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Research article

Efficacy of adding tramadol as adjunctive analgesic with levobupivacaine in modified pectoral nerve block for modified radical mastectomy surgery

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1. Introduction

Breast surgeries are usually associated with sever postoperative pain, sever acute postoperative pain after breast surgery is considered a risk factor for the development of chronic postmastectomy pain, good perioperative analgesic technique for breast surgery is always questionable [1]. Pectoral nerve block (PecS block) produces good analgesia and it is less invasive procedure compared to thoracic epidural and paravertebral blocks which may cause complications as total spinal anesthesia, inadvertent intravascular drug injection and peumothorax [2], PecS block has been used as analgesic technique firstly by Blanco in minor breast surgery, and achieved block of nerves that innervate the pectoralis muscles [3]. Later on Blanco and Colleague in Pecs II achieved a modification with involving the axilla aiming at blocking the pectoral, intercostals, intercostobrachial, and long thoracic nerves [4,5].

Different drugs such as ketamine, clonidine, opioid and neostigmine, have been used as an adjuvant to local anesthetics to improve the analgesic effect, tramadol considered as a weak μ-opioid agonist, it has multimodal mechanisms of action in addition to its opioid agonist effect, several studies showed that addition of tramadol to local anesthetics, modifies the quality of postoperative analgesia [6–8].

Levobupivacaine is "S"-enantiomer of bupivacaine, it has long duration of action with less cardio and neurotoxcity compared with bupivacaine, it have been used for regional block [9].

The primary purpose of this randomized clinical study is to evaluate the quality of analgesia after adding tramadol to levobupivacaine for modified pectoral nerve block in modified radical mastectomy surgery.

We hypothesized in the current study that addition of tramadol combined with levobupivacaine for modified pectoral nerve block would be safe and effective in the reduction of postoperative pain, postoperative opioid consumption after modified radical mastectomy surgery.

2. Methods

This study was approved by institutional ethical committee. Written informed consent was obtained from sixty female patients and American Society of Anesthesiologists (ASA) status I and II aged between 20 and 60 years, undergoing modified radical mastectomy surgery at Mansoura Oncology Center of Mansoura University, under general anesthesia. Exclusion criteria included local skin infection, bleeding disorder, coagulation abnormality, spine or chest deformity, psychiatric disease, pregnancy and patients with allergy to any of the drug used.

All patients were premedicated with diazepam 5 mg orally and ranitidine 150 mg orally the night before surgery and patients were kept fasting for 6 h prior to surgery. All patients were familiarized with standard visual analogue scale (VAS) for pain assessment (100 mm unmarked line in which 0 = no pain and 100 = worst pain). On entrance to the preoperative holding area routine monitoring (base line values) in the form of pulse oximetry, systolic and diastolic blood pressure were taken from patients, intravenous (IV) access was obtained and patients were premedicated with 3 mg midazolam 10 min before transmission to the operating room.

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Anesthetic management was standardized and induction of anesthesia was started with preoxygenation for 3 min, IV fentanyl 2 ug/kg, propofol 2 mg/k and atracurium 0.5 mg/kg, then tracheal intubation was done using suitable size of endotracheal tube. The patient's lungs were ventilated with positive pressure ventilation to maintain end-tidal carbon dioxide around 35 mmHg.

Patients were randomly assigned using a computer-generated assignment into two groups according to the drug used for pectoral nerve block either group (L) received levobupivacaine alone (n = 30) with a total volume of 20 ml of levobupivacain 0.5% or group (T) received levobupivacaine and tramadol (n = 30) with a total volume of 20 ml of levobupivacain 0.5% combined with tramadol 100 mg [10]. Allocation numbers were concealed in opaque closed envelope. Anesthesia management, modified PecS block and data collections were performed by personnel blinded to the group allocation.

