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# Comparison Of Epidural Ropivacaine And Ropivacaine With Clonidine In Patient's Undergoing Total Abdominal Hysterectomy: A Randomized Clinical Study

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***Abstract***
***Background:*** *Epidural anaesthesia is preferred technique for the patients undergoing lower abdominal surgery, owing to its ability to provide perioperative anaesthesia as well as postoperative analgesia. Ropivacaine has emerged as a possible replacement of Bupivacaine because of its favorable clinical profile. Neuraxial adjuvants augment the action of local anaesthetics and allows reductions of anaesthetic and analgesic requirement.*
***Aim:*** *Comparison of onset and duration of sensory-motor block, and any adverse effect of Epidural block of 0.5% ropivacaine (2mg/kg) versus 0.5% ropivacaine (2mg/kg) with clonidine (0.75microgram/kg).*
***Materials and Methods:*** *This prospective randomized controlled trial was carried out in 50 patients (25 in each group) of American Society of Anaesthesiologist Grade I and II, scheduled for total abdominal hysterectomy under epidural block. Group R received plain 0.5% ropivacaine (2mg/kg) and Group RC received 0.5% ropivacaine (2mg/kg) with (0.75microgram/kg) clonidine. The onset time of sensory-motor analgesia, duration of sensory & motor block, postoperative analgesic dose, hemodynamic parameters and adverse events were recorded.*
***Results:*** *Faster onset of sensory-motor blockade with significantly prolonged duration of postoperative analgesia and decreased postoperative analgesia dose requirement, was observed in RC group. The incidence of bradycardia and hypotension was more in RC group as compared to R group which was not statistically significant. No potential side effect was seen in either group.*
***Conclusions:*** *Supplementation of 0.75mcg/kg clonidine to epidural ropivacaine results in faster onset of sensory-motor blockade, prolonged duration of analgesia and significant reduction in postoperative analgesic dose, compared to plain epidural ropivacaine.*
***Keywords:*** *Total abdominal hysterectomy, Epidural anaesthesia, Ropivacaine, Clonidine*

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## I. Introduction

Regional anesthesia is widely accepted and suitable alternative to general anesthesia for patients undergoing lower abdominal surgery, owing to its lesser side effects compared to general anaesthesia, reduced postoperative hospitalization and better postoperative analgesia.

Bupivacaine has been extensively used as preferred aesthetic agent for gynaecological surgeries; however, in recent past, ropivacaine has increasingly replaced bupivacaine as local anaesthetic of choice in such procedures because of its similar analgesic properties, lesser motor blockade and decreased propensity of cardiotoxicity[1].

Although ropivacaine is considered to be less cardiotoxic, yet a slightly larger dose of ropivacaine is required as compared to bupivacaine to achieve the analgesic and anaesthetic 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[2].

Alpha 2-adrenergic agonists when used as an adjuvant in regional anaesthesia possess analgesic and sedative properties[3]. Alpha 2-adrenergic agonist administration as an adjuvant with epidural ropivacaine in spine surgeries, prolongs the duration of postoperative analgesia[4].

Clonidine, an alpha 2-adrenergic agonist, when used as an adjuvant in regional anaesthesia produces better analgesia via a non-opioid mechanism[5, 6]. The combination of epidural clonidine with ropivacaine has been shown to improve analgesia[7]. Also, addition of clonidine as adjuvant helps in reducing the dose of local anaesthetics, thereby reducing the incidence of side effects associated with larger dose of these anaesthetics[8].

There have been few studies validating the dose sparing effect of adjuvant when used with local anaesthetics; our study is an endeavor toward the same.

Keeping the pharmacologic profile of clonidine as an adjuvant in mind, a double-blind prospective randomized clinically controlled study was designed with an aim to evaluate the efficacy of combination of clonidine with epidural ropivacaine in comparison to ropivacaine with normal saline in patients undergoing total abdominal hysterectomy.

## II. Material And Methods

This prospective randomized controlled trial was carried out at Department of Anaesthesiology and Critical care, Era's Lucknow Medical College, Lucknow, Uttar Pradesh from May 2011 to May 2013. After getting Institutional Ethical Committee approval, 50 females patients aged between 40 and 60 years, of American Society of Anaesthesiologist (ASA) physical status 1 and 2, scheduled for elective total abdominal hysterectomy under epidural anaesthesia were enrolled in this randomized double-blind study. A written and informed consent of the patient and their relatives was also taken.

