Original Article

Effect of ultrasound-guided PecS II block on the incidence of chronic postmastectomy pain in patients after radical mastectomy: A randomized controlled trial

ABSTRACT

Background: The pectoral nerve (PecS) II block is a recently introduced technique utilized for surgical anesthesia and postoperative analgesia during breast surgery. This study aims to investigate the impact of ultrasound-guided PecS II block on the incidence of chronic postmastectomy pain in patients following radical mastectomy.

Methods: Ninety-eight patients undergoing selective radical mastectomy were included in this study. Based on whether the ultrasound-guided PecS II block was performed, the patients were randomly divided into the PecS II block group (group P) and the control group (group C). The primary outcomes included the incidence of chronic pain at 12 weeks after surgery, and the secondary outcomes included intraoperative dosage of remifentanil, the amount of oxycodone used in 48 h after surgery, time for the first analgesia administration, postoperative acute pain score 48 h after surgery, and HADS score at 48 h and 12 weeks after surgery. The presence or absence of pain in the previous week was recorded every 7 days after surgery (beginning on the 8th day after surgery). The postoperative pain duration curves of the two groups were plotted and compared by Kaplan-Meier estimation and log-rank test.

Results: Compared with group C, the incidence of chronic pain in group P at 12 weeks after surgery was significantly decreased by 14.13% (20.65% vs. 34.78%, $P < 0.05$). The amount of remifentanil used in group P was significantly reduced (1.46 ± 0.11 mg vs. 2.66 ± 0.18 mg, $P < 0.001$), and the amount of oxycodone used 48 h after surgery in group P was remarkably reduced than that in group C (22.57 ± 3.21 mg vs. 31.62 ± 4.71 mg, $P < 0.001$). The first analgesic requirement time of group P was significantly longer than that of group C (368.80 ± 157.68 min vs. 96.60 ± 40.12 min, $P < 0.001$). Compared with group C, the postoperative acute pain score 48 h after surgery and the HADS score 48 h and 12 weeks after surgery in group P were significantly decreased ($P < 0.05$). The postoperative pain duration curve of the two groups was significantly different ($P < 0.05$), and the postoperative pain duration of group P was lower than that of group C ($P < 0.05$).

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Conclusions: PecS II block can reduce the incidence of chronic postmastectomy pain after radical mastectomy, reduce perioperative opioid consumption, provide better analgesia, and improve the degree of anxiety and depression of patients.
Trial registration: ChiCTR2200066968, 22/12/2022.

Key words: Chronic postmastectomy pain, PecS II block, radical mastectomy

Introduction

Breast cancer is a prevalent malignancy in women, with a lifetime risk exceeding 10%.[1] Radical mastectomy may be the sole effective treatment for breast cancer patients who do not respond well to conservative treatment.[2] The advancements in diagnosis and treatment have led to an increased number of breast cancer survivors. Previously considered rare, chronic postmastectomy pain now has an estimated prevalence ranging from 20% to 65% according to the literature.[3-8] This type of pain has a neuropathic component and can manifest in various areas such as the chest wall, breast, scar, axilla, and medial upper arm or shoulder. Several predictive factors related to both patient characteristics and surgical factors have been identified for chronic postoperative pain. Strong predictors of persistent pain after surgery include preoperative pain sensitivity, presence of pre-surgery pain, acute postoperative pain experience, and analgesic consumption.[9-11]

Other predictive factors include anxiety, psychosocial factors, young age (<40 years), type of surgery, intercostobrachial nerve damage, adjuvant radiation therapy, and chemotherapy.[12-15] Adequate and effective pain management during the perioperative period may prevent and reduce chronic pain.[16-18] Preoperative loco-regional block is one of the multimodal pain management strategies used to prevent chronic pain and minimize opioid consumption as well as its associated side effects.[19,20]

The pectoral nerve (PecS) block is a novel technique utilized for surgical anesthesia and postoperative analgesia during breast surgery and involves the administration of local anesthetic between the muscles of the thoracic wall 8–9, thereby minimizing major adverse effects. The PecS II block is a superficial block that has demonstrated efficacy in various surgical procedures such as breast expander placement, subpectoral prosthesis insertion, shoulder surgery involving the deltopectoral groove, and pacemaker or intercostal drain insertion. Notably, the PecS II block is particularly advantageous for mastectomy and axillary clearance surgeries as it effectively blocks both long thoracic and thoracodorsal nerves in addition to lateral branches of intercostal nerves at the mid-axillary line level responsible for innervating the mammary gland and skin from T2 to T6.[21] This study aimed to investigate whether ultrasound-guided PecS II block influences the incidence of chronic postmastectomy pain in patients following radical mastectomy.

