Original Article

Role of tramadol as an adjuvant in ultrasound-guided serratus anterior muscle block for modified radical mastectomy - A randomized control trial

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Abstract

Background and Aims: Modified radical mastectomy (MRM) is associated with significant acute post-operative pain that may progress to chronic pain syndromes in 25–60% of patients. Serratus anterior muscle (SAM) block has proved to be an excellent analgesic option in patients undergoing MRM. Although many adjuvants have been utilized for the prolongation of analgesia, the role of tramadol in SAM has not been studied as yet. We hypothesize that the addition of tramadol to ropivacaine for SAM block may reduce morphine consumption in the post-operative period in patients undergoing elective MRM surgeries. The primary aim of the study was to compare cumulative post-operative morphine consumption over 24 h in patients receiving SAM block with or without tramadol. The secondary aims were to observe adverse events related to the procedure or medications. The other parameters recorded were non-invasive blood pressure (NIBP), pulse rate, respiratory rate, and nausea or vomiting.
Material and Methods: Patients scheduled to undergo MRM were randomly allocated by block randomization into two groups. The study group (Group T) received a SAM block with 0.25% ropivacaine (18 ml) with tramadol 100 mg while the control group (Group P) received a SAM block with 18 ml of 0.25% ropivacaine and 2 ml of saline. Patients were assessed for pain scores, analgesic requirement, time to first analgesic request, hemodynamic variables, and any side-effects at 30 min, 1 h, 4 h, 8 h, 12 h, and 24 h post-operatively.
Results: Cumulative morphine consumption over 24 h in the post-operative period was less in the group T (3.06 ± 1.53 mg vs 4.34 ± 1.53 mg; *P* 0.001). Time to the first analgesic requirement was more in group T (10.44 ± 5.04 h vs 6.11 ± 2.73 h; $P < 0.001$). Pain scores were significantly lower in the group T at all time points.
Conclusion: Tramadol, when used as an adjuvant to ropivacaine for SAM block reduces post-operative pain scores in the first 24 h and prolongs the time of first morphine requirement.

Keywords: Adjuvant, modified radical mastectomy, serratus anterior block, tramadol

Introduction

Breast carcinoma accounts for 25–32% of female cancers in our country,[1] and modified radical mastectomy (MRM) is the most common therapeutic option.[2] MRM is associated with acute post-operative pain which may progress to chronic pain syndromes in 25% to 60% of patients. The mastectomy pain syndrome is the most common[3] chronic pain syndrome and an effective post-operative analgesia can stop its development.

The serratus anterior muscle (SAM) plane block, provides analgesia to the anterior chest and axillary region and is an attractive alternative to thoracic epidural and paravertebral

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blocks for post-operative analgesia.[4,5] The adjuvants such as dexamethasone, clonidine, opioids, and magnesium, decrease the local anesthetic (LA) requirement, thereby reducing the potential for toxicity.[6,7]

Tramadol, a mu-opioid receptor agonist, with its ability to block peripheral potassium channels, has been used as an adjunct in neuraxial and some peripheral blocks recently[8-10]; however, its use in SAM block has not been explored as yet. Therefore, we in the present study hypothesized that the addition of tramadol to Ropivacaine for SAM block may reduce morphine consumption in the post-operative period in patients undergoing elective MRM surgeries. The primary aim of the study was to compare cumulative post-operative morphine consumption over 24 h in patients receiving SAM block with or without tramadol. The secondary aims were to observe adverse events related to the procedure or medications. The other parameters recorded were non-invasive blood pressure (NIBP), pulse rate, respiratory rate, and nausea or vomiting.

