Ultrasound-Guided Transversus Thoracic Muscle Plane-Pectoral Nerve Block for Postoperative Analgesia After Modified Radical Mastectomy: A Comparison with the Thoracic Paravertebral Nerve Block

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Research

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Abstract

Background: Modified radical mastectomy (MRM) is a most effective and common type of invasive surgery for breast cancer. However, it causes moderate to severe acute pain even last for a long postoperative period. Transversus thoracic muscle plane-pectoral nerve block (TTP-PECS) is a novel and promising interfacial plane block which can provide analgesia for MRM while thoracic paravertebral nerve block (TPVB) is also widely used for this purpose. This study compared the postoperative analgesia between the ultrasound-guided TTP-PECS and TPVB in patients undergoing MRM.

Methods: In this randomized controlled pilot trial, eighty female breast cancer patients were randomized to receive either ultrasound-guided TTP-PECS (TTP-PECS group, n=40) or TPVB (TPVB group, n=40). The primary outcome was 24 h postoperative fentanyl consumption. Secondary outcome measures included intraoperative fentanyl and postoperative flurbiprofen axetil consumption, duration of analgesia, pain intensity at rest and during activity, inflammatory response, and the quality of recovery 40 (QoR-40) score.

Results: Intraoperative fentanyl requirement was similar between the two groups; Postoperative fentanyl consumption was decreased in the TTP-PECS group copmared with the TPVB group, as well as the rate of postoperative flurbiprofen axetil consumption, but the duration of analgesia was longer; Pain scores at rest and during activity were dramatically decreased at postoperative 12 h; Moreover, the levels of IL-6, MCP-1 and TNF-α, as well as the levels of PGE_2, NPY and β-endorphins were decreased at 12 h after surgery; Finally, the total QoR-40 score, especially for the scores of pain, emotional state and patient support were increased.

Conclusion: Both TTP-PECS and TPVB are effective for analgesia after MRM. However, TTP-PECS reduced postoperative fentanyl and flurbiprofen axetil consumption in the first 24 h after MRM, and prolonged the duration of analgesia. Furthermore, TTP-PECS reduced postoperative pain intensity at rest and during activity, and inflammatory response at 12 h postoperation. Finally, TTP-PECS improved QoR-40 scores on the postoperative day. Thus, TTP-PECS is an attractive alternative to TPVB for postoperative analgesia after MRM.

Introduction

Breast cancer is the most common malignancy in females, with an increasing incidence in recent years (Chen W et al. 2016). Surgery is one of the mainstays of treatment of breast cancer, and MRM is the most effective and common type of invasive surgery. Despite conventional analgesia strategies, patients still suffer from moderate to severe acute postoperative pain that can impede their early recovery (Oscar PG et al. 2017). Therefore, pain management is necessary.

Many types of regional anesthesia techniques have been used during anesthesia for MRM (Dai X et al. 2015). Thoracic epidural, intercostal nerve, and interscalene brachial plexus blocks are limited by the complicated nature of their procedures and severe complications. Based on the application of ultrasound (US), TPVB block has been used for anesthesia and has gained better abirritation during MRM. However,

this technique is also limited by the complicated operation and severe postoperative complications such as hypotension, epidural or intrathecal spread, and pleural puncture (LI NL 2016).

In recent years, a novel and less invasive regional analgesia technique known as “TTP-PECS” has received increasing interest for application in breast surgery. A randomized clinical trial (Neethu M et al. 2018) reported effective postoperative pain and opioid reduction using TTP-PECS in patients undergoing MRM. However, there are still controversies regarding the efficacy of TTP-PECS compared to TPVB.

In the present study, our primary aim was to compare the effects of ultrasound-guided TTP-PESC and TPVB on postoperative fentanyl consumption in 24 h after mastectomy. Our secondary aim was to compare intraoperative fentanyl and postoperative flurbiprofen axetil consumption, duration of analgesia, postoperative pain intensity at rest and during activity, and inflammatory response (proinflammatory cytokines including IL-6, MCP-1 and TNF-α, and pain-related mediators including PGE_2, NPY and β-endorphin), as well as QoR-40 score in two groups (TTP-PECS vs. TPVB).

Methods

1. Study design

This retrospective randomized study was reviewed and approved by the Medical Ethics Committee of the Kunshan Hospital of Traditional Chinese Medicine on April 9, 2019 (Approval ID: 2019-18), and written informed consent was obtained from each patient for participation in the study. The trial was conducted from January 2017 to December 2019. The trial was registered in the Chinese Clinical Trials Registry (ChiCTR2000033943). All eligible patients were approached for enrolment.

2. Eligibility criteria

Eligible studies were required to meet all the following criteria:

Studies focusing on female patients with adult breast cancer who underwent surgery. All patients were undergoing elective unilateral MRM (including sentinel lymph node dissection (SLND) and axillary dissection (ALND)) with no ethnicity or nationality restrictions, age from 28 to 74 years, body mass index (BMI) of 17 to 29.9 kg/m^2, and American Society of Anesthesiologists (ASA) status I or II.

Studies were considered to be ineligible and were excluded if they met the following criteria:

1. patients underwent secondary or nonradical surgery and breast reconstruction;
2. patients had a history of infection around the puncture site, allergy, or contraindication to local anesthetics;
3. patients currently on anticoagulant treatment, alcohol or substance abuse, opioid dependence, or regularly receiving corticosteroids;
4. patients had systemic infectious diseases or psychiatric or neurological diseases; and

5. patients who did not cooperate during the procedure and the follow-up survey.