3. Technique of block

After induction of general anesthesia, block was done with patients were placed in supine position and abduction of the epsilateral upper limb then sterilization of the skin of the infraclavicular and the axillary regions then a high frequency linear ultrasound (Siemens, AcusonP300) probe was inserted under the lateral third of the clavicle to identify pectoralis major and pectoralis minor muscles, then moved laterally to locate the axillary artery and vein directly above the first rib and 90 mm needle (stimuplex D, B Braun, Melsungen A G, Germany) was inserted in plane with US probe and directed to the fascial plane between pectoralis major and pectoralis minor muscles then 10 ml of previously prepared study drug was injected after aspiration between the fascial plane of the pectoralis muscles, then the ultrasound probe was directed laterally in oblique manner toward the axilla with identification of serratus anterior muscle that present at level of the third rib and the needle was reinserted into the fascial plane between pectoralis minor muscle and serratus anterior muscle where the remaining volume of the prepared drug was injected after aspiration in the space between pectoralis minor muscle and serratus anterior muscle [4].

Anesthesia was maintained with minimum alveolar concentration (1MAC) of isoflurane with 50% oxygen and air, atracurium 0.2 mg/kg was given according to the anesthetist latitude, isoflurane concentration was increased if heart rate increases or blood pressure increased by more than 20% above baseline, additional bolus IV fentanyl (0.5–1 μg/kg) was injected if there was inadequate hemodynamic response to increased isoflurane concentration. Data were recorded in the patients' anesthesia sheets (heart rate, end-tidal CO_2, O_2 saturation and systolic and diastolic blood pressure) every 5 min after induction of anesthesia till the end of operation, if hypotension occurred defined as decreased by 20% of the baseline value it was treated using boluses of 250 ml of normal saline and ephedrine 0.1 mg/kg. If bradycardia occurred defined as decreased by more than 20% below baseline value it was treated with atropine 0.01 mg/kg. After completion of surgical procedure, isoflurane was discontinued and residual neuromuscular block was antagonized with neostigmine40 μg/kg and atropine 20 μg/kg and antiemetic prophylaxis with ondansetron 0.1 mg/kg was given IV, after extubation the patients were transferred to postanesthesia care unit (PACU). The Duration of surgical procedure and anesthesia time were recorded.

4. Post operative assessment

In the PACU, patients were monitored for heart rate, oxygen saturation, systolic blood pressure and diastolic blood pressure for 1 h postoperative by another anesthetist who was not aware of the study protocol. Patients were discharged to the surgical ward if they achieved score of 10 at modified Aldrete score [11].

The primary outcome of this study was the severity of pain which was assessed using VAS 1/2 h after surgery, then at 1 h, 2 h, 4 h, 6 h, 8 h, 12 h and 24 h postoperatively. All patients were given IV ketorolac 30 mg/8 h postoperatively and IV fentanyl 0.5 μg/kg was available as rescue analgesia whenever VAS continued to be >40 mm after 30 min of ketorolac injection. Fentanyl injection can be repeated. The secondary outcome were the time for the first postoperative analgesic dose requirements and the total dose of 24 h postoperative fentanyl consumption. Postoperative nausea and vomiting (PONV) were assessed using a four-point numerical scale (0 = no PONV, 1 = mild nausea, 2 = severe nausea or vomiting once, and 3 = vomiting more than once), postoperative adverse effects and complications were recorded [12].

4.1. Statistical analysis

The statistical analysis was done with SPSS version 16 (SPSS Inc., Chicago, IL). Kolmogorov–Smirnov test used for the normality of data by. Description for quantitative data was done as mean (±) SD. Unpaired student *t*-test was used to compare quantitative data, while comparison for qualitative data between two groups Chi square test was used. P-value considered significant if <0.05.

The power of this clinical trial was calculated after pilot study using the G Power analysis program with visual analog score (VAS) as the primary variant and assuming type I error protection of 0.05 and an effect size convention of 0.9 with total sample size of 54 patients. To protect against drop out cases we added 6 cases, so the total number was 60 cases with 30 patients in each group.

