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Original Research Article

Comparison of Analgesic Effect of Clonidine as Adjuvant with 0.375% Ropivacaine in Ultrasound Guided Thoracic Paravertebral Block in Modified Radical Mastectomy: A Prospective Randomized Double Blind Study

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Abstract

Background and Objectives: Thoracic paravertebral block (TPVB) provides superior analgesia for modified radical mastectomy (MRM). Various adjuvants have been added to local anaesthetics in TPVB but ideal combination is still awaited. This study aimed to evaluate efficacy of clonidine(1µg/kg) added to ropivacaine(0.375%) in USG guided TPVB for MRM.

Materials and Methods: In this prospective randomized double blind study, 78 ASA grade I,II patients aged 18-60 years undergoing MRM were divided into 2 groups- Group RC and RP to receive ultrasound guided TPVB with 0.375% Ropivacaine (19ml) added with 1µg/kg Clonidine and 1 ml normal saline, respectively followed by administration of general endotracheal anaesthesia. Primary outcome measured was duration of analgesia. Secondary outcomes included consumption of rescue analgesic drug, pain score and perioperative haemodynamic parameters. Qualitative data and quantitative data were presented as number(proportion) and mean±sd respectively. Chi square and unpaired t-test were applied where deemed appropriate. $p<0.05$ was considered statistically significant.

Results: Mean duration of analgesia was significantly prolonged when clonidine was added to ropivacaine for TPVB (16.87±1.55hrs v/s 7.00±1.17hrs,p=0.000). Total amount (84.62±25.40mg v/s 184.62±45.02mg) and number (1.13±0.39 v/s 2.46±0.60) of rescue analgesic doses were also reduced in group RC(P=0.00). HR, SBP and DBP were comparable between groups in perioperative period ($p>0.05$). VAS at rest, cough and forward hand movement showed statistically significant lower scores in group RC.

Conclusion: Addition of clonidine to ropivacaine in TPVB during breast cancer surgery results in prolonged duration of analgesia with lower pain scores and reduced postoperative requirement of rescue analgesics without major haemodynamic alterations.

Keywords: Thoracic paravertebral block, postoperative pain, Visual analog scale, Modified radical mastectomy.

Introduction

Breast Cancer is one of the common malignancies affecting the human population.[1] Among the various treatment modalities available for malignancy of breast, surgery is the most commonly used modality. These surgical procedures are typically performed under general anaesthesia but general anaesthesia alone does not produce adequate perioperative pain relief.[2] Inadequate pain management in the perioperative period leads to both short and long term complications like basal atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism and psychological trauma, which even may lead to post traumatic stress disorder. With the help of excellent pain management protocol, the anxiety, morbidity, cost and length of hospital stay in the postoperative period can be decreased.[3] Regional anaesthetic techniques offer better quality analgesia and fewer side effects than intravenous opioids. Thoracic paravertebral block (TPVB) is the technique of

injecting local anesthetic adjacent to the thoracic vertebra close to where the spinal nerves emerge from the intervertebral foramena.[4] TPVB provides superior analgesia for breast cancer surgery when used in conjunction with general anaesthesia and reduce the severity of chronic pain after mastectomy.

Lignocaine, bupivacaine, ropivacaine and levobupivacaine have been used traditionally for this block. Ropivacaine is a safer alternative to bupivacaine with minimal risk of cardiac toxicity and is equally effective as bupivacaine for its local anaesthetic action.[5] The major disadvantage of local anaesthetics is their relatively short duration of analgesia which can be overcome by addition of analgesic adjuvant to local anaesthetics.