After applying the inclusion and exclusion criteria, a total of 80 patients were enrolled. The randomization schedule generated a randomized list of numbers that were enclosed in sealed envelopes by a third party not involved in the study. These patients were randomly allocated to either TTP-PECS or TPVB group (n = 40 each).

3. Preparation before anesthesia

After intravenous access was established, the patients were routinely monitored for various parameters, including heart rate, arterial pressure, pulse oxygen saturation, electrocardiography, end-tidal CO_2, and bispectral index during the operation. All patients were administered midazolam 0.05 mg/kg prior to nerve block.

Ultrasound (US)-guided nerve blocks in each technique were performed by two anesthesiologists with more than 3 years of experience in US-guided regional anesthesia and with a record of performing more than 150 blocks. All US scans were performed using the same US machine and a linear array probe (6 to 13 MHz frequency). The US image was optimized by adjusting parameters, including depth, penetration frequency range, and gain. The blocks were performed using a 21-gauge echogenic needle. After sterile preparation, the gel was applied to the US transducer. The transducer and cable were covered with a sterile plastic sleeve, and the skin was infiltrated with 1% lidocaine.

4. Ultrasonography

1. Patients in the TTP-PECS group underwent ultrasonography in the forearm outreach position.

PECS I block (Blanco R 2011): the US transducer was placed in the lateral third of the clavicle, where pectoralis major and pectoralis minor muscles were easily identified. The anesthetist then confirmed the location of the pectoral branch of the thoracoacromial artery between the pectoralis muscles with color doppler. The pectoral nerve was consistently located adjacent to the artery. The needle was then inserted in-plane of the ultrasound transducer, and 7.5 ml of 0.5% ropivacaine was injected between the pectoralis muscles (Figure 1A).

PECS II block (Blanco R 2012): the US transducer was moved inferolaterally until the serratus anterior muscle was identified above the 2nd, 3rd, and 4th ribs. The needle was advanced in a mediolateral direction in-plane of the ultrasound transducer, and 15 mL of 0.5% ropivacaine was injected into the fascial plane between the pectoralis minor muscle and the serratus anterior muscle (Figure 1B).

TTP block (Ueshima H 2015): the US transducer was finally placed in the longitudinal plane 1 cm lateral to the sternal border, where the T_{3-4} intercostal space was identified under US. A parasternal sagittal view of the internal intercostal muscle and the transversus thoracic muscle between the 3th and the 4th rib was visualized above the pleura. The needle was inserted in-plane to the transducer until the tip was

located between the internal intercostal muscle and the transversus thoracis muscle, and 7.5 ml of 0.5% ropivacaine was then injected (Figure 1C).

2. Patients in the TPVB group underwent ultrasonography in the lateral position.

TPVB block (Marhofer P et al. 2010): the US transducer was placed at the level of the 5th thoracic vertebra, in contact with the transverse process of the 6th thoracic vertebra. The needle was then passed caudally for 1-1.5 cm into the paravertebral space, and 15 ml of 0.5% ropivacaine was injected under real-time US guidance (Figure 2). The same procedure was repeated for the 3rd thoracic vertebra.

The TTP-PECS blocks and TPVB block interventions were performed 30 min before surgical incision. After the nerve blocks were completed, the sensory level was tested with a pin prick every 10 min by another anesthesiologist not involved in the operation. Successful block performance was defined as dysesthesia of skin or absence of pain in any segment from T_1 to T_{12} within 30 min after blocks. Simultaneously, any adverse effects related to the regional anesthetic technique were also recorded.

5. Intraoperative management

General anesthesia was induced with 1.2 μg/kg fentanyl, 3 mg/kg propofol, and 0.2 mg/kg atracurium cis-benzenesulfonate for the insertion of a laryngeal mask. Initial respiratory parameters were set as follows: volume-controlled ventilator; expiratory tidal volume, 8 to 10 ml/kg; respiratory rate, 10 to 12 times/min; inhale:exhale ratio, 1:2; fraction of inspiration O_2, 100%; and end tidal carbon dioxide pressure, 35 to 45 mmHg. Sevoflurane was continuously infused to maintain anesthesia, and 0.05 μg fentanyl was injected as a supplemental analgesic and repeated if necessary. A bispectral monitor was used to determine the appropriate depth of anesthesia, with bispectral index values between 40 and 60.

A vasoactive drug was administered intravenously when the mean arterial blood pressure or the heart rate was reduced by 20% as compared to the preoperative baseline values.

6. Postoperative management

After recovery from anesthesia, the patients were shifted to postanesthesia care unit (PACU). Postoperative analgesia was provided by patient-controlled analgesia (PCA) using fentanyl. Antiemetic therapy comprised a dose of 5 mg/d prophylactic tropisetron.

The PCA pump consisted of 16 μg/kg of fentanyl, which was programmed to deliver 2 ml fentanyl bolus per press with a lockout interval of 15 min, and fentanyl consumption in 24 h postoperation was recorded.

Pain intensity was assessed using visual analogue scale (VAS, 0 to 10 cm, 0 = no pain and 10 = worst pain imaginable) at rest and during abduction of the ipsilateral upper limb at 2, 6, 12, and 24 h postoperation. When the reported VAS score was 3 at rest or 5 or greater during activity, the patients were instructed to press one or two PCA button themselves as a rescue analgesic. If the VAS score was still

unimproved, an intravenous infusion of flurbiprofen axetil 50 mg was given, and the cumulative dose was less than 200 mg per day.