Material and Methods

The present study was conducted in a tertiary care center as a prospective, randomized, controlled clinical trial after Institutional Ethics Committee (EC/2018/208) approval, and registration in Clinical Trial Registry (CTRI/2019/03/018146). A written informed consent was taken from all participants. The patients aged 18-80 years, with American Society of Anesthesiologists' (ASA) physical status I and II, scheduled to undergo elective MRM under general anesthesia were enrolled in the study. The patients with a history of drug allergy, psychiatric illness, substance abuse, severe cardiovascular, respiratory, liver, metabolic, or neurological disease, chronic treatment with analgesics, pregnancy, coagulopathy or infection at the planned injection site were excluded.

The sample size for the study was determined based on a previous study conducted by Robaux *et al.*[9], which demonstrated that using 100 mg tramadol leads to a significant reduction in post-operative opioid requirement. The study aimed to detect a difference of 0.7 standard deviation (SD) between the mean pain scores among the study groups, with a power of 80%, a type 1 error of 0.05, and a confidence interval of 95%. Accordingly, a sample size of 33 patients per group was calculated. To account for any possible dropouts, the study recruited 35 patients per group. Therefore, the sample size was deemed sufficient to detect the desired difference in pain scores.

The randomization of patients was done by computer-generated block randomization method with blocks of 4, 6, and 8 generated to allocate the patients to either of the two groups. The patients in group T received a SAM block with 0.25% ropivacaine (18 ml) with tramadol 100 mg (total volume 20 ml) and the patients in group P received a SAM block with 0.25% ropivacaine (18 ml) with a placebo 2 ml normal saline 0.9% (total volume of 20 ml). The group allocation was concealed in coded opaque sealed envelopes and decoding was done at the end of the study.

The patients were explained about linear visual analog scale (VAS) for pain (0 - no pain, 10 - worst imaginable pain) and categorical scoring system (CSS) for nausea (0-none, 1-mild, 2-moderate, 3-severe) in their own vernacular language and educated about the use of intravenous patient-controlled analgesia (IV-PCA) pump. In the operating room, after the application of ASA standard monitors, general anesthesia was induced with intravenous morphine 0.1 mg/kg and propofol 2 mg/kg, and vecuronium 0.1 mg/kg was used to facilitate endotracheal intubation. The maintenance of anesthesia was achieved by N2O/O2 (60:40) with sevoflurane (MAC 1-1.5).

The SAM block was performed as per randomization. The operating side was prepared with 10% povidone-iodine solution. After ensuring full aseptic precautions and draping of the area, a linear array ultrasound probe (5-10 MHz Sonosite, Inc. Bothell, WA 98021 USA) was used. The region of interest was scanned from the mid-clavicular region of the thoracic cage in a sagittal plane. The ribs were counted inferiorly and laterally until the fifth rib was identified in the mid-axillary line. After identifying the latissimus dorsi, teres major, and serratus muscle, the SonoPlex Stim cannula (21G × 50 mm, Pajunk, Germany) was introduced in the muscle plane between latissimus dorsi and serratus anterior with respect to ultrasound probe from supero-anterior to postero-inferior side. The muscle plane was confirmed by hydro-dissection using 2 ml of normal saline. The study drugs were drawn in identical unlabeled syringes, prepared by a person not involved in the performance of procedure or data collection. The prepared drug was administered after confirmation of negative aspiration.

The surgery commenced after this procedure. Any additional requirement of intraoperative analgesia defined as >20% increase in heart rate or blood pressure in response to a surgical stimulus with a constant depth of anesthesia in either group was noted. At the end of the surgery, the patients were extubated after the neuromuscular block was antagonized with neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg. In the post-anesthesia care unit, all the patients were connected to an IV-PCA pump with morphine in the strength of 1 mg/ml with a lockout interval of 5 min and maximum dose of morphine

being 0.2 mg/kg body weight over 4 h. Rescue analgesia of 1 g intravenous paracetamol was administered to patients in both the study groups if VAS score exceeded 4 on rest or movement, even after a maximal permissible dose of morphine.

