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Original Article

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ABSTRACT

Objectives*:* The aim of this study was to examine the effects of local anesthetics delivered through a catheter inserted in the pectoral and axillary nerves using an open technique to treat persistent post-mastectomy pain syndrome (PPMPS).

Design: A randomized, prospective, clinical study.

Setting: Istanbul University- Cerrahpasa, Cerrahpasa School of Medicine, Istanbul Turkey

Subject: Eighty-six adult females aged 18–80 years who underwent modified radical mastectomy (MRM).

Interventions: At the end of the surgery group I was infused with 100 mg tramadol. Group II had a peripheral block catheter placed in the pectoral area just before closing the surgical area.

Main outcome measures: All patients were evaluated for postoperative 1–24 hr VAS scores, mean arterial pressure, heart rate, postoperative nausea and vomiting (PONV), and additional analgesic requirements. Motor and sensorial block levels were examined

Results*:* The immobile and mobile VAS scores at all time intervals, PONV scores, and 90th day median VAS scores were lower in group II than in group I ($p<0.001$, $p<0.01$, $p<0.001$, $p<0.01$, respectively). More patients used additional analgesic in group I than in group II ($p<0.0001$).

Conclusions: Local anesthesia given through a peripheral block catheter placed on the brachial plexus in patients undergoing MRM may be effective in preventing PPMPS.

KEYWORDS: Modified radical mastectomy; Peripheral block; Postoperative pain; Persistent post-mastectomy pain syndrome; brachial plexus

INTRODUCTION

Breast cancer occurs in 1 out of every 8 women in the world and is generally prevalent in the young adult population. Breast cancer causes psychological problems due to organ loss, fear of death, and separation from the family. The anxiety caused by these problems may cause additional pain in the perioperative period, as well as hemodynamic instability (tachycardia, hypertension, etc.) [1]. Surgery by radical mastectomy or axillary curettage (also referred to as modified radical mastectomy (MRM) is the main treatment choice, but it is frequently accompanied by persistent post-mastectomy pain syndrome (PPMPS) in 20–40% of patients. Postoperative radiotherapy is a further contributor to the persistence of pain. PPMPS can develop within a short time or at different times after surgery. When this pain occurs later than 3 months after surgery, it is defined as neuropathic pain [2].

A painless period during and after mastectomy may prevent the development of PPMPS. Therefore, effective perioperative pain treatment can increase the quality of life after surgery and facilitate a return to normal life. Many techniques have been tested for post-mastectomy pain treatment, including thoracic epidural blocks, wound infiltration blocks, intercostal blocks, and pectoral nerve block (PECS). However, none of these techniques is fully successful in pain treatment for a number of reasons [3]. For example, the inadequacy of imaging techniques or

inexperience of the practitioner may result in application of drugs to the wrong area. These techniques are also invasive, so ultrasound should be used to avoid complications, but every clinic may not be adequately equipped with ultrasound equipment [4].

In the present study, our primary aim was to investigate the effect of local anesthetics given through a catheter inserted into the pectoral and axillary nerves by an open technique for the treatment of early postoperative pain. Our secondary aim was to determine the benefits of this open catheter placement technique in preventing the development of PPMPS.

SUBJECTS AND METHODS

This randomized prospective clinical study was conducted on 86 American Society of Anesthesiologists Physical Status I–II (ASA) adult females between 18–80 years of age who were scheduled to undergo MRM. The study was approved by the Ethics Committee of Istanbul University- Cerrahpasa, Cerrahpasa School of Medicine (No: 83045809/604.01) and written informed consent was obtained from all patients. The study was registered with the www.clinicaltrials.gov protocol registration system (NCT03204708). Patients with a history of local anesthetic allergy or anticoagulant use, patients with central or peripheral nerve diseases, and male patients were excluded from the study. The study was conducted between April 2016 and February 2017.