Blood samples were collected for examinations of proinflammatory cytokines including IL-6, MCP-1 and TNF-α by enzyme-linked immunoabsorbent assay (ELISA), and pain-related mediators including NPY, PGE2 and β-endorphin by radioimmunoassay at before surgery, immediately after surgery, 12 and 24 h after surgery.

QoR-40 score was administered at 24 h after surgery. The QoR-40 questionnaire consists of 40 items and five subscales that are divided in separate sections which aimed to evaluate the presence and extent of pain, symptoms, comfort, emotional well-being, physical independence, and satisfaction with treatment. All these items are rated on a five-point Likert scale from one (worst) to five (best). The total score was computed by summing all items. The possible minimum and maximum scores were 40 and 200, respectively.

7. Sample size calculation

By using SPSS Version 22.0 software (SPSS Inc., Armonk, NY, USA), the cumulative fentanyl consumption in the first 24 postoperative hours was used to calculate the sample size. Based on the results of a pre-established analysis plan for the TTP-PECS and TPVB groups (with 10 patients in each group), a sample size of 74 patients (37 blocks per group) was found to achieve 80% power at a two-sided α of 0.05 to detect a 50-μg difference between the TTP-PECS compared to the TPVB. Considering possible drop-outs, we decided to include at least 40 patients per group.

8. Statistical analysis

SPSS Version 22.0 software (SPSS Inc.) was used for all statistical tests. The *Kolmogorov-Smirnov* test was used to assess normality of data distribution. Normally distributed numerical data were expressed as mean and standard deviation, and intergroup differences were compared using the independent-sample Student's *t* test. Non-normally distributed numerical data were expressed as median and interquartile range, and intergroup differences were compared non-parametrically using the Mann-Whitney *U* test. Categorical data were expressed as number and percentage, and differences between the two groups were compared using the Pearson's *chi-square* test (for nominal data) or the *chi-square* test for trends (for ordinal data). A *P* value of <0.05 was considered significant.

Results

1. Experimental process

80 patients were screened for enrollment in the present study. After applying the exclusion criteria, 78 patients were included in the randomization process (39 patients in each group). Real time ultrasound-guided regional block was performed in all patients, but one failed in the TPVB group. Consequently, 77 patients were ultimately analyzed. Figure 3 shows the CONSORT diagram for recruitment to the trial.

2. Demographic data and perioperative characteristics

The patients in the two groups were well matched for demographic data and perioperative characteristics, and no significant difference was observed between the two groups ($P > 0.05$). The details are provided in Table 1.

Table 1
Demographic and perioperative characteristics

Variables	TTP-PECS group	TPVB group	*P* value
Age (years)	50.87 ± 12.52	49.95 ± 11.95	**0.74**
BMI (kg /m^2)	22.68 ± 3.15	22.78 ± 3.10	**0.89**
ASA grade (n, □/□)	13/26	11/27	**0.68**
Duration of operation (min)	115.20 ± 18.88	115.29 ± 18.54	**0.98**
Total loss of blood (ml)	70.51 ± 17.46	71.84 ± 16.58	**0.73**
Infusion volume (ml)	997.44 ± 126.67	986.84 ± 114.30	**0.70**
Intraoperative consumption of fentanyl (ug)	278.1±42.0	275.0±44.0	**0.75**

Demographic and perioperative characteristics were taken before and during the surgery. No significant differences were observed in Age, BMI, ASA grade, duration of operation, total loss of blood, and infusion volume among groups ($P > 0.05$). Data are expressed as mean ± SD (39 in TTP-PECS group and 38 in TPVB group). BMI = body mass index, ASA = American Society of Anesthesiologists.

2. Fentanyl, flurbiprofen axetil consumption and the duration of analgesia

The nerve blocks therapy did not affect the intraoperative consumption of fentanyl. Postoperative fentanyl and flurbiprofen axetil consumption in the first 24 h after mastectomy was lower in the TTP-PECS group than in the TPVB group ($P < 0.01$). Moreover, the duration of analgesia was longer in the TTP-PECS group ($P < 0.01$), as shown in Table 2.

Table 2
Fentanyl, flurbiprofen axetil consumption and the duration of analgesia

	TTP-PECS group	TPVB group	*P* value
postoperative fentanyl consumption (ug)	547.33 ± 57.79*	696.43 ± 96.80	**0.00**
postoperative flurbiprofen axetil consumption (n/n) (%)	1/38 (2.6)*	8/30 (26.7)	**0.029**
Intraoperative fentanyl consumption (ug)	278.1±42.0	257.9±50.0	**0.057**
duration of analgesia (h)	12.5±1.3*	9.4±1.7	**0.000**

Fentanyl consumption was recorded in the first postoperative 24 h. TTP-PECS treatment significantly reduced the fentanyl and flurbiprofen axetil consumption, prolonged the duration of analgesia. Data are expressed as mean ± SD (39 in TTP-PECS group and 38 in TPVB group). *P < 0.01, versus TPVB group.

3. Postoperative pain intensity

VAS score at rest was significantly lower in the TTP-PECS group than in the TPVB group at 12 h postoperation (p = 0.00), as shown in Table 3-1. During activity, VAS score remained significantly lower in the TTP-PECS than in the TPVB group at 12 h postoperation (p = 0.00), as shown in Table 3-2. However, no significant difference was observed at 2, 6, and 24 h postoperation both at rest and during activity.