Patients with history of end organ dysfunction, morbid obesity, history of allergy, or sensitivity to any of the study drugs, and general contraindications to epidural block were excluded from the study.

All the patients were randomly (computer generated randomization and concealment via sealed envelope technique) assigned in a double-blinded fashion to one of the two groups of 25 patients each ($n$ = 25). Group R to receive epidural anaesthesia with 2mg/kg of 0.5% ropivacaine and Group RC to receive epidural anaesthesia with 2mg/kg of 0.5% ropivacaine with 0.75 µg /kg clonidine.

Patients were asked to be nil per oral for solid food 8 h prior to surgery and nil per oral for clear liquids 2 h before surgery. Premedication included tablet alprazolam (0.25 mg) and tablet ranitidine (150 mg) administered orally, a night before surgery.

On the day of surgery, the patients were wheeled into the operation theatre, intravenous access was secured using 18G cannula in a non-dominant hand and patients were preloaded with 750 ml of lactated Ringer's solution. Routine non-invasive monitors were attached and baseline hemodynamic parameters, respiratory rate, heart rate (HR), non-invasive blood pressure (NIBP), electrocardiogram (ECG), and oxygen saturation ($SpO_2$) were recorded.

Patients were placed in the sitting position and under strict aseptic precautions; local infiltration of skin and subcutaneous tissue was performed at L3–L4 interspace with 2ml lignocaine hydrochloride. Epidural space was localized and confirmed by the loss of resistance technique (using a syringe containing air) 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. Thereafter, patients were repositioned to supine position and a test dose of 3 mL of 2% lignocaine with (1:200,000) adrenaline was administered through epidural catheter and any untoward effect was observed for. After 5 min of institution of test dose, allocated drug was administered. Intraoperative fluid was given as per Holliday-Segar formula. General anaesthesia was planned in case of inadequate or failed block and the patient was excluded from the study. Surgical procedures were initiated only after sensory level of T6-T7 was achieved.

The time of initial bolus dose of study drug was noted as "zero time". The anaesthesiologist performing the block assessed sensory-motor block at 5, 10, 15 min after completion of initial bolus dose, then once in every 15 min inside the OT and post anaesthesia care until the recovery of sensory and motor function.

The onset of sensory block was checked and confirmed by pinprick method with a 27G hypodermic needle in mid axillary line bilaterally. The time of onset was taken from zero time to loss of bilateral pinprick sensation. 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) was used to assess the degree of motor block. The onset of motor block was recorded as the time interval from zero time to the patient's inability to raise the straight extended leg (modified Bromage 1). Motor block duration was recorded from zero time to regression of motor block to modified Bromage scale 0. The duration of sensory analgesia was taken from initial bolus dose to the first request for analgesia postoperatively. The onset of pain was managed by top-up doses of 20 mg of 0.2% ropivacaine in group R, whereas 50 µg clonidine was added to 20 mg of 0.2% ropivacaine in group RC. HR, NIBP, respiratory rate, and peripheral $SpO_2$ were recorded at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 150, and 180 min after administration of epidural block. Adverse effects such as nausea, vomiting, shivering, hypotension and bradycardia were observed for, documented and managed accordingly.