Patients were taken to the preoperative anesthesia room, where a 20 G intravenous cannula was secured on the dorsum of the hand contralateral to the breast to be operated on. An infusion of balanced electrolyte solution was started at a rate of 2 ml/kg/h, and premedication was achieved with 0.03 mg/kg iv midazolam. The patients were taken to the operation room and connected to standard monitors (peripheral oxygen saturation, electrocardiography, and non-invasive blood pressure). Anesthesia was induced with 2 mg/kg propofol and 2 µg/kg fentanyl. Following the start of hypnosis, 0.6 mg/kg rocuronium was administered and endotracheal intubation was performed. Anesthesia was maintained with 2% sevoflurane in a 40% oxygen/air mixture in a 4 L fresh gas flow. Patients were ventilated in the pressure-controlled mode (PCV) at 7 cm H_2O PEEP with a 1:2 inspiratory to expiratory ratio, respiratory rate between 10 and 12, a preset airway pressure of 12–14 cm H_2O to achieve $ETCO_2$ values between 32 and 36 mm Hg, and a tidal volume of 7 ml/kg. When systolic arterial pressure and heart rate increased 20% from the initial values, an additional iv. dose of 50 µg fentanyl was given.

Patients were randomized into two groups 45 minutes prior to the end of the surgery using a computer-based application (https://www.randomizer.org/). At 20 minutes prior to the end of the surgery, patients in group I (n=43) were infused with 100 mg tramadol in 100 ml 0.9% NaCl in 5–10 minutes. Patients in group II, at the end of the surgery (20 minutes before extubation) but just before closing the surgical area, had a peripheral block catheter (Contiplex® D, BBraun, Germany) placed in the pectoral area by the surgeon general. Catheterization was done by the same surgeon (Mehmet Velidedeoğlu) in all patients. The catheter was directed from the skin and pectoralis major muscle in the infraclavicular region near the acromion, inside the breast tissue, through a 20 G

needle. The tip of the catheter was inserted and placed under the lateral one-third of the clavicle, passing through axillary vein. The catheter was advanced 3 cm above the clavicle in accordance with the axillary vein trace. This is the area where the nerves split from brachial plexus to innervate the breast and axillary region. The lateral and medial pectoral nerves, thoracodorsal nerve, nervus thoracicus longus, nervus intercostabrachialis, and 2–6 latero-anterior cutaneous intercostal nerves split from brachial plexus just below the area we place the pectoral catheter (Figure 1). No additional surgical incision was used for this intervention. After surgery closure, about 20 minutes before extubation, patients in group II received a bolus dose of a mixture of 20 ml 0.25% bupivacaine and 10 ml 1% lidocaine.

Patients in both groups were extubated with 0.15 mg/kg atropine and 0.03 mg/kg neostigmine when their spontaneous breathing effort was adequate and then taken to the post anesthesia care unit. Patients were released to the ward when their Aldrete scores were 9 or above. Further evaluations included the postoperative 1st, 6th, 12th and 24th hour Visual analog scale (VAS) scores, temperature, mean arterial pressure, heart rate, postoperative nausea and vomiting (PONV), and additional analgesic requirements. Motor and sensorial block levels (pinprick test) were examined postoperatively at 1st hour. When the VAS scores were 4 or higher in group I, 50 mg dexketoprophen trometamol in 100 ml 0.9% NaCl was administered as a rescue analgesic, and the administration was recorded. When the VAS scores were 4 or higher in group II, the patients were administered a mixture of 5 ml of 0.5% bupivacaine and 5 ml 0.9% NaCl through the catheter.

Subsequently, at the 24th postoperative hour, the catheter was removed slowly, after the dressing was opened by the surgeon who had placed the catheter.

On the 90th postoperative day, patients were called by telephone and queried regarding VAS scores of the area of scar and shoulder or arm at rest and movement at the time of the call, burning and evoked pain, and edema in the arm. Any additional analgesic usage or complaints were noted. If VAS scores were >3 during rest and movement at the time of the call, the patient was considered to have PPMPS.

Statistical Analysis

For the Shapiro-Wilk test, the normality audit was conducted using a histogram, Q-Q plot, and box plot. The data were input as the mean and standard deviation. The variables that showed normal distributions between the two groups were analyzed using an independent samples t- test, and the variables not normally distributed were analyzed using the Mann-Whitney U test. The normal variables were evaluated using a chi-squared test with the Yates correction and Fisher's exact probability test. The significance was two-tailed, with a cutoff point of $p < 0.05$. All analyses were conducted using NCSS 10 statistical software (2015, NCSS, LLC, Kayaville, UT, USA).