Table 3.1
Effects of TTP-PECS and TPVB on postoperative pain intensity at rest

	TTP-PECS group	TPVB group	*P* value
Postoperative 2 h	1.25 ± 0.71	1.32 ± 0.68	**0.66**
Postoperative 6 h	1.70 ± 0.71	1.78 ± 0.68	**0.62**
Postoperative 12 h	2.11 ± 0.69*	2.60 ± 0.50	**0.00**
Postoperative 24 h	2.21 ± 0.48	2.29 ± 0.45	**0.45**

TTP-PECS treatment significantly decreased pain intensity at rest and during activity at 12 h postoperation. Data are expressed as mean ± SD (39 in TTP-PECS group and 38 in TPVB group). *P < 0.05, versus the TPVB group.

Table 3.2
Effects of TTP-PECS and TPVB on postoperative pain intensity during activity

	TTP-PECS group	TPVB group	*P* value
Postoperative 2 h	1.86 ± 0.68	1.81 ± 0.72	**0.76**
Postoperative 6 h	2.30 ± 0.73	2.27 ± 0.80	**0.86**
Postoperative 12 h	2.68 ± 0.68*	3.42 ± 0.57	**0.00**
Postoperative 24 h	3.12 ± 0.57	3.07 ± 0.62	**0.71**

TTP-PECS treatment significantly decreased pain intensity during activity at 12 h postoperation. Data are expressed as mean ± SD (39 in TTP-PECS group and 38 in TPVB group). *$P < 0.05$, versus the TPVB group.

4. Perioperative inflammatory response

Expressions of the pro-inflammatory cytokines including IL-6, MCP-1 and TNF-α were overall up-regulated in 24 h after surgery between the two groups ($P < 0.05$). Compared with TPVB group, administration of TTP-PECS significantly decreased the average levels of IL-6, MCP-1, and TNF-α at 12 h after surgery ($P < 0.05$), as showed in Table 4-1. The same trend were found in the levels of PGE_2, NPY and β-endorphin ($P < 0.05$), as showed in Table 4-2.

Table 4.1
Effects of TTP-PECS and TPVB on pro-inflammatory cytokines

Indicator	Group	before surgery	immediately after surgery	12 h after surgery	24 h after surgery
IL-6 (pg/ml)	TTP-PECS group	36.22 ± 5.71	39.69 ± 4.92$^{\#}$	46.42 ± 5.38$^{\#*}$	42.45 ± 4.90$^{\#}$
	TPVB group	36.20 ± 6.10	39.21 ± 5.59$^{\#}$	49.37 ± 6.08$^{\#}$	42.92 ± 5.11$^{\#}$
	P value	**0.99**	**0.69**	**0.03**	**0.68**
MCP-1 (pg/ml)	TTP-PECS group	16.63 ± 1.58	20.85 ± 1.77$^{\#}$	36.28 ± 2.28$^{\#*}$	29.15 ± 2.36$^{\#}$
	TPVB group	17.06 ± 1.66	20.17± 2.02$^{\#}$	40.23 ± 2.86$^{\#}$	29.19 ± 2.41$^{\#}$
	P value	**0.25**	**0.12**	**0.00**	**0.94**
TNF-α (pg/ml)	TTP-PECS group	4.42 ± 0.73	8.06 ± 0.65$^{\#}$	13.59 ± 0.93$^{\#*}$	8.80 ± 0.79$^{\#}$
	TPVB group	4.48 ± 0.64	8.18 ±0.99$^{\#}$	16.14 ± 1.07$^{\#}$	8.82 ± 1.05$^{\#}$
	P value	**0.70**	**0.53**	**0.00**	**0.93**

TTP-PECS treatment significantly decreased levels of pro-inflammatory cytokines at 12 h after surgery. Data are expressed as mean ± SD (39 in TTP-PECS group and 38 in TPVB group). $^{*}P < 0.05$, versus TPVB group. $^{\#}P < 0.05$, versus before surgery.

Table 4.2
Effects of TTP-PECS and TPVB on pain-related mediators

Indicator	Group	before surgery	immediately after surgery	12 h after surgery	24 h after surgery
PGE_2 (ng/l)	TTP-PECS group	28.60 ± 3.82	34.53 ± 5.69#	38.18 ± 6.25#*	42.38 ± 6.81#
	TPVB group	28.51 ± 3.81	34.80 ± 5.96#	46.66 ± 8.50#	42.66 ± 8.35#
	P value	**0.92**	**0.84**	**0.00**	**0.87**
NPY (ug/ml)	TTP-PECS group	79.01 ± 12.55	122.07 ± 15.74#	142.29 ± 22.93#*	149.11 ± 23.02#
	TPVB group	79.53 ± 12.39	122.67 ± 16.91#	160.22 ± 21.78#	148.13 ± 22.16#
	P value	**0.86**	**0.87**	**0.00**	**0.85**
β-endorphin (ng/l)	TTP-PECS group	65.14 ± 6.69	69.64 ± 6.04#	74.37 ± 5.71#*	79.97 ± 5.67#
	TPVB group	64.36 ± 6.02	69.50 ± 6.72#	83.72 ± 8.17#	79.87 ± 7.76#
	P value	**0.59**	**0.92**	**0.00**	**0.95**

TTP-PECS treatment significantly decreased levels of pain-related mediators at 12 h after surgery. Data are expressed as mean ± SD (39 in TTP-PECS group and 38 in TPVB group). *P < 0.05, versus TPVB group. #P < 0.05, versus before surgery.