Various adjuvants such as opioids,[6] epinephrine,[7] dexamethasone,[7] magnesium,[8] clonidine,[7,9] and dexmedetomidine,[9] has been added to local anaesthetics in TPVB to achieve quick, dense and prolonged block.Clonidine, a selective α2 adrenergic agonist, blocks conduction of C and A-delta fibers and increases potassium conductance in neurons, thus intensifying conduction block.[10]

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. This study was planned to evaluate analgesic efficacy of clonidine (1µg/kg) as an adjuvant to ropivacaine (0.375%) in USG guided thoracic paravertebral block by single injection technique at T4 level for postoperative analgesia in breast carcinoma patients undergoing modified radical mastectomy surgery.

Material and Methods

After obtaining approval from institutional ethical committee (IEC), registration in Clinical Trials Registry of India (CTRI) and informed written consent from all patients, this prospective, randomized double blind comparative clinical study was carried out in a tertiary care centre in southern rajasthan.

Patients aged 18-60 years, ASA physical status grade I and II, normotensive or treated hypertensives undergoing MRM surgery were included in this study.

Patients who were not fulfilling eligibility criteria, refusing for participation, having severe respiratory, cardiac or renal disorders, infection at the injection site, acute psychiatric illness, allergy to study drugs, coagulation disorders, severe spine and chest wall deformities, pregnancy, lactating mothers were excluded from the study.

Sample size was calculated on the basis of previous study by Mukherjee et al [11] who showed that the mean duration of analgesia upon addition of clonidine to 0.5% ropivacaine in TPVB was 19.65±4.73 hours. We hypothesized that the minimum reduction in the duration of analgesia by using ropivacaine 0.375% alone would be 3 hours for it to be clinically significant. Therefore for the study to have a power of 80% with α error<0.05, 39 patients were required in each group.

Selected patients were randomized into two groups using computer generated random numbers in opaque sealed envelope as depicted in consort diagram(Fig.1).

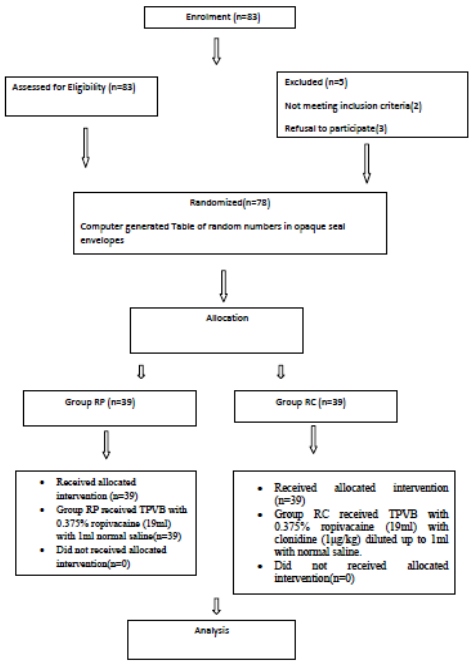

Figure 1: Consort Flowchart

Blinding was ensured by involving two anaesthesiologists in the study. Drugs were prepared by one anaesthesiologist who was not involved further in the study. Another anaesthesiologist and radiologist performed ultrasound guided TPVB and recorded data in the proforma and were kept unaware of group allocation. Patient, surgeon and staff nurse were also kept unaware of group allocation.

All enrolled patients underwent detailed preanaesthetic evaluation with proper history taking and relevant investigations. All patients were kept fasting 6 hours before the surgical procedure. On arrival in preoperative room, peripheral IV access with 20G IV cannula was taken in the upper limb. Patients were preloaded with Ringer Lactate 500ml and received midazolam 1mg iv as premedication 30 min before the block. After shifting to operation theatre (OT), standard monitoring which included noninvasive blood pressure(NIBP), pulse oximetry (SpO_2)and Electrocardiogram (ECG) were attached to the patient and baseline vital signs like Systolic blood pressure(SBP), Diastolic blood pressure (DBP), Mean arterial pressure(MAP), Heart rate(HR), Peripheral Oxygen Saturation(SpO_2) were recorded.