5. Results

Sixty adult female patients aged between 20 and 60 years completed this randomized clinical trial with 30 patients in each group (Fig. 1). As regard the demographic data as shown in (Table 1) both groups were comparable. As regard the duration of surgery and duration of anesthesia, there was no significant difference between the studied groups (Table 2). Meanwhile, according to postoperative pain assessment using VAS, postoperative visual analogue score (VAS) was significantly decreased in group T in comparison to group L throughout the study period (with P-value was 0.000) except for the VAS at 24 h postoperative where there was no significant difference between the studied groups (Fig. 2). As regard the onset of first analgesic request, a significantly longer duration of effective analgesia was encountered in group T in comparison to group L, (246.93 ± 53.46 min vs. 212.00 ± 17.20 min, P-value was 0.001 (Table 2). The total postoperative fentanyl consumption was significantly decreased in group T compared to group L (132.00 ± 9.24 μg/day vs. 169.33 ± 7.84 μg/day) and P value was 0.000 (Table 2).

As regard hemodynamic changes both groups showed perioperative hemodynamic stability and insignificant differences throughout the perioperative systolic blood pressure, diastolic blood pressure and heart rate in between both groups, similarly perioperative SpO2 and end-tidal CO2 showed no significant differences between the studied groups, none of patients in both groups required additional intraoperative fentanyl or increased isoflurane concentration. There was no difficulty in viewing the structures during the block or serious adverse effects as inadvertent intravascular drug injection or peumothorax were reported during the study period. No patient in both groups developed postoperative respiratory depression, purities, hypotension or bradycardia while

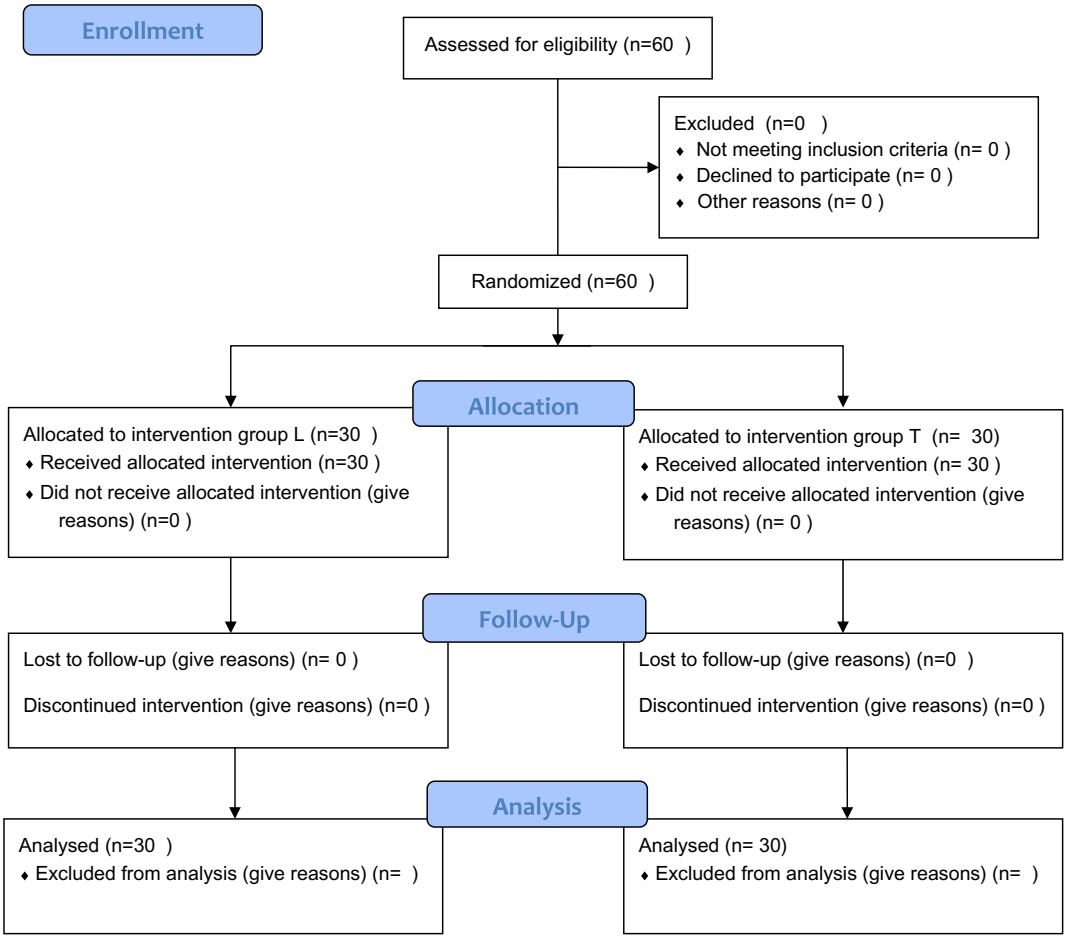

Fig. 1. Flow diagram of patient progress through the randomized trial.