5. Patients' recovery quality

The global QoR-40 score was significantly higher in the TTP-PECS group than in the TPVB group. Of the five dimensions of the QoR-40, the scores for support, pain, and emotional state were also significantly increased in patients receiving TTP-PECS on the postoperative day (P < 0.01), as shown in Table 5.

Table 5
The scores of QoR-40 on the postoperative day

QoR-40 (score)	Physical comfort	Emotional state	Physical	Patient support	Pain	Total score
TTP-PECS group	53.38 ± 1.79	42.92 ± 0.77*	16.49 ± 1.10	31.64 ± 0.96*	31.69 ± 0.69*	176.13 ± 2.66*
TPVB group	53.08 ± 1.81	40.39 ± 1.48	16.34 ± 1.07	29.66 ± 1.12	29.26 ± 1.54	168.74 ± 3.42
P value	0.47	0.00	0.55	0.00	0.00	0.00

The scores of QoR-40 were taken on the postoperative day. TTP-PECS treatment significantly increased the support, pain, and emotional state scores, as well as total score after surgery. Data are expressed as mean ± SD (39 in TTP-PECS group and 38 in TPVB group). *P < 0.01, versus TPVB group.

Discussion

The present study showed that both TTP-PECS and TPVB are effective for analgesia after MRM. Although the two groups showed no significant differences in postoperative analgesia at 2, 6, and 24 h postoperation, TTP-PECS reduced postoperative fentanyl and flurbiprofen axetil consumption in the first 24 h after mastectomy, and prolonged block duration. Furthermore, TTP-PECS reduced postoperative pain intensity at rest and during activity, and inflammatory response at 12 h postoperation. Finally, TTP-PECS improved the QoR-40 scores on the postoperative day. These findings indicated the apparent superiority of the TTP-PECS in terms of postoperative analgesia. Thus, TTP-PECS might be an attractive alternative to TPVB in patients undergoing MRM.

In recent years, various regional anesthetic techniques have been used for pain management during breast surgery. TPVB as the “gold standard” has been widely studied for the prevention and treatment of acute pain and has been used with varying degrees of success to provide analgesia after MRM (Simpson J et al. 2014). However, TPVB requires special skills to perform the needle manipulations under ultrasonography guidance toward the paravertebral space. In addition, adverse effects such as pneumothorax, sympathetic block, and hypotension and even spinal anesthesia have been documented. MRM involves the removal of not only the breast but also the axillary lymph nodes. The main shortage of adequacy of TPVB is revealed during axillary dissection. In the presence of axillary dissection, TPVB is reported to have inadequate block (Altıparmak B et al. 2019). Thus, patients undergoing TPVB frequently complain of postoperative pain in the axilla and upper limb due to sparing of the medial and lateral pectoral nerves (Mohamed M 2020). Hence, better analgesia strategies are urgently needed.

From the anatomic point of view, the nerve supply to the breast is very complex. Innervations may be divided into 3 groups originating from the superficial cervical plexus, the brachial plexus, and the anterior branches of the thoracic nerves. US-guided TTP-PECS is a myofascial plane block based on the anatomical structure and the neural supply of the anterior chest wall and breast (Pusch F et al. 1999).

This type of blocking technique was initially performed as PECS I; it was then modified as PECS II, and finally, TTP was added to suit the extent of surgery. The TTP-PECS can better target the web of nerves innervating the anterior chest wall including the breast, such as the lateral and anterior cutaneous branches of the intercostal nerves, the intercostobrachial nerve, the long thoracic and thoracodorsal nerves, and the lateral and medial pectoral nerves. Our study observed that TTP-PECS shows consistent dermatomal spread in T_2 -T_6 segments, even spread up to T_7 segment or more widely. For TPVB, sensory spread was usually observed at the level of injection (T_3-T_7), and less spread to T_2 was observed, with very limited cephalad spread. The duration of analgesia was significantly prolonged in patients receiving TTP-PECS as compared to that in patients receiving TPVB. In the TTP-PECS group, the analgesia duration reached to 12 h or more.

An important aspect is that the TTP-PECS may reflect better mastering of the technique with time relative to the paravertebral technique. Furthermore, the incidence of complications such as spinal cord injury, epidural blockade, sympathectomy, and epidural hematoma was reduced in the TTP-PECS (Tighe SQ 2013). It was also reported that most cases of TTP-PECS are performed under general anesthesia due to the advantage of easy positioning of the patient in the supine position.

Several retrospective studies (Zhang JY et al. 2018), (Jiacen Li et al. 2021) have found TTP-PECS to be effective as a postoperative analgesic technique and to reduce postoperative opioid consumption following breast surgeries. Under real-time US guidance, with the deposition of local anesthetic drugs into the fascial planes, the TTP-PECS would be more accurate to provide higher analgesic efficacy for mastectomy and axillary clearance because of its complete paranesthesia of the hemithorax (Ueshima H 2017). In this retrospective study, we monitored fentanyl consumption and postoperative flurbiprofen axetil consumption in the first 24 h postoperation between the two groups. We observed marked advantages with the use of TTP-PECS.

VAS scores are commonly used to determine pain scores (Petersen PL et al. 2012). VAS scores at rest and during activity were used as a pain index in this study. We observed that VAS scores at rest and during activity were significantly lower in the TTP-PECS group than in the TPVB group at 12 h postoperation. A similar result was reported by Kulhari *et al* (Kulhari S et al. 2016) where they showed that PECS had a significantly prolonged duration of postoperative analgesia with less requirement of 24 h morphine consumption than TPVB; this finding was consistent with the results of our study.