The number of patients included in the study was determined based on an expectation that the VAS pain score reduction rate would be 25% between the two groups, according to the results of a prior study [5]. Based on a type I error of 5% (two-tailed), a type II error of 20% (80% power), and a VAS reduction rate 25% in the catheter group when compared to the iv analgesia group, a

total of 43 patients was considered ideal for each group for evaluating postoperative acute pain and PPMPS. Taking into account the fact that a certain number of patients would be excluded from this study, we decided to include 45 patients in each group.

RESULTS

No significant differences were observed between the two groups in terms of demographic data and ASA scores (Table 1). The immobile and mobile VAS scores were lower in group II than in group I for all time intervals ($p<0.001$, $p<0.01$, respectively) (Table 2).

The mean arterial pressure was lower at the 1st hour in group II than in group I ($p<0.05$), (Table 2). Heart rates at the 1st, 6th and 12th hours were lower in group II than in group I ($p<0.05$), (Table 2).

The PONV scores were lower at the 1st and 6th hours in group II than in group I ($p<0.001$) (Table 2). The PONV scores at other times were similar in both groups. Additional analgesic requirements were lower in group II than in group I ($p<0.001$) (Table 2).

The 90th day median VAS scores when mobile and immobile were lower in group II than in group I ($p<0.001$) (Table 3). The number of patients diagnosed as having PPMPS and requiring additional analgesic was higher in group I than in group II ($p<0.0001$) (Table 3). The occurrence of edema in the arm was similar in both groups (Table 3).

The sensorial block at 1st hour after the operation was at level of T1–T8 in 18 patients (40%), T1–T10 in 10 patients (22.2%), T2–T8 in 15 patients (33.3%), and T2–T4 in 2 patients (4.4%) (Table 4). In two patients in group II, a motor block developed in the forearm and elbow and their catheters were removed in the postoperative unit. These two patients were not included in the final evaluation (Figure 2).

DISCUSSION

This study describes the first use of an open catheter insertion technique through to the brachial plexus in the operation area of MRM. In this technique, the peripheral nerve catheter is placed under the clavicle on the axillary vein tracing and on the clavipectoral fascia so that it falls outside the nerve sheath and into the division part of the brachial plexus. A local anesthetic drug delivered from the inserted catheter then spread downward through the hole of the catheter due to gravity. With this spread, the block consists of the lateral and medial pectoral nerves, the upper subscapular nerve (T4), the intercostabracial nerves, and the nervus thoracicus longus (T8), which are the nerves in the area of axillary curettage performed during MRM [6]. In our study, our aim was to increase the efficacy of the drug by delivering a large volume. In addition, this block, with the intercostabracial nerves originating in the T2 cutaneous sensory nerve, constitutes a sensorial block that includes the upper inner arm, the axilla, and the upper outer quadrant of the breast. The cutaneous sensorial branch of T2 is also the nerve responsible for phantom pain (occurring in 17.4% of patients) and the burning-stinging after mastectomy[7,8].

Today, several postoperative analgesia techniques are used following MRM. These techniques include intravenous analgesia, but central and peripheral nerve blocks are the most preferred ones. Epidural analgesia is the gold standard in the treatment of postoperative analgesia; however, its use in breast surgery is still limited. The reason for this is the hemodynamic changes that arise due to the large volume of local anesthetic that must be used for effective analgesia [9,10].

The PECS blocks described by Blanco are now widely used. In fact, the region of the PECS I and II blocks is similar to the block area we provided in the current study[6]. An ultrasonography device is required for PECS blocks, and this necessitates a physician competent with this device[6]. By contrast, our technique requires no ultrasonography, because the catheter is visible in the surgical area during insertion. Consequently, our technique carries little risk of complications and failure of insertion or of application of the drug to the wrong area. In addition, inserting the catheter takes only a few seconds, so the duration of anesthesia is shortened.

In our study, the patients in group II had lower VAS scores and required no additional analgesics. These group II patients were also more stable hemodynamically. No PONV was observed in group II, whereas group I patients displayed PONV at the 1st and 6th postoperative hours. The pain scores and additional analgesic requirements at the 1st, 6th and 12th hours were also higher in the group I patients. We preferred lidocaine as an initial local anesthetic for the rapid onset of the block applied to group II, and we added bupivacaine as a long acting analgesic. Therefore, the analgesic effect of the block had a rapid onset, as well as a long duration. The VAS scores and additional analgesic requirements were higher in group I at the 90th day, and more patients in group I developed PPMPS.

