DOI: 10.7860/JCDR/2023/60344.17735

Original Article

Anaesthesia Section

# Comparison of Analgesic Effect of Clonidine as an Adjuvant with Different Concentration of Ropivacaine (0.35% and 0.2%) in Thoracic Paravertebral Block among Modified Radical Mastectomy Patients: A Randomised Double Blinded Clinical Study

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## ABSTRACT

**Introduction:** Thoracic Paravertebral Block (TPVB) appears promising for reduction of postoperative pain in Modified Radical Mastectomy (MRM). Various combinations of local anaesthetics and adjuvants have been tried in TPVB but search for an ideal combination is still on.

**Aim:** To evaluate analgesic efficacy of clonidine (1 µg/kg) as adjuvant with different concentrations of ropivacaine (0.35%, 0.2%) for TPVB in MRM surgery.

**Materials and Methods:** This randomised double blind comparative clinical study was carried out in a tertiary care centre in Southern Rajasthan from January 2019 to March 2020, clinical study, 120 American Society of Anaesthesiologists (ASA) grade I, II patients aged 18-60 years female patients undergoing MRM surgery were randomised into three groups- RP, RC and LDRC to receive 0.35% Ropivacaine 19 mL, 0.35% Ropivacaine 19 ml+Clonidine (1 µg/kg) and 0.2% Ropivacaine 19 ml+Clonidine(1 µg/kg) diluted upto total 20 ml with normal saline, respectively. TPVB was performed at T4 level as single injection followed by administration of general endotracheal anaesthesia. The primary outcome measured was duration of analgesia. Secondary outcomes measured included consumption of rescue analgesic, Visual analog scale and perioperative haemodynamic parameters. Quantitative and qualitative data were analysed using Analysis of Variance (ANOVA) and Chi-square test respectively. $p<0.05$ was considered statistically significant.

**Results:** Mean duration of analgesia was prolonged in clonidine groups RC and LDRC (811.5±110.99 and 753±119.76 min, respectively) as compared to group RP (400.125±108.13 min), although no statistically significant difference was noted between group RC and LDRC. Similar observations were noted when total dose of rescue analgesic in group RC (82.50±7.21 mg) and LDRC (99.38±35.57 mg) was compared to group RP (142.50±53.169 mg) as well as when total number of rescue analgesic doses in group RC (1.10±0.496) and group LDRC (1.32±0.474) were compared to group RP (1.92±0.694). Visual Analogue Scale (VAS) was noted at rest, cough, movement at 0, 4, 8, 12, 24 hours and showed a statistically significant difference between ropivacaine group RP and ropivacaine clonidine groups.

**Conclusion:** Addition of clonidine to ropivacaine in TPVB during breast cancer surgery results in lower pain scores, prolong duration of analgesia and reduce postoperative requirement of rescue analgesics. Both lower (0.2%) and higher (0.35%) concentrations of ropivacaine provide equally effective postoperative analgesia.


**Keywords:** Breast carcinoma, Postoperative pain, Thoracic paravertebral block, Visual analog scale

## INTRODUCTION

Majority of breast carcinoma patients undergo definitive surgery and these surgical procedures are typically performed under general anaesthesia. General anaesthesia alone does not produce adequate postoperative pain relief. So, further need of other modalities for post operative pain relief have emerged like opioids [1], nerve blocks, TPVB [2] etc. TPVB, a regional anaesthetic technique of injecting local anaesthetic adjacent to the thoracic vertebra close to where the spinal nerves emerge from the intervertebral foramina, appears promising for reduction of postoperative pain [3]. TPVB has been tried at single [4] level or multiple [5] level (four or seven) injection technique under anatomical landmark guided or Ultrasonography (USG) guided approach. The role of paravertebral analgesia as an effective method of perioperative pain relief for breast surgeries warrants more research on combinations of local anaesthetics and adjunctive analgesics.