In the present study, we detected the inflammatory response and tried to explore whether there was any difference between the two blocks. Our results showed that invasive MMR surgical procedures can cause inflammatory response in varying degree. Previous studies revealed that surgery-associated tissue and organ injury can trigger inflammatory responses, accompanied by elevated levels of pro-inflammatory cytokines (Desborough JP. 2000). As reported, IL-6, MCP-1 and TNF-α are the key proinflammatory cytokines that upregulated after surgery (Waltho D 2016) Thus, we examined IL-6, MCP-1 and TNF-α to determine the effects of TTP-PECS and TPVB on inflammation response in the present study. We found that the serum levels of these proinflammatory cytokines were all lower in TTP-PECS group than those in

TPVB at postoperative 12 h. Our finding is consistent with previous report by Bagry et al (Bagry H et al. 2008). They reported a positive correlation between lower levels of inflammatory markers and pain in patients after knee surgery.

On the other hand, inflammation mediators could activate protein kinases, with the increased intensity of acute pain, accompanied by elevated levels of pain-related mediators (Joseph J et al. 2019). The release of proinflammatory cytokines and pain-related mediators increased during surgery and general anesthesia. While experimental studies reported that appropriate pain intervention will inhibit inflammatory response, and inhibit the active upregulation of cytokines and substance P secretion and production, thus directly inhibiting pain transmission, alleviating pain consecutive at different levels, and potentially influencing changes postoperative analgesia (Evelyne Combettes et al. 2010).

Moreover, previous clinical observation also showed that NPY, PGE2 and β-endorphin positively correlated with pain which can induce peripheral and central nerve system sensitization and lead to pain augmentation, accompanied by elevated levels of pain stimulation (Iannuccelli C et al. 2017), (Liu Y et al. 2018), (Anand J et al. 2019). We therefore detected the NPY, PGE2 and β-endorphin in the patient blood and found that the serum levels of these pain-related mediators were also lower in TTP-PECS group than those in TPVB at postoperative 12 h. These results indicate that TTP-PECS may relieve acute pain more effectively not only by inhibiting the inflammation response at postoperative 12 h, but also by reducing the NPY, PGE2 and β-endorphin production compared with TPVB block.

Postoperative pain can reduce the quality of life of patients. Controlling postoperative pain can help patients to participate actively in postoperative rehabilitation and improve short-term and long-term recovery after surgery. It is the most important outcome measure of effective analgesic management (Myles PS 2018). QoR-40 has undergone extensive psychometric testing (validity, reliability, consistency, and responsiveness), and it has shown excellent performance in all dimensions (Gornall BF et al. 2013). Our results suggested that TTP-PECS treatment increased the impact as expected at 24 h after surgery. Previous reports have shown that the use of pain control significantly improved the component of the QoR-40 score (Onaka H et al. 2016), and this may be the reason why the QoR-40 scores were significantly improved in the TTP-PECS group.

This meta-analysis comprehensively evaluated a series of short-term indicators related to analgesic treatment and particularly focused on different time points (2, 6, 12, and 24 h) after surgery as outcome indicators. However, this meta-analysis has several limitations. First, a multicenter analysis and an intervention control group were lacking. Second, the postoperative pain outcomes and early recovery quality of patients were assessed only up to 24 h. Third, with the lack of a large clinically relevant effect, it remains questionable whether the risk of long thoracic nerve blockade by the TTP-PECS and intraoperative damage by the surgical procedure are worth the minimal benefits? Some studies have shown that younger patients undergoing breast cancer surgery are more prone to develop persistent postoperative pain. However, on the basis of the available data from the current studies, we could not

evaluate the efficacy of the PECS in patients of different ages and for those with chronic pain. Clinical trials are needed to further explore and optimize this technique.

Conclusion

Our results have revealed that application of ultrasound-guided transversus thoracic muscle plane-pectoral nerve block is the more desirable and promising analgesic strategies than thoracic paravertebral nerve block.

Abbreviations

MRM
Modified radical mastectomy
TTP-PECS
Transversus thoracic muscle plane-pectoral nerve block
TPVB block
Thoracic paravertebral nerve block
QoR-40
Multidimensional patient-reported QoR-40 questionnaire
US
Ultrasound
SLND
Sentinel lymph node dissection
ALND
Axillary dissection
BMI
Body mass index
ASA
American Society of Anesthesiologists
PACU
Postanesthesia care unit
PCA
Patient-controlled analgesia
VAS
Visual analogue scale
. ELISA
enzyme-linked immunoabsorbent assay.

Declarations

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Availability of data and materials

All data generated or analyzed during this study are included in this published article. The data used to support the findings of this study are available from the first author and corresponding author upon request.