Materials and Methods

Population

The randomized controlled trial was approved by the Ethics Committee of General Hospital of Central Theater Command of People's Liberation Army, China, on October 20, 2022 (reference number: [2022]046-01). The trial was registered with the Chinese Clinical Trial Registry (ChiCTR2200066968) on December 22, 2022. It was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement and Helsinki Declaration. Written informed consent was obtained from all participants prior to surgery. After obtaining written informed consent, a total of 98 patients undergoing selective radical mastectomy between December 22, 2022 and December 31, 2023 were enrolled. Figure 1 illustrates the study flowchart.

Inclusion criteria

Eligibility criteria for inclusion in this study were as follows: participants aged between 28 and 65 years, with a body mass index ranging from 18 to 32 kg/m^2, an American Society of Anesthesiologists classification of either I or II, and a minimum life expectancy of 2 years. Patients who underwent radical mastectomy with axillary lymph node dissection were included.

Exclusion Criteria

An occurrence of any previous cancer other than breast cancer; allergy to local anesthetics and morphine; reported history of substance abuse; pregnancy; ipsi-lateral breast surgery in the past 3 years; preoperative analgesic use (12 h); severe renal, pulmonary, or hepatic dysfunction; active malignant disease; alcohol or long-term drug addiction; poor ultrasound imaging quality on sonogram; and those unable to comply with the protocol for any reason were excluded.

Randomization

All patients were assigned to group P and group C in a 1:1 ratio by using both the computer random number