An anesthesiologist, blinded to the intervention group recorded the observations in the post-operative period. The VAS scores were recorded at rest and on movement at 30 min, 1 h, 4 h, 8 h, 12 h, and 24 h post-operatively. If at the time of observation, the patient was sleeping comfortably, then VAS was considered <4. The time to the first analgesic requirement and any adverse event related to the procedure or medications were recorded in both groups. The other parameters recorded were non-invasive blood pressure (NIBP), pulse rate, respiratory rate, and nausea or vomiting as per CSS.

Statistical analysis

The statistical analysis was carried out using Statistical Package for the Social Sciences version 21.0 (SPSS Inc. Chicago, Illinois, USA). The normality of data was tested by Kolmogorov–Smirnov test. The categorical variables were presented in numbers and percentages (%), and the continuous variables as mean ± SD. The quantitative variables were compared using the unpaired *t*-test or Mann-Whitney test between the two groups. Repeated measure analysis of variance (ANOVA) was also applied to see the trend of the mean VAS scores over time and find the pairwise comparisons between the follow-ups with Bonferroni correction. The qualitative variables were compared using the Chi-square test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

Of all the patients assessed during the period of study, 70 patients were eligible and were randomized into two groups [Figure 1]. The demographic data and pre-operative hemodynamic variables were comparable between the two groups [Table 1].

The mean cumulative morphine requirement in group T during 24 h after surgery (3.06 ± 1.53 mg vs 4.34 ± 1.53 mg, $P = 0.001$) [Figure 2] and the VAS scores were lower as compared to group P at 1 h post-operatively [Table 2]. The time to first morphine bolus requirement was longer in group T (10.44 ± 5.04 h vs 6.11 ± 2.72 h, $P < 0.001$) as compared to group P [Figure 3].

Table 1: Baseline patient characteristics of the two study groups

Patient characteristics	Group P (*n*=35)	Group T (*n*=35)	*P*
Age (years)	52.54±14.37	54.14±10.89	0.60
Body weight (kg)	63.91±10.49	63.46±9.72	0.85
ASA I	16 (45.7%)	11 (31.4%)	0.22
ASA II	19 (54.3%)	24 (68.6%)	
Baseline PR (beats/min)	78.46±8.43	76.29±10.19	0.33
Baseline SBP (mm Hg)	128.11±11.18	129.86±12.82	0.55
Baseline DBP (mm Hg)	78.11±9.31	77.69±7.56	0.83
Baseline RR (breathsmin^{-1})	13.63±1.03	13.97±1.54	0.60

*ASA: American Society of Anesthesiologist; DBP: diastolic blood pressure; PR: pulse rate; RR: respiratory rate; SBP: systolic blood pressure; Data is represented as mean±SD or number (%); P<0.05 – significant**