**Statistical analysis**

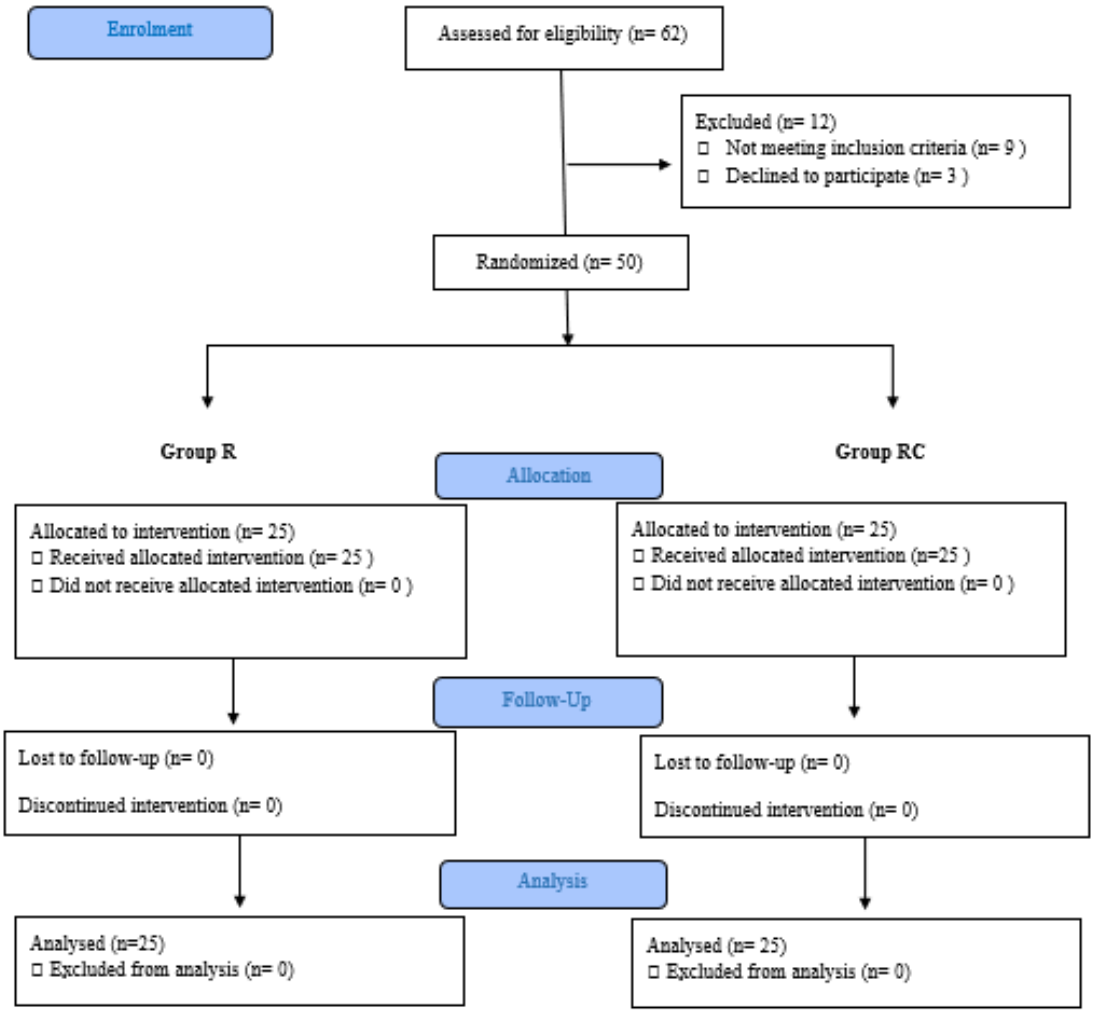
The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0. The data was expressed as either mean or standard deviation (SD) for quantitative data variable and as percentage for qualitative data variable. For categorical variables, differences were analyzed with $\chi^2$ (chi square) tests. Differences among continuous variables with normal distribution were analyzed by Student's $t$-test; for

continuous variables without normal distribution, we used non-parametric tests and differences were analyzed by the Mann–Whitney U-test. All tests were 2 tailed, p-values <0.05 was considered statistically significant.

## III. Results

A total of 62 patients were assessed for eligibility, of which 12 patients did not meet the inclusion criteria, epidural block was successful in all the patients and all the patients completed the study as shown in consort diagram [Figure 1].

**Figure 1**




The study groups (Group R and RC) were found to be comparable with respect to age, weight, height, duration of surgery and ASA physical status [Table 1].

**Table 1: Comparison of demographic characteristics between the groups**

| Parameters | Group R | | Group RC | | Significance of difference | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | $X^2$ | P |
| Age (years) | 59.67 | 11.87 | 57.97 | 12.99 | 0.483 | 0.631 |
| Body weight (kg) | 53.97 | 11.10 | 53.33 | 9.73 | 0.217 | 0.829 |
| Height (cm) | 163.76 | 7.88 | 160.60 | 5.50 | 1.64 | 0.105 |
| Duration of surgery (min) | 107.3 | 19.8 | 105.0 | 22.3 | 0.386 | 0.701 |
| ASA Grade I:II | 21:4 | | 23:2 | | 0.757 | 0.384 |