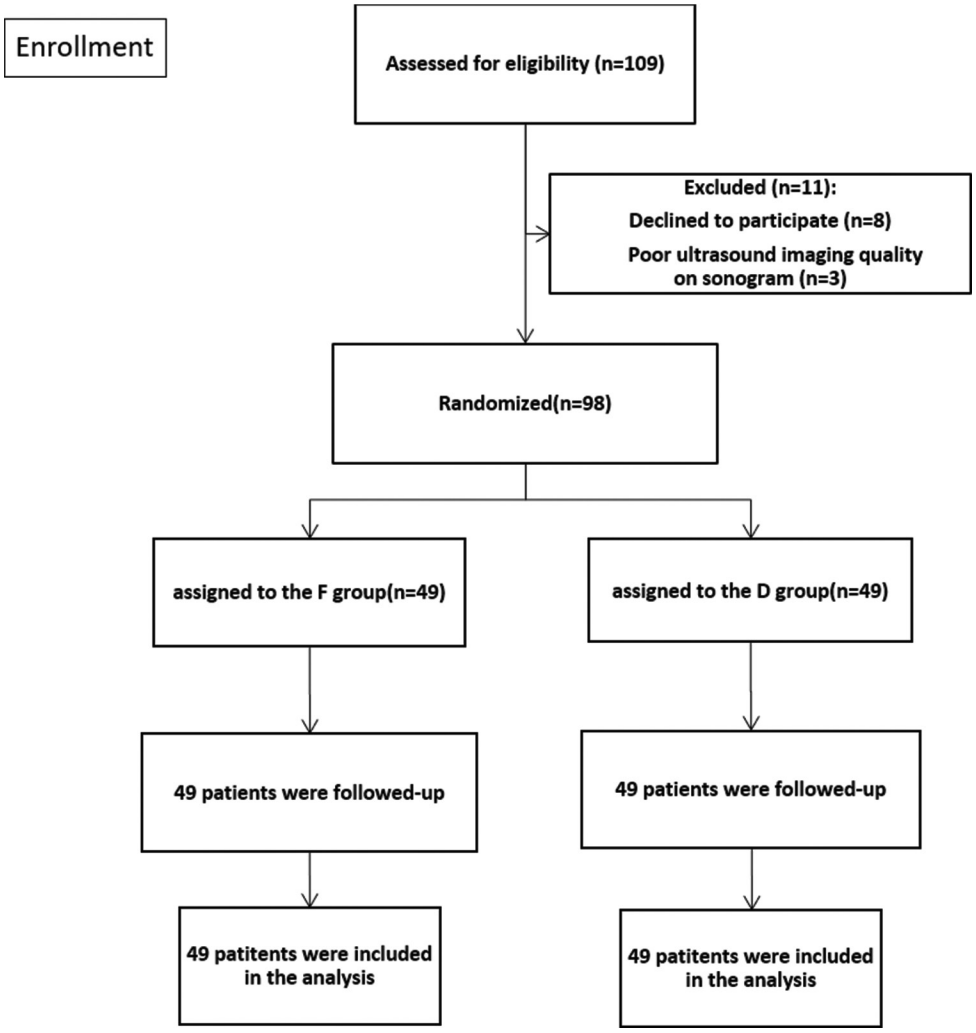

Figure 1: Flow chart of study selection

table method and the sealed envelope method. Prior to commencing the study, an independent individual randomly allocated participants by using computer-generated numbers, which were then placed inside sealed envelopes. Each patient selected an envelope and was grouped accordingly based on its contents. The researchers responsible for randomizing the groups did not participate in any further follow-up evaluations. All surgical procedures were performed by a consistent team of surgeons, led by a highly experienced chief surgeon specializing in radical mastectomy surgery. Trocar insertion was consistently carried out by the same first assistant.

Ultrasound-guided PecS II block

The patients were randomized into two groups by using computer-generated random numbers, and the group allocation numbers were concealed in sealed opaque envelopes until after patient enrollment. Group P received a PecS II block with ropivacaine 0.5% (25 mL), while group C did not receive this intervention. The blocks were performed under strict aseptic precautions in the preoperative room 30 min prior to surgery by using an echogenic needle (Pajunk Sonoplex Stim Cannula, Geisingen, Germany; 80 mm) and ultrasound machine (Sonosite Inc., Bothell WA USA) with a linear-array probe (38 mm, 7–12 MHz frequency). An anesthetist who was not involved in preoperative or postoperative assessments of the patient, anesthesia management, or data collection conducted all procedures.

The PecS II block was performed on the surgical side by using the technique described by Blanco *et al*. The patient was positioned supine with the abducted arm. An ultrasound probe was placed inferolaterally at the midclavicular level to locate the axillary artery and vein and then moved laterally until identifying the pectoralis minor and serratus anterior muscles at the level of the third rib. Following skin infiltration with 2% lidocaine, a needle was obliquely advanced in the plane of the probe from medial to lateral until reaching between the pectoralis major and minor, where 10 mL of 0.5% ropivacaine was injected. After depositing local anesthetic,

further advancement of the needle into potential space between the pectoralis minor and serratus anterior muscles allowed for the deposition of 15 mL of 0.5% ropivacaine.