USG guided TPVB was performed at T_4 level with the patients in sitting position. The site of the paravertebral block was sterilized using povidone iodine solution and a high-frequency linear transducer probe (6-12 MHz) connected to ultrasound (USG) machine was covered by a disposable sterile cover. The probe was placed vertically lateral to the spinous process at the same side of surgery to attain a parasagittal view of the transverse processes, pleura, and superior costotransverse ligaments.

After localization of the paravertebral space by USG, a 25gauge hypodermic needle was inserted 2.5 cm lateral to the cephalic edge of the spinous process of the fourth thoracic vertebra, skin and subcutaneous tissue was infiltrated with 3 ml of 2% lidocaine. Afterwards, a 23 gauge 3.5 inch long Quincke spinal needle, was directed in an in-plane approach relative to the ultrasound transducer towards the paravertebral space. The needle was advanced under direct vision in a cephaled orientation to puncture the superior costotransverse ligament at the desired level. After negative aspiration for blood, CSF and air, study medications were injected. Proper spread of the drug in the paravertebral space was confirmed by visualising anterior displacement of the pleura on ultrasound.

A pinprick was utilized to ensure the successfulness of the sensory block and the onset of sensory block was recorded. If no block was attained within 30 minutes, patients were excluded from the data analysis. All patients were administered general anesthesia using fentanyl 2µg/kg and propofol 2mg/kg. Atracurium 0.5 mg/kg intravenously was used to facilitate endotracheal intubation. Maintenance of anaesthesia was achieved by inhalational agent isoflurane (0.8-1%) with oxygen - air mixture and intermittent doses of atracurium 0.1mg/kg as required. All vital parameters were monitored throughout the procedure. After completion of the surgical procedure, the residual neuromuscular block was antagonised by neostigmine 0.05 mg /kg with glycopyrrolate 0.01 mg /kg and patients were extubated. All patients were thereafter kept under observation for 24 hrs.

Haemodynamic parameters [SBP, DBP, HR, SpO_2] were recorded at predefined time intervals vizpreblock, post block, after induction of general anesthesia and post extubation. After shifting the patient to postoperative ward, vital parameters were noted and this time was considered to be 0 hrs thereafter at 4th, 8th, 12th and 24 hrs, vital parameters were recorded.

Pain score was noted using a 10 points Visual Analogue Scale (VAS) where 0 = no pain and 10 = worst pain imaginable. The VAS was recorded on rest (R), cough(C) and forward hand movement (FHM) at 0, 4, 8, 12 and 24 hours postoperatively. Inj. diclofenac 75mg iv was given as rescue analgesic whenever VAS ≥4 at rest and the time for administration of 1st rescue analgesic dose was noted. The cumulative number of doses & quantity of rescue analgesic during 24 hours of postoperative period was recorded.

Arterial hypotension was defined as systolic blood pressure below 90 mm Hg or fall of 20% of the preoperative value and managed with administration of inj. mephentermine 6 mg IV in graded doses till desired effect was achieved. Bradycardia was defined as heart rate less than 50/min. & managed with inj. atropine 0.3 mg in graded doses till desired effect was achieved.

24 hours after the surgery, the patients were asked to rate their whole experience of anaesthesia with single level TPVB as unsatisfactory, satisfactory or very satisfactory.

The primary outcome measured was the duration of analgesia as determined by the time of administration of first rescue analgesic dose. Secondary outcomes included cumulative number of doses and amount of rescue analgesic drug in 24 hrs postoperatively, haemodynamic parameters intraoperatively and postoperatively as well as adverse effect if any. Statistical data was entered and analyzed by using MS excel and SPSS 20.0 version. Quantitative data was represented as mean±sd and analyzed using student's t test. Qualitative data was represented as number

(proportion) and analyzed with chi-square test. $p<0.05$ was considered statistically significant.

