that has minimal side effects with maximum postoperative analgesic efficiency.

For many years, bupivacaine has been used for epidural block because of its long duration of action. However, bupivacaine is one of the most cardiotoxic local anesthetics in current use and motor block is still a problem. Ropivacaine is an amide local anesthetic produced in the pure levorotatory form addresses some of the concerns related to bupivacaine. To attain an equal or better potency and to enhance the postoperative analgesic effect, use of adjuvants plays an important role. It has been seen that addition of an adjuvant sometimes enhances the effect of the principle anesthetic agent synergistically. Clonidine, an alpha-adrenergic agonist, is one of the main drugs that can be used for this purpose owing to its production as a preservative-free preparation.

In the present study, we evaluated the efficacy of clonidine in terms of hemodynamic stability, ability to achieve and maintain the sensory and motor blockade, minimize the postoperative analgesic requirement, and the side effects when used in combination with ropivacaine in patients undergoing abdominal hysterectomy.

### Table 5: Diastolic blood pressure in the study population at different time intervals

| Time intervals | Mean ± SD | Statistical significance (ANOVA) ($P$) |
|----------------|-----------|-----------------------------------------|
|                | Group 1 (RC) | Group 2 (R) |                               |
| Baseline       | 82.32±3.45  | 80.80±6.71 | 0.589                      |
| After 5 min    | 81.04±3.83  | 81.76±7.17 | 0.252                      |
| After 10 min   | 78.64±4.75  | 81.04±7.51 | 0.022                      |
| After 15 min   | 74.00±5.13  | 80.16±7.05 | <0.001                     |
| After 30 min   | 69.68±6.24  | 74.40±8.77 | 0.025                      |
| After 60 min   | 69.36±7.13  | 74.24±9.24 | 0.025                      |
| After 120 min  | 70.40±7.96  | 75.92±9.84 | 0.033                      |
| After 180 min  | 72.16±7.61  | 75.04±10.25| 0.263                      |
| After 240 min  | 74.48±7.62  | 79.36±9.25 | 0.087                      |

SD=Standard deviation, RC=Ropivacaine-clonidine, R=Ropivacaine

### Table 6: Mean arterial pressure in the study population at different time intervals

| Time intervals | Mean ± SD | Statistical significance (ANOVA) ($P$) |
|----------------|-----------|-----------------------------------------|
|                | Group 1 (RC) | Group 2 (R) |                               |
| Baseline       | 97.12±3.09  | 96.72±4.30 | 0.855                      |
| After 5 min    | 95.84±3.86  | 96.96±4.73 | 0.074                      |
| After 10 min   | 93.44±4.79  | 96.24±5.03 | 0.002                      |
| After 15 min   | 88.20±3.92  | 93.84±4.50 | <0.001                     |
| After 30 min   | 85.96±5.69  | 90.88±5.87 | 0.002                      |
| After 60 min   | 85.64±6.16  | 89.48±6.82 | 0.025                      |
| After 120 min  | 86.44±5.84  | 92.36±6.48 | <0.001                     |
| After 180 min  | 87.76±5.74  | 92.84±7.06 | 0.013                      |
| After 240 min  | 90.48±5.80  | 95.80±6.44 | 0.007                      |

SD=Standard deviation, RC=Ropivacaine-clonidine, R=Ropivacaine

### Table 7: Block characteristics in different groups

| Characteristic          | Mean ± SD ($n=25$) | Statistical significance (ANOVA) ($P$) |
|-------------------------|---------------------|-----------------------------------------|
| Onset of motor block    | 11.20±2.42          | 21.80±1.98                              | <0.001                      |
| Total duration of motor | 117.76±2.60         | 107.84±1.72                             | <0.001                      |
| Onset of sensory block  | 8.56±2.47           | 15.76±1.42                              | <0.001                      |
| Total duration of sensory block | 109.04±2.01 | 97.84±5.68                              | <0.001                      |
| Mean duration of analgesia (h) | 5.48±0.82 | 3.60±1.08                              | <0.001                      |

### Table 8: Side effects

| Characteristic          | n (%) ($n=25$) | Statistical significance ($P$) |
|-------------------------|---------------|-------------------------------|
| Nausea/vomiting         | 6 (24)        | 3 (12)                        | 0.521                      |
| Sedation                | 4 (16)        | 0 (0)                         | 0.129                      |
| Shivering               | 1 (4)         | 2 (8)                         | 0.363                      |
| Respiratory depression  | 0 (0)         | 0 (0)                         | -                           |
| Headache                | 1 (4)         | 0 (0)                         | 0.363                      |
| Dry mouth               | 6 (24)        | 3 (12)                        | 0.356                      |
For this purpose, a prospective, randomized controlled study was planned in which a total of 50 ASA Grade 1/2 female patients aged 40–60 years, scheduled to undergo abdominal hysterectomy, were enrolled as study subjects and randomly allocated to two study groups viz., patients who received epidural 0.75 μg/kg clonidine with 20 ml (0.5%) ropivacaine (Group RC) and patients who received epidural 20 ml (0.5%) ropivacaine with normal saline (Group R). All these doses have been reported to be optimum and safe for use as a local anesthetic with or without the use of epinephrine. The groups were matched for demographic, anthropometric characteristics, and baseline hemodynamic parameters.