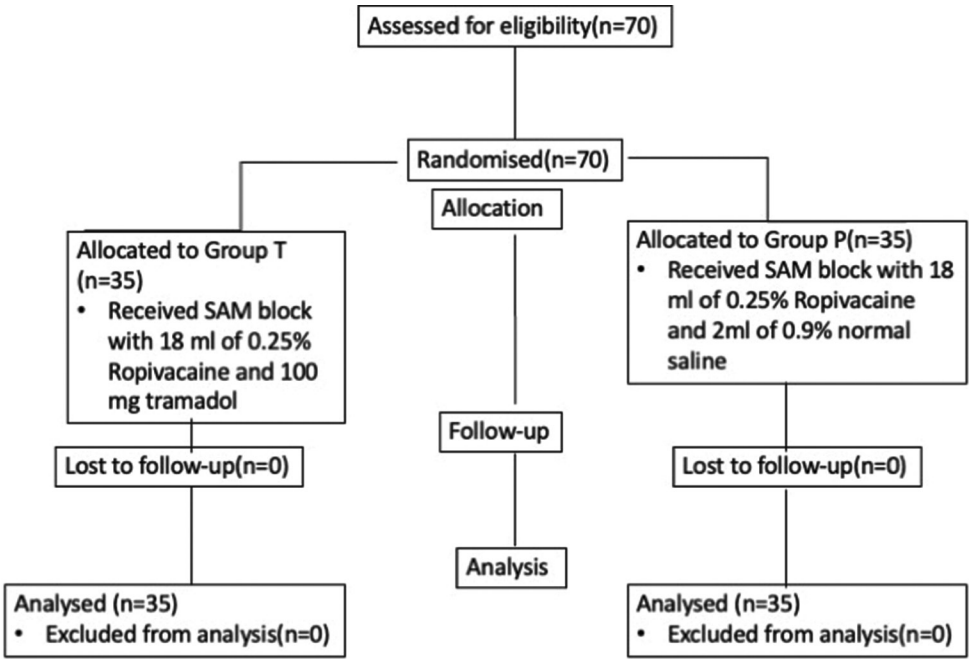

Figure 1: Consort diagram

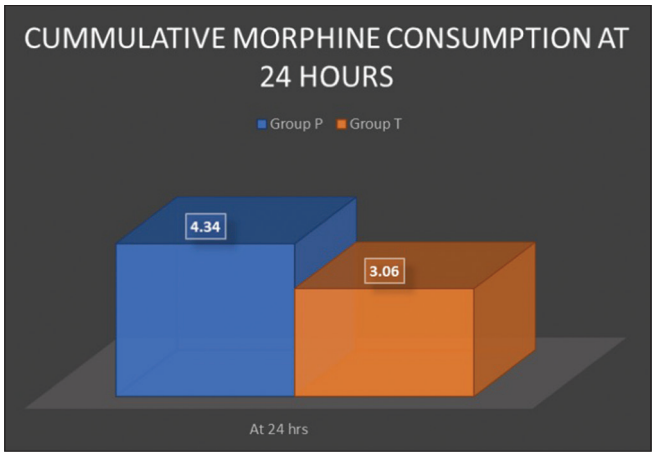

Figure 2: Figure showing cumulative morphine requirements during first 24 hours in two groups

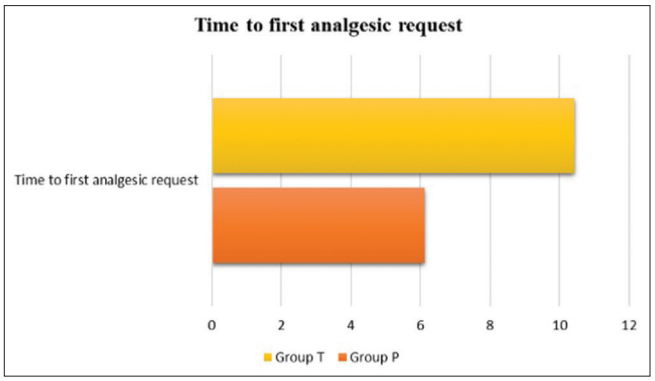

Figure 3: Figure showing time to first morphine requirements in two groups (SAM: Serratus anterior muscle block)

Table 2: Post-operative pain scores

	Group P	Group T	*P*
VAS at rest			
At 30 min	0.43±0.66 [0.20-0.65 (0-2)]	0.43±0.70 [0.19-0.67 (0-3)]	0.95
At 1 h	1.00±0.60 [0.80-1.20 (0-3)]	0.46±0.70 [0.22-0.70 (0-3)]	<0.001*
At 4 h	2.03±1.34 [1.57-2.49 (0-5)]	0.86±0.65 [0.63-1.08 (0-2)]	<0.001*
At 8 h	2.46±1.15 [2.06-2.85 (0-4)]	1.31±0.53 [1.13-1.50 (0-2)]	<0.001*
At 12 h	2.71±1.13 [2.33-3.10 (0-5)]	1.86±0.65 [1.63-2.08 (1-4)]	<0.001*
At 24 h	2.69±1.23 [2.26-3.11 (0-5)]	1.83±0.66 [1.60-2.06 (0-3)]	<0.001*
VAS on movement			
At 30 min	0.89±0.96	0.88±1.12	0.99
At 1 h	1.86±0.81 [1.58-2.14 (-4)]	1.34±0.91 [1.03-1.65 (0-4)]	0.005*
At 4 h	3.00±1.37 [2.53-3.47 (1-6)]	1.86±0.73 [1.61-2.11 (0-3)]	<0.001*
At 8 h	3.37±1.19 [2.96-3.78 (0-5)]	2.31±0.53 [2.13-2.50 (1-3)]	<0.001*
At 12 h	3.49±1.36 [3.02-3.95 (0-6)]	2.71±0.71 [2.47-2.96 (1-5)]	0.001*
At 24 h	3.43±1.42 [2.94-3.92 (0-6)]	2.83±0.71 [2.59-3.07 (1-4)]	0.02*