Results

Both groups were comparable with respect to distribution of patients according to age and body weight ($p>0.05$). No statistically significant difference was observed between the groups with respect to HR, SBP and DBP in perioperative period ($p>0.05$). None of the patient had episode of hypotension or bradycardia in both the groups (Table 1,2)

Table 1: Haemodynamic parameters intraoperatively. Data are expressed as mean ± standard deviation

Heart Rate(bpm)			
Time interval	**Group RP**	**Group RC**	**p value**
Pre block	79.36±9.43	77.18±8.10	0.277
After block	79.95±8.57	77.74±7.64	0.234
After induction	81.05±6.48	78.77±8.20	0.177
Post extubation	76.83±6.86	76.33±6.32	0.733
SBP (mmHg)			
Pre block	121.28±10.68	122.59±10.88	0.594
After block	123.99±11.09	122.79±9.9	0.622
After induction	125.26±9.13	125.26±4.88	1.000
Post extubation	121.87±8.48	119.36±8.43	0.194
DBP (mmHg)			
Pre block	75.10±5.88	77.13±6.56	0.155
After block	77.12±6.08	78.36±6.35	0.385
After induction	78.36±5.46	79.08±6.07	0.585
Post extubation	74.49±4.71	75.74±5.52	0.284

Table 2: Haemodynamic parameters postoperatively. Data are expressed as mean ± standard deviation

Heart rate (bpm)			
Time interval (hrs)	**Group RP**	**Group RC**	**p value**
0	77.10±5.72	74.90±4.74	0.068
4	76.69±5.72	74.38±4.58	0.054
8	78.74±5.99	76.18±5.45	0.052
12	79.64±4.99	77.56±5.38	0.081
24	81.69±5.18	82.44±5.51	0.309
SBP (mmHg)			
0	123.13±7.44	121.44±8.64	0.357
4	125.08±6.64	123.05±7.88	0.224
8	126.97±7.82	124.74±8.74	0.239
12	128.72±8.09	125.56±8.73	0.102
24	129.33±7.37	130.03±5.58	0.642
DBP (mmHg)			
0	75.92±4.61	75.62±5.81	0.796
4	76.11±5.07	75.49±4.67	0.563
8	77.81±5.27	77.23±4.67	0.572
12	81.23±4.35	78.95±5.30	0.041
24	81.69±5.18	82.44±5.51	0.542

Pain intensity at rest, cough and forward hand movement measured using VAS showed statistically significant lower scores in group RC at 4, 8, 12 postoperative hrs ($p<0.05$) (Table 3)

Table 3: Comparison of VAS score. Data are expressed as mean ± standard deviation

VAS at rest			
Time interval (hrs)	**Group RP**	**Group RC**	**P value**
0	0 (0%)	0 (100%)	---
4	0.44±0.90	0.00	0.04
8	2.26±1.29	0.23±0.58	0.00
12	2.92±0.98	1.36±1.34	0.00
24	3.36±0.93	3.03±0.99	0.129

VAS at cough			
0	0.08±0.27	0.00±0.00	0.079
4	0.92±1.15	0.05±0.22	0.00
8	3.41±1.20	0.41±0.80	0.00
12	4.03±0.98	2.33±1.40	0.00
24	4.44±0.91	4.08±0.87	0.079
VAS at FHM			
0	0.36±0.587	0.03±0.16	0.001
4	1.92±1.01	0.10±0.30	0.00
8	4.38±1.12	0.87±1.03	0.00
12	5.03±1.01	3.33±1.43	0.00
24	5.49±0.91	5.13±0.86	0.079

Mean duration of analgesia was statistically significant prolonged when clonidine was added to ropivacaine for TPVB (16.87±1.55hrs v/s 7.00±1.17hrs, p=0.000) (Table 4).