With respect to HR during the study period, statistically no significant differences among groups were observed for the initial part of the study, however, from 30 min onward till 120 min, Group 1 (RC) had significantly lower HR as compared to Group 2 (R alone). In a study by Bajwa et al., while using clonidine in combination with ropivacaine during epidural block as compared to ropivacaine alone similar variations in HR were observed but at different time intervals. In their study, the addition of 75 μg clonidine to isobaric epidural ropivacaine resulted in longer, complete, and effective analgesia with similar block properties and helped to reduce the effective dose of ropivacaine when compared with plain ropivacaine for cesarean delivery. In our study also we found prolonged analgesia in RC group.

The pattern of change and intergroup differences observed for BP variables, i.e. SBP and DBP were also similar to those observed for HR with RC groups showing lower mean value and a decremental trend for the major part of the study as compared to an incremental trend and higher mean value for ropivacaine alone group. Clonidine suppresses sympathetic outflow resulting in lower BP. Addition of clonidine either as a fixed dose or as an infusion has been shown to have a lowering effect on arterial pressure as observed in the present study. Despite reduction in mean BP levels, no event of hypotension was noticed in any group thus highlighting that the given dosages of adjuvant use of clonidine did not reduce the arterial pressure substantially.

Clonidine is lipophilic, and as a result is quickly redistributed systemically despite neuraxial injection. It therefore has both central and peripheral effects. At lower doses, the central effects cause sympatholysis leading to hypotension, whereas the peripheral effects at higher doses cause vasoconstriction. Clonidine administered in the low thoracic or lumbar region typically produces BP effects similar to that seen with intravenous administration. When given in the mid or upper thoracic regions, epidurally administered clonidine causes an even greater decrease in BP. In the present study, we administered clonidine through lumbar region and obtained a less hypotensive effect of clonidine, which was within the safe limits.

With respect to onset of motor and sensory block, both the blocks were achieved earlier in Group 1 (RC) as compared to Group 2 (R alone). Similarly, regression of sensory and motor blockade took longer time in Group 1 (RC) as compared to Group 2 (R alone). Group 1 (RC) had significantly shorter onset time and longer regression time for motor and sensory block as compared to Group 2 (R alone). The results are in agreement with the study of Bajwa et al., who observed that addition of clonidine reduces the onset time for blocks and enhance the duration of block when added to ropivacaine.

With respect to duration of analgesia, Group 1 had significantly longer duration of analgesia as compared to Group 2. Co-administration of clonidine with local anesthetic has been documented to show better analgesia than the drug alone and observations in the present study support the same. The effects of epidurally administered clonidine are seen as early as 20 min after injection, with peak effects occurring in 1 h. The analgesic potency has been described as being comparable to epidurally administered morphine. Adding clonidine as an adjuvant in the epidural space has an additive effect, which results in a lower dose of narcotic necessary for optimal pain control.

The present study did not have any severe side effect. Dry mouth and nausea/vomiting were the most common side effects observed in both the groups. None of the patient had respiratory depression. Although side effects were minimum in ropivacaine alone group, yet for none of the side effects, a significant intergroup difference was observed. As stated earlier addition of clonidine in the epidural space has an additive effect, which results in a lower dose of narcotic necessary for optimal pain control. As a consequence of which the incidence of respiratory depression is diminished. It has a known side effect of dry mouth as reflected in the present study too though with less potent and significant effect.

Addition of clonidine enhanced the efficacy of epidurally administered ropivacaine without any potential side effect. RC appears well suited to achieve long-lasting nerve blockade without having to resort to adjuvant medications.

The findings in the present study show that ropivacaine in combination with clonidine provides a hemodynamically stable, faster, and prolonged epidural block and a longer analgesic effect as compared to ropivacaine alone. No potential side effect or bradycardia or hypotensive event took place thus showing that the adjuvant use of clonidine can be done safely.

**Conclusion**

On the basis of present study, the following conclusions can be drawn:
- Ropivacaine in combination with clonidine (Group 1) provided a better hemodynamic control as compared to ropivacaine (Group 2) alone
- Ropivacaine with clonidine provided a faster and longer sensory and motor block as compared to ropivacaine alone group.

Duration of analgesia was prolonged in ropivacaine with clonidine group as compared to ropivacaine alone group. Group 2 had a lower prevalence of any type of side effect.
The findings of the study suggest that adjuvant use of clonidine helps in achieving a better hemodynamic regulation, faster block onset, longer duration of block, and analgesia and manageable side effects. Given the relative superiority of ropivacaine with clonidine as compared to ropivacaine alone, it may be recommended for the use in epidural block in cases of abdominal hysterectomy.

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Conflicts of interest
There are no conflicts of interest.

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