Authors' contributions

Peng Pan and Junyan Yao conceived and designed the experiments. Ying Zhao and Shuquan Feng performed the experiments. Shuquan Feng and Danyun Fu analyzed the data. Ying Zhao and Junyan Yao wrote the manuscript. Weilin Jin contributed reagents, materials, and analysis tool. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

This retrospective randomized study was reviewed and approved by the Medical Ethics Committee of the Kunshan Hospital of Traditional Chinese Medicine on April 9, 2019 (Approval ID: 2019-18), and written informed consent was obtained from each patient for participation in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

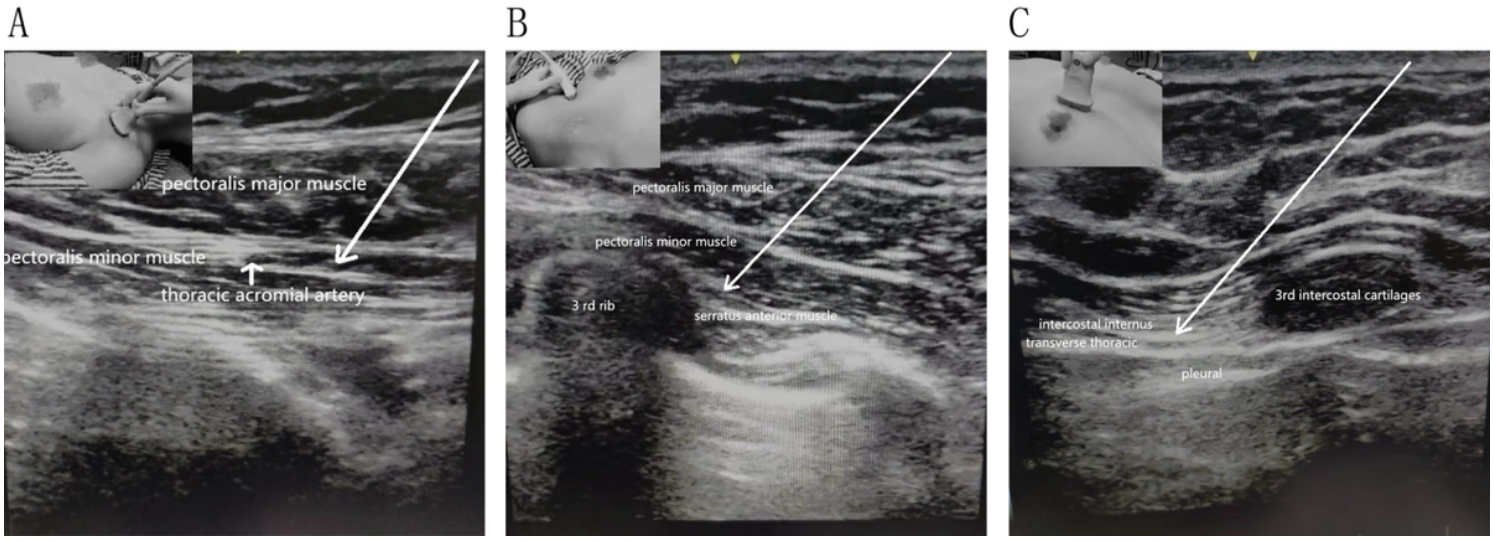

Figure 1

For the TTP-PECS blocks, the position of the ultrasound transducer are shown in the upper left of the images. During ultrasound scanning of PECS I block, a local anesthetic was injected in the plane between the PMM and Pmm (A); in PECS II block, a local anesthetic was injected in the plane between the Pmm and SM (B); in TTP block, a local anesthetic was injected in the plane between the IIM and TTM (C). The arrow indicates the injection direction and point. PMM = pectoralis major muscle; Pmm = pectoralis minor muscle; SM = serratus muscle; IIM = internal intercostal muscle; TTM = transversus thoracic muscle