Thomas *et al*. [11] gave ropivacaine by an infiltration technique in one group after surgery in their prospective randomized controlled triple-blind study of 60 patients undergoing MRM. They gave 20 ml of ropivacaine to the fascia on the serratus anterior and 10 ml to the fascia between the pectoralis major and minor at the level of the third rib (PECS II). In their control group, the same techniques were applied, but saline was infiltrated into the same regions. They found that the pain scores and analgesic requirements were significantly lower in the patients administered ropivacaine and PECS II than in the control group. This technique by Thomas *et al.* [11] was similar to ours in terms of making the block from the open surgical field. However, the infiltration of the block and the type of local anesthetic used were different. Thomas *et al*. [11] also did not focus on PPMPS development in their study.

Razek *et al*. [12] in their study published in 2018, compared PECS and a serratus anterior intercostal plane block (SIPB) applied to the fascia between the serratus anterior and the intercostal external muscles for the treatment of intra- and postoperative pain in breast surgery. Their prospective clinical study showed that both techniques, in combination with general anesthesia, provide sufficient analgesia for post-mastectomy pain with or without axillary curettage. They also showed that the SIPB was more successful than PECS for the treatment of postoperative pain. In SIPB, the local anesthetic drug is introduced between the serratus anterior and the external intercostal muscles using ultrasonography. Therefore, the drug is given through the location where

the brachial plexus is not separated into anterior and posterior branches and the block level is between T2–T9. In addition, the thoracic longus and thoracodorsal nerves in this region are blocked and a sensorial block develops.

In our study, we placed the catheter before the branching of the brachial plexus and a block extending up to T8 developed. Therefore, the level of analgesia in our block technique is similar to the level of analgesia achieved by the PECS and SIBP techniques. The advantage of our technique was that we made the block under direct visualization to reduce intervention- related failure rate. When we consider that not every clinic has readily available ultrasound equipment, this is a major benefit of our procedure.

One of the limitations of our study is that we did not infuse the local anesthetic from the peripheral catheter. If we perform local anesthetic infusion in future, we might provide longer postoperative pain treatment with safer borders. A second limitation is that we did not survey our patients for chronic pain. In future, we could query the patients about chronic pain by examining their VAS scores beyond 90 days and subsequent to radiotherapy treatments.

CONCLUSION

In conclusion, we suggest that analgesia provided by local anesthesia given through a peripheral block catheter placed on the brachial plexus in patients undergoing MRM may be effective in the treatment of post-mastectomy pain and for prevention of PPMPS. Further randomized prospective clinical studies are needed to confirm this possibility.

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Table 1: Demographic Data

Demographic data	Group I (n=43)	Group II (n=43)	p
Age (year±SD)	52.1±10.9	51.9±9.6	**>0.05**
BMI (kg/m^2 ±SD)	24.8±1.6	25.1±1.9	**>0.05**
ASA I/II (n)	22/11	23/12	**>0.05**

ASA: American Society of Anesthesiologists Physical Status; BMI: Body mass index; SD: Standart deviation; n: number

Table 2: Acute Pain, Hemodynamic parameters, PONV and additional analgesic requirement according to groups

Groups	Pain, Hemodynamic parameters, PONV, additional analgesic	**1st hour**	**6th hour**	**12th hours**	**24th hours**
Group I (n=43)	VAS immobil	4.1±0.3	4.0±0.6	4.3±0.4	3.8±0.5
	VAS mobil	5.3±0.2	5.2±0.5	5.3±0.6	4.3±0.6
	Mean Art Press (mmHg)	76.7±38.0	65.4±27.4	68.9±26.3	60.3±28.5
	Heart rate(beat/min)	88.4±23.6	80.6±42.7	83.5±33.6	70.4±32.3
	PONV	2.1±0.2	1.4±0.4	0	0
	Add. Analg.(n)	20	18	13	0
Group II (n=43)	VAS immobil	2.2±0.2**	2.4±0.5**	2.3±0.7**	0±0.4***
	VAS mobil	3.7±0.5**	3.1±0.3**	2.8±0.6**	1.3±0.7***
	Mean Art Press (mmHg)	70.4±34.9*	65.8±25.8	65.5±34.2	60.8±21.4
	Heart rate(beat/min)	80.5±26.8*	75.7±27.4*	75.4±35.4*	72.5±28.3
	PONV	0***	0***	0	0
	Add. Analg.(n)	0***	0***	0***	0***