Ropivacaine is a safer alternative to bupivacaine with minimal risk of cardiac toxicity and is equally effective as bupivacaine for its local anaesthetic action [6]. Clonidine, a selective $\alpha_2$ adrenergic agonist, blocks conduction of C and A-delta fibres and increases potassium conductance in neurons, thus intensifying conduction block. Various studies have tried different combinations of ropivacaine and clonidine for TPVB and have shown prolongation of duration of analgesia with addition of clonidine. Use of higher concentrations of ropivacaine increases chances of adverse effects. Hence, the search for an ideal dose combination needs more researches in future.

This study was planned to evaluate analgesic efficacy of clonidine (lµg/kg) as an adjuvant to two different doses of ropivacaine (0.35% and 0.2%) in TPVB by single injection technique at $T_4$ level for postoperative analgesia in patients undergoing MRM Surgery. The primary outcome measured in

this study was the duration of analgesia whereas the secondary outcomes measured were the rescue analgesic requirement over first 24 hour postoperatively, haemodynamic changes and adverse effects, if any.

## MATERIALS AND METHODS

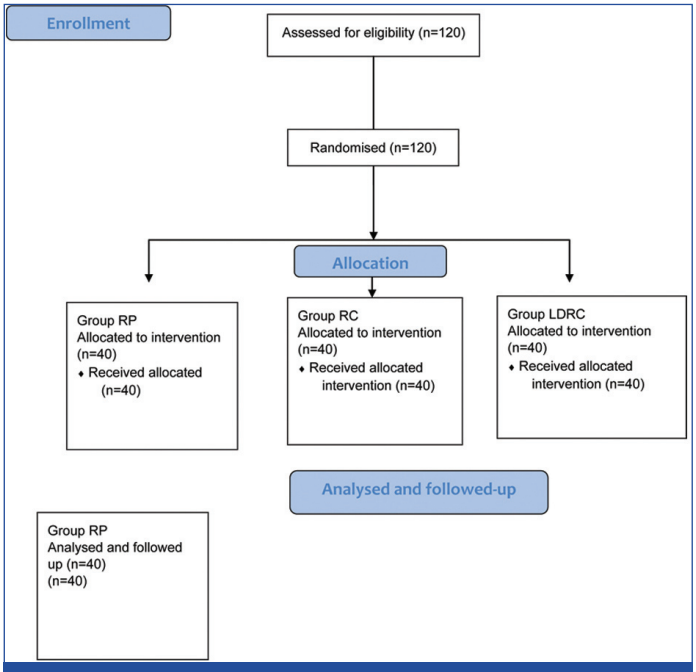
This randomised double blind comparative clinical study was carried out in a tertiary care centre in Southern Rajasthan from January 2019 to March 2020 after obtaining Institutional Ethics Committee approval (RNT/Stat./IEC/2019/) and Clinical Trials Registry India registration (CTRI/2019/12/02237).

**Sample size calculation:** Sample size was calculated on the basis of previous study by Mukherjee A et al., (2018) [7]. A sample size of 40 patients was needed in each group to have a power of 80% with alpha error of <0.05 to detect a difference of 7.28 hours in mean duration of analgesia and superiority limit of the difference in mean was assumed one hour.

**Inclusion criteria:** After obtaining written informed consent, one hundred twenty ASA grade I, II patients aged 18-60 years undergoing MRM surgery in general endotracheal anaesthesia were enrolled in the study.

**Exclusion criteria:** Patients with ASA grade III and higher, coagulopathies, history of cardiovascular disease, pregnancy, lactating mother, body mass index >35 kg/m$^2$, severe spine and chest wall deformities, renal diseases, cerebrovascular diseases, any acute psychiatric illness, allergy to study drug and refusal for participation were excluded from the study.

Patients were randomly allocated into three groups using computer generated random table in opaque sealed envelopes as depicted in consort diagram [Table/Fig-1].




**[Table/Fig-1]:** CONSORT flow diagram.

- Group RP received TPVB with 20 mL of 0.35% Ropivacaine,
- Group RC received TPVB with 1 µg/kg Clonidine added to 0.35% Ropivacaine upto 20 ml total volume and
- Group LDRC received TPVB with 1 µg/kg Clonidine added to 0.20% Ropivacaine upto 20 ml total volume.