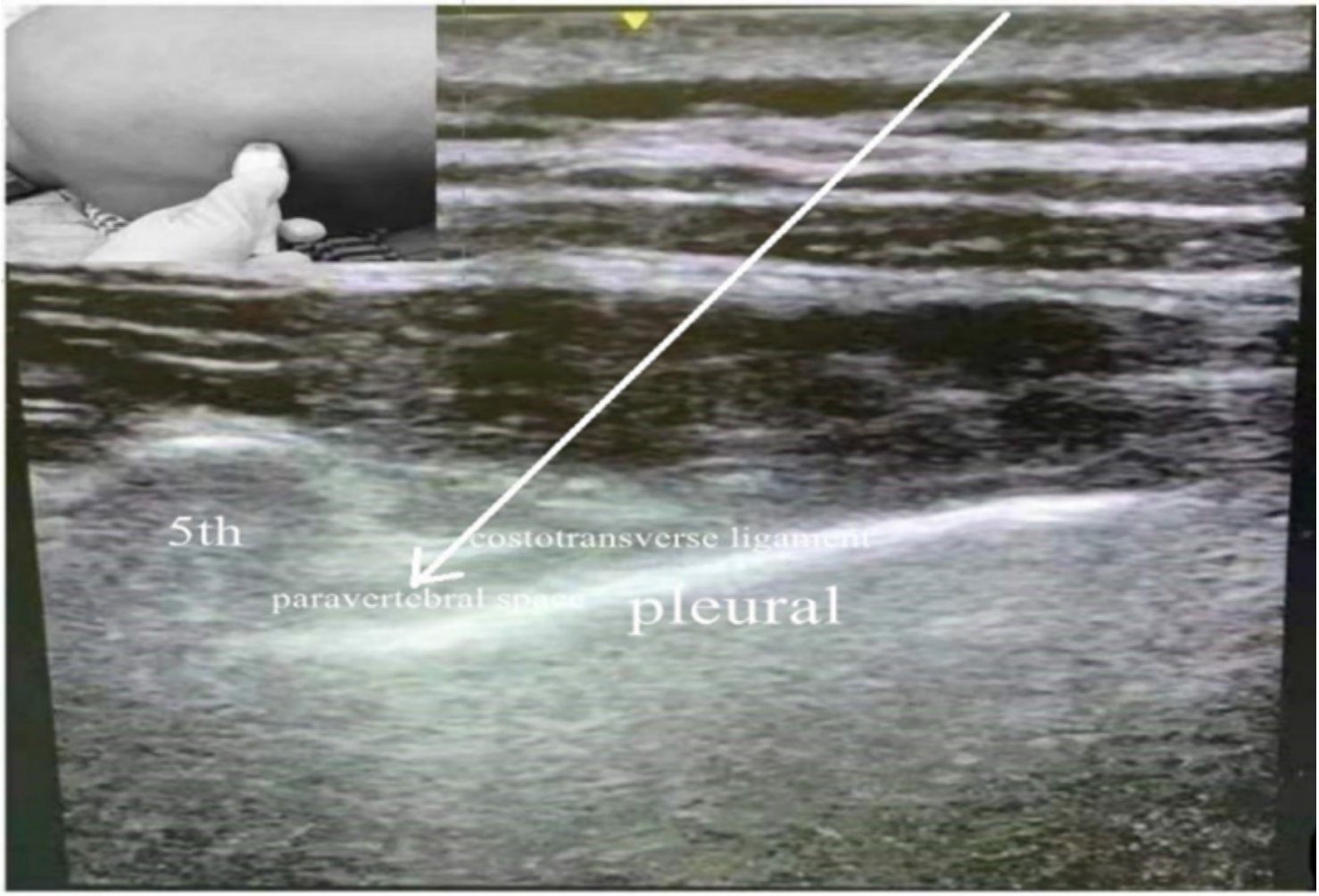

Figure 2

For the TPVB block, the position of the ultrasound transducer is shown as an inset in the upper left of the image. During ultrasound scanning of TPVB block, a local anesthetic was injected into the paravertebral space. The arrow indicates the injection direction and point. 5th = the fifth thoracic vertebra

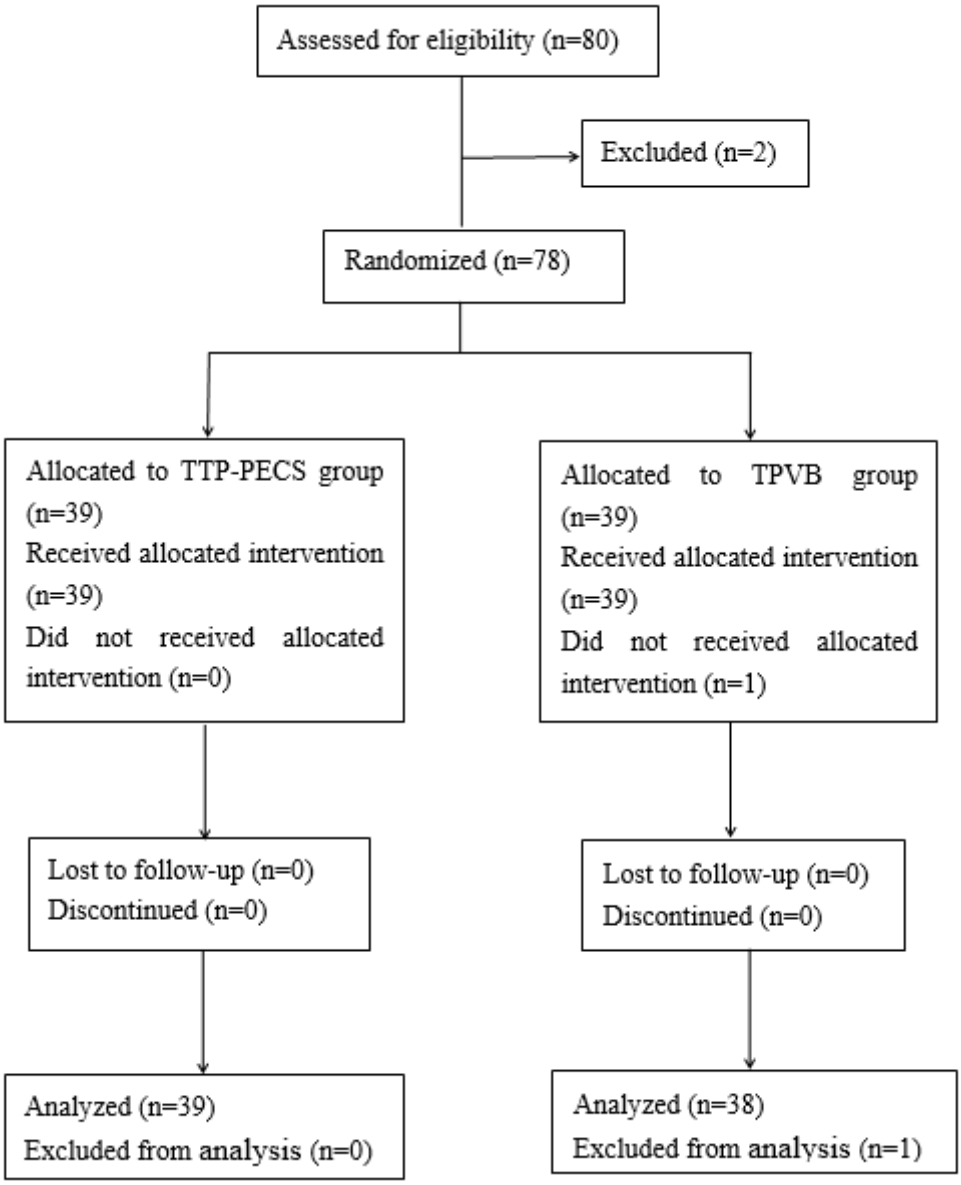

Figure 3

Flow diagram.