Anesthesia management

The enrolled patients underwent radical mastectomy following admission. Noninvasive heart rate (HR), invasive blood pressure, pulse oxygen saturation, end-expiratory partial pressure of carbon dioxide, and arterial blood gas analysis were routinely performed upon admission to the operating room. Both groups of patients received identical general anesthesia induction and maintenance drugs, including intravenous injection of midazolam (Nhwa Pharmaceutical Co., Ltd, Jiangsu, China) at a dose of 0.05 mg/kg, etomidate (Nhwa Pharmaceutical Co., Ltd, Jiangsu, China) at a dose of 0.3 mg/kg, sufentanil (Humanwell Pharmaceutical Co., Ltd, Hubei, China) at a dose of 0.5 μg/kg, and cisatracurium besylate (Hengrui Pharmaceuticals Co., Ltd, Jiangsu, China) at a dose of 0.3 mg/kg for anesthesia induction and tracheal intubation. During the operation, propofol (Corden Pharma S.P.A., Caponago, Italy) was continuously infused at a rate of 4–8 $mg^{-1}kg^{-1}$ h^{-1}, and remifentanil (Humanwell Pharmaceutical Co., Ltd, Hubei China) was continuously administered at a rate of 0.1–0.5 $\mu g^{-1}kg^{-1}$ min^{-1}. In addition, cisatracurium besylate was intermittently injected at a dosage of 0.1 mg/kg to maintain anesthesia. The depth of anesthesia was controlled throughout the procedure, with BP and HR maintained within ±20% deviation from baseline values while BIS remained between 40 and 60. When necessary, epinephrine (Northeast Pharm Shenyang China) and atropine (Runhong Pharmaceutical Co. Ltd Henan China) were utilized for treating hypotension and bradycardia, respectively. Nicardipine (Nipro Pharma Corporation Ise Plant Matsusaka-shi Japan) was employed for managing hypertension. The arterial blood gas was monitored at 30-min intervals. Approximately 30 min prior to the completion of the surgery, the patient-controlled intravenous analgesia pump was connected, and both groups received a combination of oxycodone (0.40 mg/kg), tropisetron (8 mg), and 0.9% normal saline up to a total volume of 100 mL for postoperative pain management through self-administered intravenous infusion. The analgesic parameters included a background infusion rate of 2 mL/h, patient-controlled analgesia dose of 2 mL, lockout interval of 10 min, and maximum cumulative dose limit of 16 mL. Following the procedure, the patients were transferred to the anesthesia resuscitation room.

Evaluation

The primary outcomes assessed the incidence of chronic pain at 12 weeks post surgery. The secondary outcomes included the intraoperative dosage of remifentanil, the amount of oxycodone used within 48 h after surgery, time to first analgesia administration, acute pain score 48 h post surgery, and HADS score at 48 h and 12 weeks post surgery. Pain presence or absence in the previous week was recorded every 7 days starting from the eighth day after surgery. Kaplan-Meier estimation and log-rank test were employed to plot and compare the postoperative pain duration curves between both groups.

Statistical analysis

The study was conducted as a randomized controlled trial, with the experimental group receiving PecS II block (group P) and the control group not receiving PecS II block (group C). According to previous studies, the incidence of CPSP in group C was reported as 42% at 3 months. PecS II block was hypothesized to reduce the incidence of CPSP by half, specifically to 21%. Using PASS 15 software (NCSS, Kaysville, Utah, USA) for calculations, a minimum number of 98 patients (49 patients per group) was required to reach a study power of 90% and an alpha error of 0.05. Considering the loss and refusal of follow-up, the calculation was based on 10%. Finally, at least 49 subjects in the experimental and control groups were required, with a total of at least 109 subjects to be included.

The data were collected and inputted into the computer as numerical or categorical variables. Statistical processing and mapping were performed using SPSS 26.0 software. The Shapiro-Wilk test was utilized to assess the normality of continuous data distributions. For normally distributed measurement data, mean ± standard deviation was employed for representation purposes; independent sample tests were conducted for comparing the two groups. In cases where measurement data did not follow a normal distribution, median M (P25, P75) was used for representation. The count data were expressed as percentages (%), and the Chi-square test or Fisher exact probability method was utilized to compare the two groups. Repeated measurement analysis of variance was employed for analyzing the repeated measurement data. The Kaplan-Meier analysis was conducted to evaluate the time until first analgesia administration. Kaplan-Meier estimation and log-rank test were used to plot and compare postoperative pain curves between the two groups. A significance level of $P < 0.05$ was considered indicative of a significant difference.

Results

1. In total, 109 patients were enrolled in the study [Figure 1]. Eight patients refused to participate in the study. Three patients with poor-quality ultrasound imaging were excluded from this study. The remaining 98 patients were

randomly allocated into two groups (n = 49/group), and none of them dropped out of the study. In the end, the case data of 49 patients in each group were analyzed.