Blinding of study was ensured by asking one anaesthesiologist to prepare the drug solutions who was not involved in further study. Another anaesthesiologist performed the block and recorded data. The patients and the anaesthesiologist involved in the anaesthetic technique and data recording were kept unaware of the group allocation.

### Study Procedure

All patients received midazolam 1 mg i.v. as premedication 1/2 hour before the block. Standard monitoring Electrocardiogram (ECG), Non-invasive Blood Pressure (NIBP), Oxygen Saturation ($SpO_2$) were applied and baseline parameters were recorded. After ensuring peripheral venous access with 18 Gauge (G) cannula, patients were given TPVB on ipsilateral side of operated breast under all aseptic precautions in sitting position [8].The superior spinous processes of thoracic vertebras from $T_1$ to $T_7$ were identified. The injection site was marked 2.5 cm lateral to spinous process of T4 and infiltrated by 2% lignocaine (3-4 mL) with a 25 gauge hypodermic needle. PVB was then administered as a single shot injection using a 22 gauge, 3.5 inch long quincke spinal needle. The needle was inserted through entry site and advanced anteriorly, perpendicular to the skin until it contacts the transverse process of particular vertebrae. Usually, this depth is 2-5 cm depending on the body habitus of the patient. This distance from the skin to transverse process was measured. The needle was grasped at this point distal from its tip, as a safety measure, to prevent inadvertent depth placement. The needle was then withdrawn to the subcutaneous tissue and angled to walk off the caudal edge of the transverse process. Then advanced anteriorly to an approximate of 1 cm depth. As the needle passed through the superior costotransverse ligament and enters the paravertebral space, loss of resistance or a "pop" was felt. After gentle aspiration to check for blood, Cerebrospinal Fluid (CSF) and air, the drug (according to the group allocation) was administered. After completion of block, patient was returned to the supine position. The time for performance of block (initiation. completion and duration of procedure) was noted.

General anaesthesia was administered using inj. fentanyl (1 µg/kg) i.v. and propofol (2 mg/kg) i.v. followed by injatracurium (0.5 mg/kg) i.v. After three minutes of atracurium administration, intubation was performed with cuffed endotracheal tube 7.0 mm size and the patient was ventilated with oxygen: air mixture. Anaesthesia was maintained with isoflurane (0.8-1.2%) and intermittent doses of atracurium (0.1 mg/kg). After completion of surgical procedure, the residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and patient was extubated. Haemodynamic parameters were recorded before blockade, after blockade, after insertion of Endotracheal Tube (ET) tube and after extubation.

After shifting the patient to postoperative ward, vital parameters were noted (0 hrs) and thereafter at 4th, 8th, 12th and 24 hours.

**Primary outcome:** The primary outcome measured was the duration of analgesia as decided by time of request for 1$^{st}$ rescue analgesic. Pain score was noted using a 10-point VAS on rest (R), cough(C) and movement {Forward Hand Movement (FHM)} at 0, 4, 8, 12 and 24 hours postoperatively Inj. diclofenac 75 mg i.v. was given as rescue analgesic whenever VAS ≥4 at rest.

**Secondary outcomes:** Secondary outcomes measured included cumulative consumption of rescue analgesic over 24 hours, pain score, haemodynamic parameters, perioperative complications of the block. These were sedation, hypotension, bradycardia, headache, hyperesthesia, urinary retention, pleural puncture, pneumothorax and haematoma.

Arterial hypotension was defined as Systolic Blood Pressure (SBP) below 90 mm Hg or fall of 20% of the preoperative value and treated with inj. mephentermin 6 mg i.v. Bradycardia was defined as pulse rate less than 50/minute and managed with inj. atropine 0.6 mg i.v. Patient satisfaction score was also recorded 24 hours after the operation by asking the patients to rate on scale of 1-10 their whole experience of anaesthesia with single level TPVB as unsatisfactory (1-3), satisfactory (4-7) or very satisfactory (8-10).