Table 1
Patient characteristics. Age (years), weight (kg), height (cm) and body mass index BMI (kg2).

Variable	Group L N (30)	Group T N (30)	p-value
Age (yr)	50.66 ± 8.89	52.46 ± 8.03	0.414
Weight (kg)	72.80 ± 5.52	73.50 ± 5.82	0.635
Height (cm)	165.76 ± 2.35	166.30 ± 3.58	0.499
BMI (kg m^2)	26.51 ± 2.15	26.56 ± 1.79	0.914

Data are expressed as mean ± standard deviation.
Group L = levobupivacaine.
Group T = levobupivacaine and tramadol.
P-value considered significant if <0.05.
No significant differences between both groups.

Table 2
Duration of surgery and anesthesia (min), first analgesic request (min), total analgesic consumption (μg).

Variable	Group L N (30)	Group T N (30)	p-value
Duration of surgery (min)	123.16 ± 2.21	123.06 ± 2.46	0.869
Duration of anesthesia (min)	149.53 ± 3.17	149.23 ± 3.01	0.709
First analgesic request (min)	212.00 ± 17.20	246.93 ± 53.46*	0.001
Total analgesic consumption (μg)	169.33 ± 7.84	132.00 ± 9.24†	0.000

Data are expressed as mean ± standard deviation.
Group L = levobupivacaine.
Group T = levobupivacaine and tramadol.
P-value considered significant if <0.05.
* Significant prolonged time to take first analgesic request in group T in comparison to group L.
† Significant decreased total analgesic consumption in group T in comparison to group L.

one patients in group T had vomiting but it was single attack and did not need any medication.

6. Discussion

The findings of this clinical study demonstrated that adding tramadol to levobupivacaine for modified pectoral nerve block after induction of general anesthesia and before surgery was safe and effective technique that provided good quality of analgesia, significantly prolonged time to first analgesic request, more significantly reduced the analgesic consumption and statistically significant lower postoperative pain scores than using levobupivacaine alone.

Different regional anesthetic techniques including thoracic paravertebral block (TPVB) and thoracic epidural block have been used to decrease postoperative pain after radical mastectomy surgery and it is considered invasive techniques. Less invasive novel technique is the modified pectoral nerve block which recently used for radical mastectomy surgery. PecS II block achieved complete block of medial and lateral pectoral nerves, long thoracic and thoracodorsal nerves due to deposition of local anesthetic in the fascial planes at the nerve sites that leading to more good quality of analgesia [13].

Several studies reported that pectoral nerve block decreased systemic analgesic requirements and significant lower visual