2. There was no significant difference in age, height, weight, BMI, ASA classification, and duration of surgery between the two groups ($P > 0.05$; Table 1).
3. The incidence of chronic pain in group P at 12 weeks post surgery was significantly decreased than that in group C by 14.13% (20.65% vs. 34.78%, $P < 0.05$; Figure 2).
4. The amount of remifentanil used in group P was significantly reduced by 45.11% (1.46 ± 0.11 mg vs. 2.66 ± 0.18 mg, $P < 0.001$; Figure 3), and the amount of oxycodone used 48 h after surgery was remarkably reduced by 28.62% (22.57 ± 3.21 mg vs. 31.62 ± 4.71 mg, $P < 0.001$; Figure 3).
5. The time for first analgesia administration in group P was markedly prolonged in comparison with group C (368.80 ± 157.68 min vs. 96.60 ± 40.12 min, $P < 0.001$; Figure 4).
6. The acute pain score during the perioperative period and the NRS score at 12 weeks after surgery in group P were significantly decreased than those in group C ($P < 0.05$; Table 2). The HADS scores at 48 h and 12 weeks after surgery in group P were significantly decreased than those in group C ($P < 0.05$; Table 2).
7. Removal of postoperative pain (NRS score 0) was used as a truncation. The Kaplan-Meier method was used to plot the curve depicting the duration of postoperative pain for both groups. The median duration of pain was found to be 8 weeks in group P (95%CI: 7.683–8.367) and 10 weeks in group C (95%CI: 9.524–10.458). The duration of postoperative pain in group P was shorter, and pain recovery was faster ($P < 0.05$; Figure 5).

Discussion

Chronic postmastectomy pain following radical mastectomy is a recognized complication, imposing significant physical and psychological burdens on patients while diminishing their quality of life and functional abilities.[17] The term "chronic postmastectomy pain" refers to persistent pain that exceeds the normal healing time for tissues (3 months) and primarily affects areas such as the axilla, upper arm, chest wall, and scapula on the same side as the surgery. This type of pain manifests as a range of symptoms, including intermittent or continuous pinprick sensations, burning discomfort, dull ache, tactile sensitivity, and skin numbness.[22] The pathogenesis of chronic postmastectomy pain is multifactorial with numerous influencing factors. A number of studies[23-25]

Table 1: Demographic and clinical characteristics

Variable	Group P (n=49)	Group C (n=49)	P
Age (years)	46.89±12.45	45.87±13.43	0.434
Height (cm)	162.21±6.56	161.67±6.56	0.468
Weight (kg)	68.46±17.56	67.87±16.97	0.945
BMI (kg/m^2)	25.53±6.64	24.54±6.35	0.843
ASA classification (I/II)	24/25	25/24	0.665
Duration of surgery (min)	72.67±12.43	71.42±11.83	0.756

Numerical variables are expressed as mean±SD. Categorical variables are expressed as number of patients. BMI, body mass index; ASA, American Society of Anesthesiologists

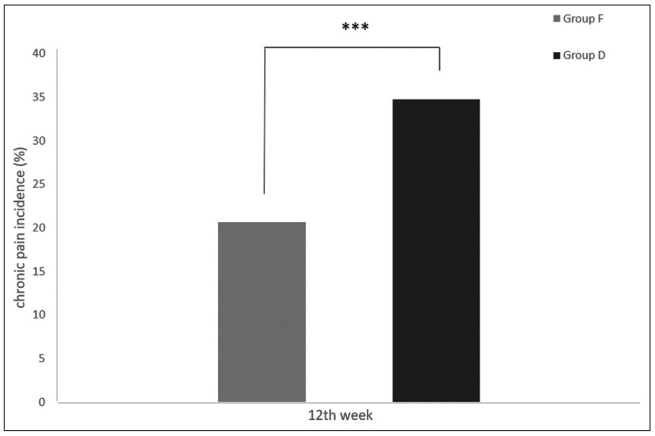

Figure 2: Comparison of the incidence of chronic pain at 12th week after surgery between the two groups. ***$P < 0.05$

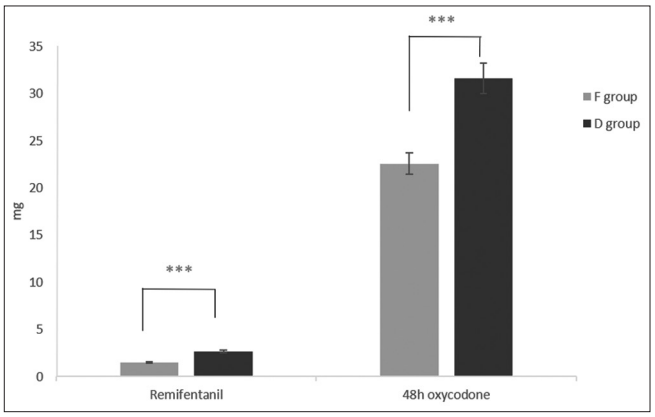

Figure 3: Comparison of intraoperative remifentanil and postoperative oxycodone dosage between the two groups. ***$P < 0.001$