ASA= American Society of Anaesthesiologists, SD= Standard Deviation

The time taken for the onset of sensory as well as motor block was shorter in group RC as compared to group R. The mean time for onset of sensory block was 12.36 ± 2.39 in group R and 7.85 ± 2.05 min in group RC, and the difference between the two groups was highly significant (P<0.0001). However, once sensory level of T6–T7 was established, there was no notable difference in sensory anaesthesia in either of the groups throughout the surgical procedure. The mean time for onset of motor block was 21.80 ± 2.00 in group R and 15.20 ± 2.42 min in group RC, and the difference between the two groups was statistically significant (P<0.0001) [Table 2].

**Table 2: Comparison of initial block characteristics between the groups**

| Parameters | Group R | | Group RC | | Significance of difference | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | $X^2$ | P |
| Onset of sensory block (min) | 12.36 | 2.39 | 7.85 | 2.05 | 7.162 | <0.0001 |
| Onset of motor block (min) | 21.80 | 2.00 | 15.20 | 2.42 | 10.405 | <0.0001 |

SD= Standard Deviation

At baseline, both the groups were matched for all the hemodynamic parameters (HR, systolic blood pressure, diastolic blood pressure, $SpO_2$ and respiratory rate) and did not show a significant intergroup difference for any of the parameters ($P > 0.05$) [Table 3].

**Table 3: Comparison of baseline hemodynamic variables between the groups**

| Hemodynamic variables | Group R | | Group RC | | Significance of difference | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | $X^2$ | P |
| Heart rate (/min) | 90.1 | 12.25 | 86.12 | 11.54 | 1.182 | 0.242 |
| Systolic blood pressure (mmHg) | 128.72 | 10.83 | 125.55 | 10.13 | 1.069 | 0.290 |
| Diastolic blood pressure (mmHg) | 80.32 | 6.45 | 78.8 | 7.22 | 0.785 | 0.436 |
| Oxygen saturation (%) | 98.53 | 1.81 | 99.04 | 1.04 | 1.222 | 0.227 |
| Respiratory rate (/min) | 14.23 | .82 | 14.28 | .87 | 0.209 | 0.835 |

SD= Standard Deviation

While comparing the HR between both the groups, statistically no significant difference was observed at baseline, after 5 min and at 10 min interval. But after 10 min, mean HR remained lower as compared to baseline in both the study groups, however statistically significant (P<0.05) decrease in HR was seen only in group RC. This difference in HR remained significant until 120 min. Thereafter no statistically significant difference in mean HR was observed between the study groups. One patient in R group and 3 patients in RC group had incidence of bradycardia with HR < 50 beats/min and 0.6 mg bolus dose of intravenous injection atropine had to be given [Table 4].

**Table 4: Comparison of Heart rate between the groups at different time intervals**

| Time interval (min) | Group R | | Group RC | | Significance of difference | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | $X^2$ | P |
| 0 | 90.1 | 12.25 | 86.12 | 11.54 | 1.182 | 0.242 |
| 5 | 91.70 | 20.74 | 87.43 | 16.57 | 0.804 | 0.425 |
| 10 | 89.57 | 16.42 | 88.17 | 12.09 | 0.343 | 0.732 |
| 15 | 84.47 | 18.01 | 74.30 | 13.70 | 2.247 | 0.023 |
| 20 | 84.17 | 18.96 | 74.00 | 13.65 | 2.177 | 0.034 |
| 25 | 81.03 | 15.30 | 72.10 | 15.69 | 2.037 | 0.047 |
| 30 | 79.99 | 16.67 | 71.06 | 14.34 | 2.031 | 0.047 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 40 | 79.57 | 16.10 | 71.20 | 12.31 | 2.065 | 0.044 |
| 50 | 78.99 | 15.22 | 70.99 | 11.15 | 2.120 | 0.039 |
| 60 | 78.60 | 16.56 | 69.93 | 7.86 | 2.365 | 0.022 |
| 90 | 76.23 | 15.50 | 69.27 | 7.13 | 2.040 | 0.046 |
| 120 | 77.83 | 17.07 | 69.87 | 7.80 | 2.121 | 0.039 |
| 150 | 86.27 | 14.53 | 80.27 | 13.16 | 1.530 | 0.132 |
| 180 | 86.63 | 17.77 | 85.37 | 14.53 | 0.274 | 0.784 |

SD= Standard Deviation

With regard to systolic blood pressure, statistically no significant intergroup difference was observed at baseline. However five minutes after administration of epidural drug, a fall in systolic blood pressure was observed in both groups but it was more pronounced in group RC which remained significant till 60 min after drug administration. Thereafter systolic blood pressure was comparable between the two groups [Table 5].