Table 4: Analgesia characteristics

Duration of analgesia(hrs)			
	Group RP	Group RC	**P value**
Mean±SD	7.00±1.17	16.87±1.55	0.00
Total dose of rescue analgesic(mg)			
Mean±SD	184.62±45.02	84.62±25.40	0.00
Total number of rescue analgesia			
Mean±SD	2.46±0.60	1.13±0.39	0.00

Total amount (84.62±25.40mg v/s 184.62±45.02mg) and number (1.13±0.39 v/s 2.46±0.60) of rescue analgesic doses were also statistically significantly lower in group RC (P=0.00).
Majority of patients in group RC reported very satisfactory anaesthesia experience whereas in group RP, majority of patients had a satisfactory experience & this difference was statistically significant(p<0.001)(Fig 2).

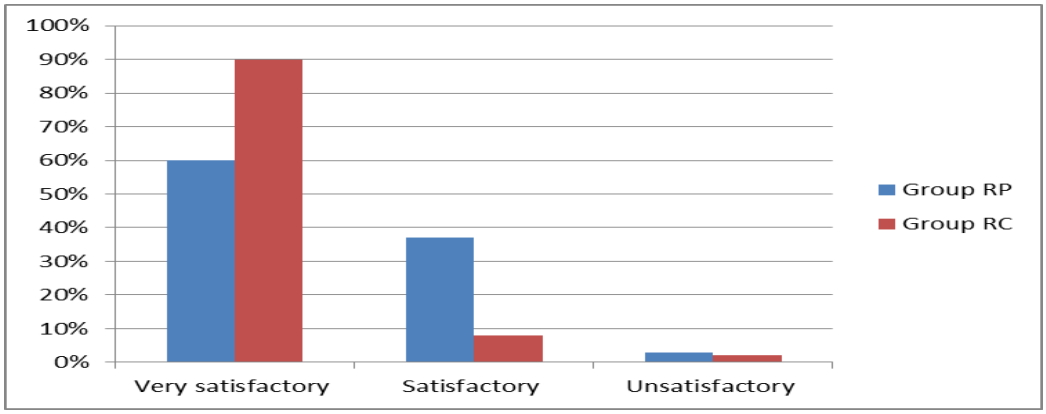

Figure 2: Mean patient satisfaction score

Discussion

Breast malignancy patients undergoing surgery under general anaesthesia may experience severe postoperative pain, which have serious physiological, psychological and financial repercussions. Regional anaesthesia provides better quality of analgesia compared to intravenously administered opiates & nonopiates. Regional analgesia techniques that suits breast surgery includes thoracic paravertebral block (TPVB), erector spinae plane block (ESPB) and pectoral nerve block.[12] Choice of regional anaesthesia technique depends on physician experience & institutional policy. Various local anaesthetics like lignocaine, bupivacaine, levobupivacaine, ropivacaine with adjuvant like opiates and non opiatesviz epinephrine, dexamethasone, magnesium, clonidine, dexmedetomidine have been tried in TPVB for producing analgesia in breast surgeries but the results are still inconclusive.[5,6,7,8,9] Hence the search for better suited combination of a local anaesthetic and adjuvant is still on.

We conducted this study to evaluate the effect of adding clonidine in dose of 1mcg/kg to ropivacaine(0.375%) in USG guided TPVB for patients undergoing modified radical mastectomy (MRM) for breast malignancy .

We observed that addition of clonidine lead to reduced pain score (VAS) at rest, cough as well as on forward hand movement. Our findings are similar to study conducted by Mayur N et al,[3] Tawfik SA et al,[4] Sankaran C et al [13] and Kamble TS et al.[14] The α2 agonists like clonidine and dexmedetomidine dose dependently enhance the potency and prolong the duration of local anaesthetic by combining with α2 receptors at the peripheral level. The other action includes vasoconstriction around the site of injection. Thus, the systemic absorption of the local anaesthetic drug will be delayed, resulting in a prolongation of the local anaesthetic effect. Moreover, the alpha 2 agonist also directly inhibits the peripheral nerve action.[13]

We also noted that the duration of analgesia was significantly prolonged along with a decreased requirement of postoperative analgesic doses in clonidine-ropivacaine group. Our results find support in studies conducted by Mayur N et al,[3] Sankaran C et al,[13] and Kamble TS et al.[14]