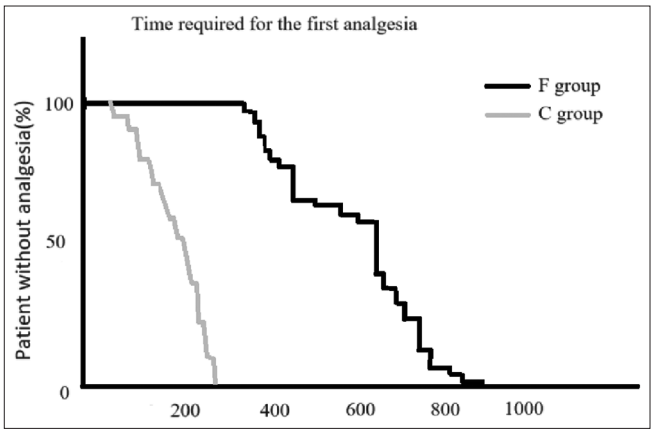

Figure 4: Kaplan-Meier estimate of time to first analgesia

Table 2: Perioperative pain score, HADS score, and Harris score

Index	Group P (n=49)	Group C (n=49)	χ^2/Z	P
Postoperative acute pain score [M (P25, P75)]	1 (1, 1)	4 (3, 4)	−3.876	<0.001
48 h after surgery HADS score [M (P25, P75)]				
Depression	3 (4, 5)	6 (5, 8)	−3.332	0.002
Anxiety	3 (3, 5)	6 (4, 8)	−3.976	<0.001
NRS score 12th week after surgery [M (P25, P75)]	1 (1, 1)	5 (4, 6)	−2.341	0.032
HADS score 12th week after surgery [M (P25, P75)]				
Depression	2 (2, 3)	5 (4, 6)	−3.476	<0.001
Anxiety	3 (2, 4)	5 (4, 6)	−4.498	<0.001

Numerical variables are adopted as the median M (P25, P75)

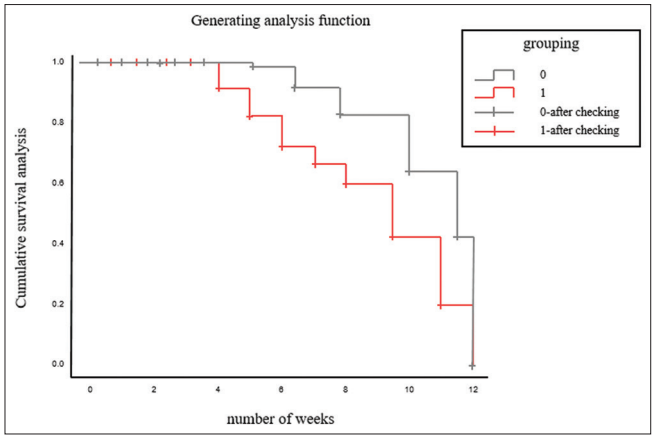

Figure 5: The median duration of pain and postoperative pain duration between the two groups (P < 0.05). Postoperative pain duration curve

suggest that postoperative acute pain, pain sensitization, and psychological factors in patients may play a significant role in its occurrence. Currently, there are no specific medications or interventions available for the treatment of chronic post-surgical pain. These findings indicate that perioperative interventions could potentially prevent the development of chronic pain following radical mastectomy. Existing studies[5] have demonstrated that the occurrence of chronic pain is closely associated with mechanisms such as intraoperative nerve injury, neuroplasticity changes, and continuous stimulation of peripheral receptors by inflammatory mediators leading to hypersensitivity pain and subsequent central sensitization. The speculation is that PecS II blockade may potentially prevent the development of chronic postmastectomy pain by providing preemptive analgesia, effectively inhibiting nerve transmission in the chest wall prior to nociceptive stimulation. This mechanism aims to reduce or eliminate pain resulting from nociceptive stimuli and subsequently prevent peripheral or central sensitization.