**Table 5: Comparison of systolic blood pressure between the groups at different time intervals**

| Time interval (min) | Group R | | Group RC | | Significance of difference | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | $X^2$ | P |
| 0 | 128.72 | 10.83 | 125.55 | 10.13 | 1.069 | 0.290 |
| 5 | 122.13 | 13.61 | 113.60 | 14.82 | 2.120 | 0.039 |
| 10 | 120.23 | 12.22 | 112.43 | 15.42 | 2.135 | 0.037 |
| 15 | 118.73 | 11.86 | 111.20 | 15.26 | 2.013 | 0.049 |
| 20 | 118.13 | 11.46 | 110.07 | 16.23 | 2.021 | 0.048 |
| 25 | 116.47 | 17.36 | 106.23 | 15.29 | 2.213 | 0.031 |
| 30 | 116.97 | 15.37 | 106.93 | 16.89 | 2.198 | 0.032 |
| 40 | 117.40 | 15.42 | 106.63 | 17.65 | 2.298 | 0.025 |
| 50 | 116.03 | 15.68 | 107.23 | 14.37 | 2.069 | 0.044 |
| 60 | 117.70 | 15.54 | 106.36 | 14.92 | 2.632 | 0.011 |
| 90 | 118.40 | 13.93 | 113.17 | 11.93 | 1.426 | 0.160 |
| 120 | 119.20 | 13.71 | 113.23 | 14.17 | 1.514 | 0.136 |
| 150 | 122.10 | 14.13 | 118.83 | 19.48 | 0.679 | 0.500 |
| 180 | 122.67 | 16.28 | 119.73 | 25.09 | 0.491 | 0.625 |

SD= Standard Deviation

Mean duration of sensory-motor block was significantly higher in group RC as compared to group R. The mean duration of sensory analgesia was 370.10 ± 12.80 min in group R and 445.70 ± 8.49 min in group RC and statistically very highly significant between the two groups ($P < 0.0001$) [Table 6]. The duration of motor block was 252.90 ± 6.77 min in group R and 283.62 ± 20.5 min in group RC, and it was statistically very highly significant between the two groups ($P < 0.0001$) [Table 6]. Postoperatively, the demand for rescue analgesic was early in the group R as compared to group RC. The difference between the groups was statistically very highly significant ($P < 0.0001$) [Table 6]. The time interval between top-up analgesics doses varied significantly with increased time interval between successive doses in the group RC compared to group R. The intergroup difference was statistically very highly significant ($P < 0.0001$) [Table 6]. The total postoperative dose requirement of ropivacaine significantly decreased in RC group.

**Table 6: Comparison of peroperative and postoperative block characteristics between the groups**

| Characteristics | Group R | | Group RC | | Significance of difference | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | $X^2$ | P |

| | | | | | | |
|---|---|---|---|---|---|---|
| Duration of sensory block (min) | 370.10 | 12.80 | 445.70 | 8.49 | 24.610 | <0.0001 |
| Duration of motor block (min) | 252.90 | 6.77 | 283.62 | 20.5 | 7.115 | <0.0001 |
| Time interval between postoperative top up analgesics doses (hours) | 4.69 | 1.39 | 7.51 | 1.45 | 7.269 | <0.0001 |

SD= Standard Deviation

Although incidence of side effects was higher in group RC as compared to group R, yet the difference between two groups was found to be statistically significant only for sedation ($P$ = 0.040) and dry mouth ($P$ = 0.047) [Table 7].