Two techniques have been described in literature for performing TPVB: multilevel injection and single level injection. 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. Use of ultrasound for administering the block further decreases the time needed to perform the block and is associated with minor patient discomfort.[2] Hence, we decided to use USG guided single level injection technique for performing TPVB**.**

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.[15]

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 level achieved.[16]

TPVB results in ipsilateral somatic and sympathetic nerve blockade in multiple contiguous thoracic dermatomes above and below the site of injection.[4] A cadaver study observed distribution of 20ml injected dye over three to four TPVS (range 1-10) with 40% incidence of epidural spread. Therefore, the analgesic effect produced by the volume of 15 or 20 ml in TPVB may also include the effect of the epidural spread.[17]

In this present study, both the groups were comparable haemodynamically throughout the study period. No clinically significant hypotension or bradycardia was noted in both the groups.. This observation may be attributed to the fact that TPVB produces only unilateral and limited sympathetic block.[2]

Patients in both ropivacaine & ropivacaine+clonidine group reported a satisfactory experience of anaesthesia although addition of clonidine leads to better patient satisfaction score.

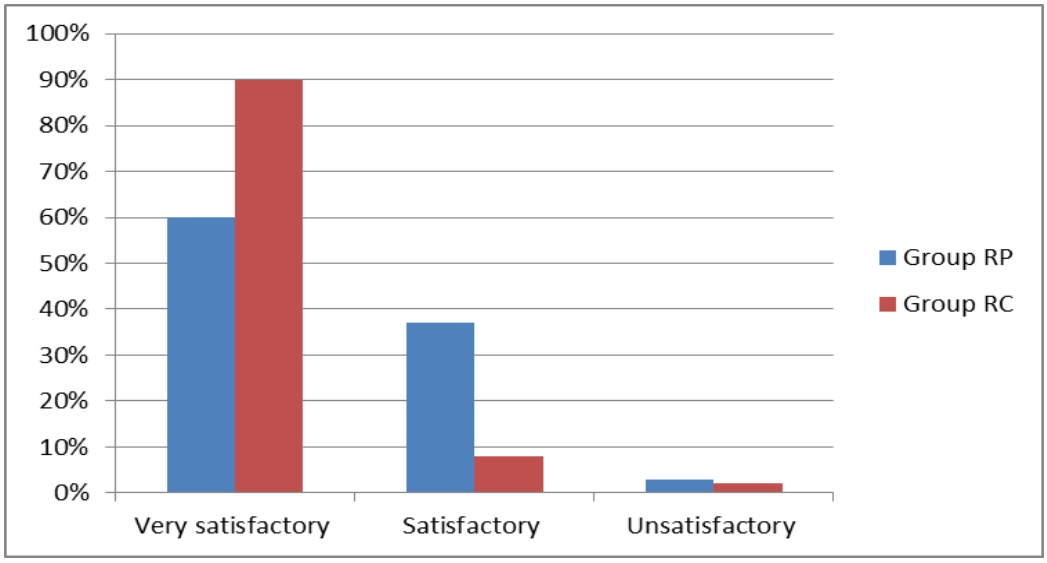

Figure 2: Mean patient satisfaction score

Our study has few limitations. No mapping of sensory block area was performed in our study. Intraoperative analgesic requirement was also not assessed in the present study. Moreover, different

doses of clonidine were not compared to find out the optimal dose. Further studies should consider these limitations.

Conclusion

Administration of clonidine as adjuvant to ropivacaine in TPVB during breast cancer surgery results in lower pain scores, prolonged duration of analgesia and reduced postoperative requirement of rescue analgesics without major haemodynamic alterations and side effects. We suggest that use of lower concentration of ropivacaine(0.375%) along with clonidine (1μg/kg) in TPVB is effective for providing adequate postoperative analgesia in breast cancer surgery.

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