Data are represented as mean±standard deviation; VAS: visual analog scale; P<0.05 considered significant

Among the secondary parameters, the heart rate was lower in group T. However, there was no difference between the blood pressure and the incidences of nausea and vomiting between the two groups. There were no complications associated with block application or drugs.

Discussion

The results of this study show tramadol when used as an adjuvant for SAM block in patients undergoing MRM reduces the post-operative morphine consumption and prolongs the duration of analgesia. Tramadol exerts its analgesic effect via central and peripheral actions. The central analgesic effect occurs through opioid agonistic and monoaminergic activity and the peripheral and LA-like action via the blockade of potassium channels. Ropivacaine and tramadol exert their local anesthesia actions by two separate mechanisms and this may be the reason for the combined additive analgesic effect.[9,10]

The use of tramadol along with a modified pectoral nerve block for MRM surgery has been demonstrated previously by Hayes *et al.*[11] However, compared to our study, rescue fentanyl was required earlier (246.93 ± 53.46 min vs 6.11 ± 2.72 h). This difference can be associated with a better spread of injection in SAM.[12] The results of our study are comparable to the study of El-Kabariety[13] which showed 100 mg tramadol used as an adjuvant with 20 ml of 0.5% levobupivacaine in transverse abdominis plane block had lesser morphine requirements in the first 48 h (18.1 ± 2.4 mg vs 26.1 ± 3.3 mg; $P < 0.001$) compared to levobupivacaine alone. However, the time to first morphine requirement was longer in our study group (6.11 ± 2.72 h vs 250.8 ± 23.3 min). This can be due to the nurse-controlled analgesia utilized by the authors in their study.

The results of our study are in contrast to the study done by Kesimci *et al.*[14] who used 100 mg of tramadol with 7.5 mg/ml of ropivacaine for axillary brachial plexus block and found no difference in time to the first analgesic requirement. This was attributed to a high dose of LA agent used that could have masked the beneficial effect of tramadol and the absence of proper pain score assessment.

There was no serious adverse effect pertaining to the block reported during the study like pneumothorax, neuronal injury, or accidental intravascular injection. This may be as a result of ultrasound guidance and also as the drug was deposited superficially to the SAM, the injection site is away from pleura

and major vascular structures. Both groups showed a similar incidence of nausea and vomiting. None of the patients had respiratory depression, sedation, or hemodynamic instability, showing tramadol in the dose of 100 mg, when given as an adjuvant to ropivacaine for SAM block is safe and effective.

Limitations

The time of block onset of the block effect could not be assessed as it was performed after general anesthesia. We did not study the effect on analgesia beyond 24 h and further studies need to be conducted to evaluate this. This was a single-shot deposition of the drug, and the insertion of the catheter could have enabled continuous infusion and titration of the drug as per the patient's requirements. A fixed dose of tramadol was used in the current study, and further studies may be aimed at finding out the median effective dose of tramadol as an adjuvant to LA.

Conclusions

Tramadol in the dose of 100 mg, when given as an adjuvant to 0.25% ropivacaine for SAM block in patients undergoing MRM surgery, decreases post-operative pain scores in the first 24 h and prolongs the time of first morphine requirement, without side-effects.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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