## STATISTICAL ANALYSIS

Statistical data was entered and analysed by using MS excel and Statistical Package for Social Sciences (SPSS) 20.0 version. Quantitative data was represented as arithmetic mean±standard deviation and analysed using ANOVA test. Qualitative data was represented as number (proportion or %) and analysed with Chi-square test. p<0.05 was considered statistically significant.

## RESULTS

Demographic profile of patients (age and weight distribution) was comparable between the three groups [Table/Fig-2]. The mean duration of analgesia was statistically significantly higher in clonidine groups RC and LDRC (811.5±110.99 and 753±119.76, respectively) as compared to ropivacaine alone group RP (400.125±108.13) [Table/Fig-3]. The total dose of rescue analgesic requirement in 1st 24 hours of postoperative period was also lesser in RC (82.50±7.210) and LDRC (99.38±35.576) group compared to group RP (142.50±53.169). However, the total dose of rescue analgesic required in group RC and LDRC demonstrated no statistically significant difference [Table/Fig-3].

| Parameters | Group RP (n=40) | Group RC (n=40) | Group LDRC (n=40) | p-value |
|---|---|---|---|---|
| Age (years) Mean ±SD | 48.42±9.04 | 49.42±7.80 | 46.80±10.14 | 0.464 |
| Weight (kg) Mean±SD | 55.95±4.73 | 57.85±7.87 | 55.92±5.46 | 0.282 |
| Duration of surgery(min) Mean±SD | 91.85±15.3 | 91.75±5.37 | 91.60±9.81 | 0.955 |
| ASAI/II physical status | 25:15 | 30:10 | 28:12 | 0.475 |

**[Table/Fig-2]:** Demographic characteristics.
(Data are presented as Mean±SD, Test applied: Anova test, p<0.05 is significant)

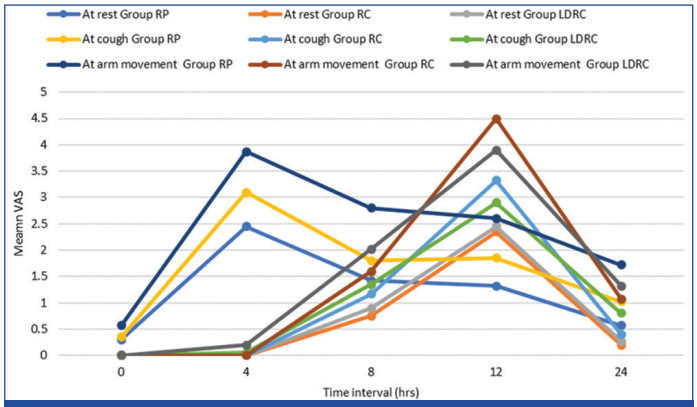
| Parameter | Group RP (n=40) | Group RC (n=40) | Group LDRC (n=40) | p-value |
|---|---|---|---|---|
| **Mean duration of analgesia (min)** | | | | |
| Mean±SD | 400.125±108.13 | 811.5±110.99 | 753±119.76 | Group RP/RC <0.001<br>Group RP/LDRC <0.001<br>Group RC/LDRC 0.057 |
| **Total dose of rescue analgesic (mg)** | | | | |
| Mean±SD | 142.50±53.169 | 82.50± 7.210 | 99.38±35.576 | Group RP/RC <0.001<br>Group RP/LDRC <0.001<br>Group RC/LDRC 0.08 |
| **Total number of rescue analgesic doses** | | | | |
| Mean±SD | 1.92±0.694 | 1.10±0.496 | 1.32±0.474 | Group RP/RC <0.001<br>Group RP/LDRC <0.001<br>Group RC/LDRC 0.077 |

**[Table/Fig-3]:** Comparison of analgesia characteristics in between groups.

The total number of doses of rescue analgesia needed in 1st 24 hours of postoperative period was also lesser in group RC (1.10±0.496) and group LDRC (1.32±0.474) as compared to group RP (1.92±0.694). The total number of doses of rescue analgesic needed was comparable in between clonidine groups (group RC and LDRC) [Table/Fig-3]. VAS was noted at rest, cough, movements at 0,4,8,12,24 hours and showed a statistically significant difference between ropivacaine alone group (group RP) and ropivacaine clonidine group (group RC and LDRC). The VAS was comparable in between the two clonidine groups [Table/Fig-4].