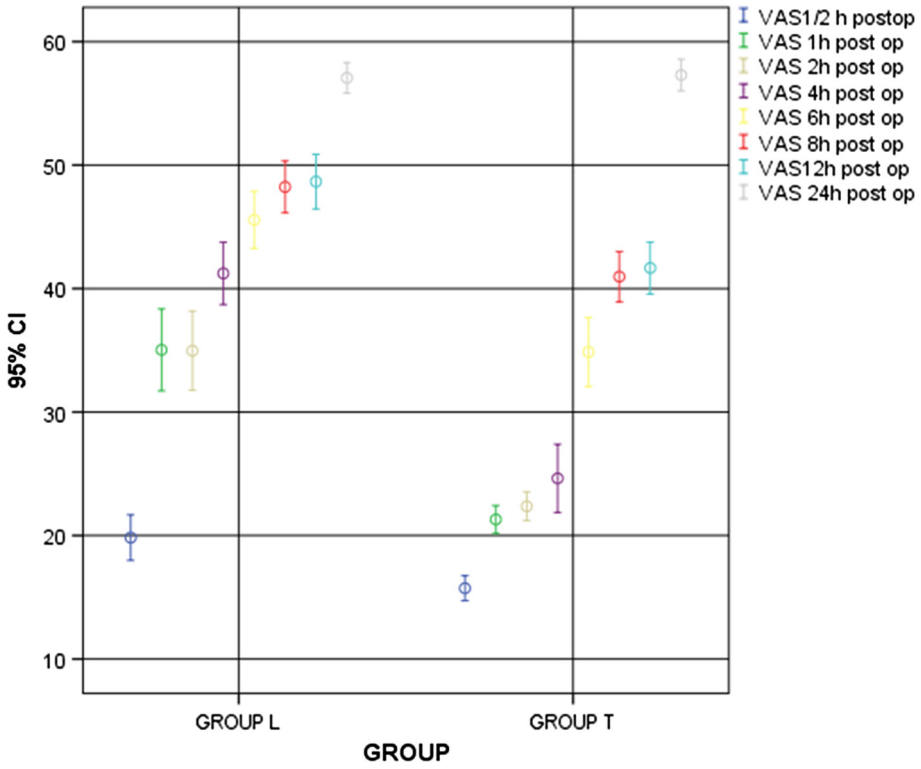

Fig. 2. 95% Confidence Interval (CI) of mean difference of postoperative visual analogue scale (VAS) at 1/2 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h postoperative. The figure showed significant lower postoperative VAS in group T (levobupivacaine and tramadol) than in group L (levobupivacaine) in all the study period with p-value (0.000) except at 24 h postoperative in which the figure showed no significant difference between both groups with p-value (0.067).

analog scores in patients undergoing modified radical mastectomy without causing any adverse effect [14,15]. In more recent study by Kulhari et al. they reported more postoperative analgesia, prolonged duration of analgesia, decreased morphine consumption postoperatively and lower postoperative pain scores in patients receiving pectoral nerve block [12].

Tramadol inhibits the reuptake of 5 hydroxytryptamine (5-HT) and norepinephrine, and stimulates the presynaptic release of 5-HT causing enhancement of the spinal descending inhibitory pathway, 5-HT3 receptors are present on the peripheral and spinal terminals of the nociceptive primary afferent fibers, and also on the superficial lamina of the dorsal horn, this may explain the possible local analgesic effect of tramadol in the peripheral sites [16,17].

Alagol and colleagues used tramadol 100 mg intraarticularly without administration of local anesthetic and reported lower postoperative VAS pain scores with longer duration of postoperative analgesia in comparison to intravenous injection of same dose of tramadol without any side effects [6].

Furthermore, several studies [10,18]. reported that addition of tramadol to local anesthetics improve postoperative analgesia as the study by Kapral et al. reported that tramadol when added to mepivacaine increased the duration of analgesia for axillary plexus blockade which support our study [19].

The pectoral nerve block was easy to done in all cases without any difficulty in viewing the structure in the current study and this may result due to performing the block guided with ultrasound which facilitate identification of the anatomical landmarks and optimum spread of local anesthetic that decreased incidence of complications or failure of the block. Although tramadol causes more nausea and vomiting mostly after intravenous injection [20] but in the present study one case in group T suffered single attack of vomiting although prophylactic antiemetic were given to all patient before the end of surgery.

7. Limitations

The only limitation of this study was that we did not add control group because of ethical considerations.

8. Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

9. Conclusion

This study demonstrated that adding tramadol with levobupivacaine for modified pectoral nerve block before surgery and after induction of general anesthesia in patients undergoing modified radical mastectomy surgery provides more good quality of analgesia with statistically significant lower postoperative pain scores, significantly prolonged time to first analgesic request and more significantly reduced analgesic consumption than using levobupivacaine alone without causing adverse effects.

Autho's contributions

Study design: Salwa M.S. Hayes, Reem Abd El Raouf, Tamer El Metwally Farahat and Emad El Deen Hamed.

Patient recruitment: Tamer El Metwally Farahat and Emad El Deen Hamed.

Surgical procedure: Emad El Deen Hamed.

Data collection and analysis: Reem abd el raouf and Salwa MS Hayes.

Writing up of the first draft of the paper: Salwa MS Hayes.

Conflict of interest

All authors have no conflict of interest.

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