All data are given as ±SD. VAS: Visuel analog scale, PONV: Postoperative nause and vomiting, Add analg: number of patients required additional analgesic; SD: standart deviation; n: number

***p<0.05 group I compared to group II**

****p<0.01 group I compared to group II**

*****p<0.001 group I compared to group II**

Table 3: VAS, PPMPS, edema and analgesic requirement at 90th day according to groups

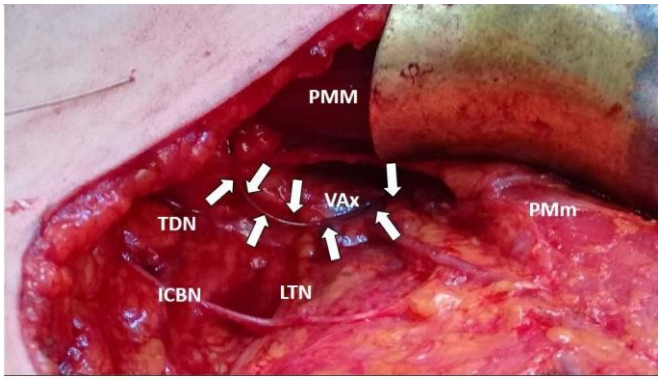
VAS scores	**Group I (n=43)**	**Group II (n=43)**	**p**
VAS mobile (±SD)	4.2±1.1	1.1±0.2	**<0.001**
VAS immobile (±SD)	5.4±1.6	1.2±0.6	**<0.001**
PPMPS (n)	13	0	**<0.0001**
Edema (n)	0	0	**>0.05**
Add Analg (n)	15	0	**<0.0001**

VAS: Visuel analog scale, PPMPS: Persistent post-mastectomy pain syndrome, n: number; SD: standard deviation; Add analg: number of patients required additional analgesic

Table 4: Pin prick and motor block levels of group II at 1st hour after the operation (n=45)

Pin prick and motor block	**Dermatomes involved**			
Pin prick and motor block	**T1-T8**	**T1-T10**	**T2-T8**	**T2-T4**
Pin prick (n) (%)	18 (40.0%)	10 (22.2%)	15 (33.3%)	2 (4.4%)
Motor block (n) (%)	0	2 (4.4%)	0	0

n: number of patients; T: thoracic.



Arrows mark the catheter
LTN: Long thoracic nerve, TDN: Thoracodorsal nerve, PMM: Pectoralis Major Muscle
ICBN: Intercostobrachial nerve, VAx: Axillary Nerve, PMm: Pectoralis Minor Muscle

Figure 1: Catheter placement in the pectoral area

Figure 2. Consort flow diagram

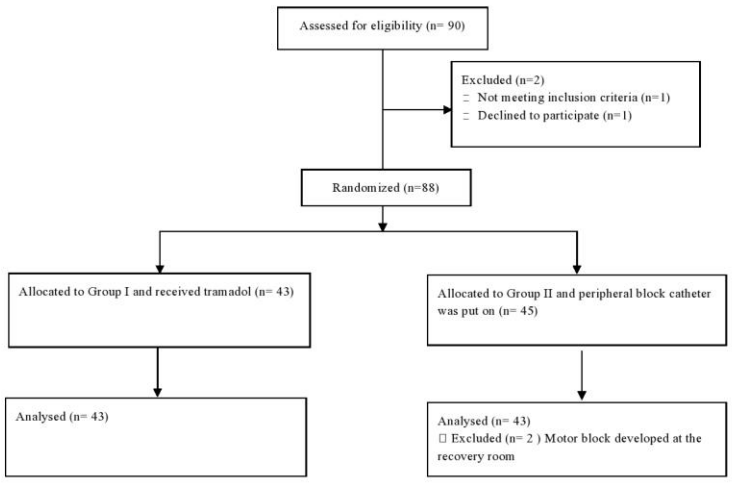


Figure 2: Consort flow diagram of the study