Haemodynamic parameters (SBP, Diastolic Blood Pressure (DBP), Heart Rate (HR))- preblock, afterblock, after intubation and at the time of extubation were statistically comparable. However, four patients in group RC (10%) and five patients in Group LDRC (12.5%) developed hypotension intraoperatively and seven patients in group RC and five patients in group LDRC experienced bradycardia in intraoperative period [Table/Fig-5].

Patients of all the three groups who had received TPVB with single drug or combination of drugs had a comparable mean patient satisfaction score indicating a satisfactory experience of anaesthesia [Table/Fig-6]. The haemodynamic parameters at studied time intervals (0,4,8,12,24 hours) postoperatively demonstrated no statistically significant difference.



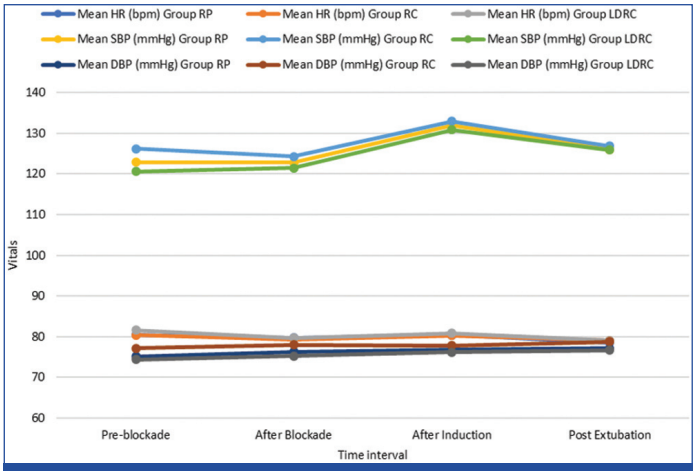

**[Table/Fig-4]:** Comparison of VAS at rest, cough and movement in between groups.

## DISCUSSION

Acute postoperative pain occurs after breast cancer surgery in most of the patients and is a key risk factor for the development of chronic pain [9]. Persistent pain after breast cancer surgery is increasingly recognised as a potential problem facing a sizeable subset of millions of women who undergo breast cancer surgery [7]. TPVB provides superior analgesia for breast cancer surgery when used in conjunction with general anaesthesia and reduces the severity of chronic pain after mastectomy [9]. TPVB results in ipsilateral somatic and sympathetic nerve blockade in multiple contiguous thoracic dermatomes above and below the site of injection [10].

The use of ropivacaine as a single injection into the TPVBs is increasingly being chosen. Compared with bupivacaine, ropivacaine produces a greater sensorimotor differential block with the benefit of a shorter elimination half-life, with a possibly lower potential for accumulation [11]. The addition of adjunctive analgesics, such as fentanyl and clonidine to local anaesthetics has been shown to enhance the quality and duration of sensory neural blockade, and decrease the dose of local anaesthetic and supplemental analgesia. Consequently, smaller doses of local anaesthetic may be used and non toxic plasma levels achieved [12].

Two techniques have been described in literature for performing TPVB: multilevel [5] and single level [4]. Both techniques have been reported to provide good analgesia. The single puncture technique provides more patient comfort by virtue of need of single prick for performing the block and lowers the need for sedation during the procedure, thereby improves the patient satisfaction. Hence, single level injection technique was used for performing TPVB. It is well established fact that lower concentration of any




**[Table/Fig-5]:** Comparison of haemodynamic parameters in between groups.

| Parameter | Group RP (n=40) | Group RC (n=40) | Group LDRC (n=40) | p-value |
|---|---|---|---|---|
| Very Satisfactory | 29 (72%) | 35 (88%) | 32 (80%) | 0.065 |
| Satisfactory | 8 (20%) | 4 (10%) | 6 (16%) | 0.07 |
| Unsatisfactoy | 3 (08%) | 1 (02%) | 2 (04%) | 0.075 |

**[Table/Fig-6]:** Comparison of mean patient satisfaction score.
(Data are presented as n (%), Test applied: chi-square test, p<0.05 is significant)

local anaesthetic drug produces a more differential block with more sensory component. A lower concentration of drug also decreases the chances of drug toxicity. Hence, it was decided to compare two different concentrations of ropivacaine so as to identify an optimal dose of Ropivacaine needed for producing effective analgesia. Clonidine in dose of 1 µg/kg is effective for TPVB for both intraoperative and postoperative analgesia so this dose was chosen for TPVB [13,14].