**Table 7: Comparison of side effects/ adverse events between the groups**

| Characteristics | Group R | | Group RC | | Significance of difference | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | $X^2$ | P |
| Nausea/Vomiting | 2 | 8 | 5 | 20 | 1.22 | 0.113 |
| Sedation | 0 | 0 | 3 | 12 | 1.786 | 0.040 |
| Shivering | 0 | 0 | 2 | 8 | 1.443 | 0.077 |
| Respiratory depression | 0 | 0 | 0 | 0 | 0 | 0 |
| Headache | 1 | 4 | 2 | 8 | 0.595 | 0.277 |
| Dry mouth | 3 | 12 | 8 | 32 | 1.706 | 0.047 |

SD= Standard Deviation

## IV. Discussion

Epidural anaesthesia with local anaesthetics ensures optimal perioperative conditions, better hemodynamic stability with minimal side effects, and superior postoperative analgesic efficiency. Addition of adjuvant to local anaesthetic epidurals augments the quality of block, increases the duration of analgesia, and results in better postoperative outcome with fewer complications. Although intrathecal clonidine as an adjuvant to ropivacaine has been studied extensively, there is a dearth of literature on the epidural use of ropivacaine and clonidine for lower abdominal surgeries. Therefore, the present study was planned to evaluate the efficacy of clonidine with ropivacaine as compared to ropivacaine alone in patients undergoing total abdominal hysterectomy

There are innumerable studies on the use of epidural ropivacaine for inducing painless labour and deliveries[9], but literature available for lower abdominal surgeries is scarce. Ropivacaine, although slightly less potent as compared to bupivacaine, its pharmacological efficacy is almost comparable to the latter. Also, various studies suggest that cardiotoxicity of ropivacaine is far less than that of bupivacaine[10, 11].

Clonidine is used as an adjunct in regional anaesthesia in various settings[5]. A dose determination study by Brichant et al.[12] concluded that 75 µg of clonidine is the optimal epidural dose when added to bupivacaine for analgesia, as smaller doses do not provide adequate analgesia while larger doses were associated with bradycardia , hypotension, sedation and other side effects. Therefore, we administered a single bolus dose of 75 µg for operative purpose while top-up doses of 50 µg clonidine were administered with 0.2 % ropivacaine for the postoperative analgesia.

In our study, the mean time for onset of sensory and motor block was significantly earlier in group RC compared to group R. Similarly, the mean duration of motor and sensory block was significantly prolonged in group RC as compared to group R. The results of our study are in agreement with the study of Bajwa et al.[13] and Ogun et al.[14] who observed that addition of clonidine reduces the onset time for blocks and enhances the duration of block when added to ropivacaine.

Clonidine has a potent regressive effect on heart rate within 15-90 minutes of epidural administration[15] that is why, in this study, group RC had significantly lower mean HR as compared to group R between 15 and 120 min interval. The results of our study were similar to those observed by Bajwa et al.[13] who showed similar variations in HR but at different time intervals. Few patients developed bradycardia in both the groups, which was treated with 0.6 mg of injection atropine. The incidence of bradycardia was slightly higher in group RC but it was not clinically significant.

Clonidine inhibits sympathetic outflow and reduces blood pressure as was observed in the present study. Despite reduction of blood pressure levels, no event of hypotension was observed in any of the study groups. Our results were similar to those obtained by Eisenach et al.[6] who observed that clonidine does not produce additional hypotensive effect when combined with epidural local aesthetics.

With respect to duration of analgesia, group RC not only had significantly longer duration of analgesia, but also, decreased frequency of top up doses and total dose consumption of ropivacaine as compared to group R. Co-administration of clonidine with local anaesthetic has been documented to have better analgesia than either drug alone[16] and results of the present study support the same.

No severe side effects were observed in either of the study groups. Dry mouth and nausea/vomiting were the most common side effects observed in both the study groups. None of our patient had respiratory depression. Although side effects were minimum in group R, yet except for dry mouth and sedation, no significant intergroup difference was observed. Dry mouth is known side effect of clonidine as reflected in our study too. Sedative effect of epidural clonidine is due to its systemic absorption and vascular redistribution to higher centres[17]. Sedation with use of clonidine has been documented in solitary use as well as when used as adjuvant[18], and observations in the present study support the same.

## V. Conclusion

The findings in the present study suggest that adjunct use of clonidine augments the efficacy of epidural ropivacaine, thereby resulting in better block characteristics in terms of faster onset, prolonged duration and longer analgesic effect without any undesirable side effects. Given the relative superior profile of ropivacaine with clonidine as compared to ropivacaine alone, we recommend the routine use of epidural ropivacaine and clonidine for patients undergoing total abdominal hysterectomy.

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