In this study, haemodynamic parameters (pulse rate, SBP, DBP) pre TPVB, post TPVB, after induction of anaesthesia and after extubation were comparable between all three groups. Very few patients developed hypotension (12%) and bradycardia (18%) in clonidine-ropivacaine group, however, this was easily manageable. The study findings are similar to the findings of Mukherjee A et al., and Burlacu CL et al., who reported the incidence of hypotension (18% & 91%, respectively) and bradycardia (38% and 16%, respectively) [7,12]. The occurrence of hypotension and bradycardia can be attributed to the centrally acting sympatholytic action of clonidine. In the present study, lower pain scores along with prolonged duration of analgesia were noted in clonidine-ropivacaine groups as compared to ropivacaine alone group however no such difference was noted between the groups where two different concentrations of ropivacaine were used along with clonidine. A few other researchers [9,15,16] too reported the same where administration of clonidine as an adjuvant to local anaesthetic leads to lower pain scores with prolongation of duration of analgesia. Findings of the present study signifies the fact that a lower concentration of ropivacaine (0.2%) is as effective as a higher concentration of ropivacaine for providing adequate analgesia in TPVB. The $\alpha_2$ agonists like clonidine and dexmedetomidine dose-dependently enhance the potency and prolong the duration of local anaesthetic by combining with $\alpha$2 receptors at the peripheral level. It also causes vasoconstriction around the site of injection. Thus, the systemic absorption of the local anaesthetic drug is delayed, resulting in a prolongation of the local anaesthetic effect. Moreover, the $\alpha_2$ agonist also directly inhibits the peripheral nerve action [16].

In the present study, inj. diclofenac was administered as rescue analgesic intravenously. It was noted that lower consumption of rescue analgesia on adding clonidine to ropivacaine although demand for rescue analgesia was similar between the two strengths of ropivacaine. Burlacu CL et al., had also noted a lower consumption of morphine as rescue analgesic in postoperative period when they added clonidine to levobupivacaine [13]. Patients of all the three groups had received TPVB with single drug or combination of drugs and reported a satisfactory experience of anaesthesia. This study findings are similar to study by Terheggen M A (2002) who noted a better patient satisfaction in PVB group as compared to which did not receive PVB.

### Limitation(s)

Firstly, the use of ultrasound guidance could have made the study more objective and more reproducible. Secondly, effect on intraoperative analgesic requirement was not assessed. Moreover, no comparison of Bispectral index score for anaesthetic depth was done in the present study. Future studies should consider these limitations.

## CONCLUSION(S)

Administration of clonidine as adjuvant to ropivacaine in TPVB during breast cancer surgery results in lower pain scores, prolong duration of analgesia and reduce postoperative requirement of rescue analgesics without major haemodynamic alterations and side effects. Both the lower (0.2%) and higher concentration (0.35%) of ropivacaine provided equally effective postoperative analgesia of similar duration. So, it is concluded that the use of lower concentration of ropivacaine (0.2%) along with clonidine (1 µg/kg) in TPVB effective for providing adequate postoperative analgesia in breast cancer surgery.

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**PLAGIARISM CHECKING METHODS:** [Jain H et al.]
- Plagiarism X-checker: Sep 29, 2022
- Manual Googling: Jan 27, 2023
- iThenticate Software: Feb 16, 2023 (11%)

**ETYMOLOGY:** Author Origin

**AUTHOR DECLARATION:**
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Sep 20, 2022**
Date of Peer Review: **Dec 08, 2022**
Date of Acceptance: **Feb 27, 2023**
Date of Publishing: **Apr 01, 2023**