Thanks to the widespread utilization of ultrasound technology in nerve block procedures, thoracic epidural anesthesia (TEA), thoracic paravertebral block (TPVB), PecS, and other regional nerve block techniques have gained significant popularity in breast surgery. Among these techniques, TPVB has been extensively supported by numerous studies for its ability to reduce the incidence of chronic pain following breast cancer surgery.[26-28] However, the performance of TPVB is challenging and demands proficient puncture techniques, with a failure rate ranging from 6% to 12%. Moreover, even a single segmental block failure can result in inaccurate blockade effects. The PecS II block, proposed by Blanco R *et al.*,[29] is a chest wall nerve block based on PECS. From an anatomical perspective, its analgesic effect primarily stems from the blockade of the lateral cutaneous branch of the intercostal nerve. In addition, there is also some infiltration into the thoracic dorsal and long thoracic nerves. This comprehensive sensory blockade extends from T2 to T9 levels, rendering anterolateral chest wall analgesia more optimal than what TPVB and TEA alone can achieve.

The objective of the PecS II block is to effectively block the pectoral, intercostobrachial, intercostals III and VI, and the long thoracic nerves to achieve comprehensive analgesia during breast surgery. Joseph *et al.*[30] conducted a study involving 50 patients undergoing modified radical mastectomies and reported favorable postoperative analgesia for a duration of 8 h. In a recent investigation by Bashandy and Abbas,[28] it was also demonstrated that patients who received the PecS II block with general anesthesia experienced lower NRS scores and reduced postoperative morphine consumption compared to those who received only general anesthesia.

The findings of this study suggest that in comparison to group C, the incidence of chronic pain following radical mastectomy is significantly reduced in group P. In addition, the degree of anxiety and depression after surgery can be improved. Remarkably, the results consistently demonstrate that the PecS II block effectively mitigates the risk of postoperative chronic pain. In addition, we employed the K-M method to construct the postoperative pain curve, revealing that the PecS II block also expedites the rate of postoperative

pain recovery. We hypothesize that this phenomenon may be attributed to the mechanism through which the PecS II block diminishes the occurrence of chronic postoperative pain by alleviating perioperative anxiety and depression on one hand and directly inhibiting pain sensitization by mitigating acute perioperative pain on the other hand, as well as by indirectly exerting an anti-hyperalgesic effect by reducing opioid dosage.

In our study, the amount of remifentanil administered in group P during surgery was 45.11% lower compared to that in group C. In addition, the quantity of oxycodone used 48 h post surgery showed a reduction of 28.62%, indicating that the PecS II block can significantly decrease opioid consumption both during and after radical mastectomy. A recently published study by Wahba and Kamal[30] also reported an extended time until first rescue analgesia and reduced morphine usage following breast cancer surgery among patients who received a PecS block as opposed to a thoracic para-vertebral block, which aligns with our findings.

Our study revealed that patients in group P exhibited a mean extension of 368.80 min for the initial postoperative pain relief, which was significantly associated with reduced NRS scores at various time points following surgery. These findings further suggest that PecS II block can effectively decrease opioid dosage and enhance postoperative analgesia, thereby potentially reducing the incidence of chronic pain among patients with opioid dependence.

The presence of anxiety and depression in patients represents a significant risk factor for the development of chronic pain following surgery.[31] This study revealed that the PecS II block not only resulted in reduced anxiety and depression scores 48 h post surgery but also sustained these improvements up to 12 weeks after the procedure. However, it is important to note that in cases of chronic pain, there exists a reciprocal relationship between pain and anxiety-depressive states.[32]

We documented the presence or absence of pain and plotted the duration of postoperative pain during weekly telephone follow-up. Our findings revealed that the impact of PecS II block on chronic postmastectomy pain extended beyond the 12-week mark, playing a role throughout the entire transition from acute to chronic pain. Regrettably, we solely recorded whether patients experienced any pain, without measuring and documenting weekly changes in their pain scores. This limitation hindered our ability to analyze whether the PecS II block had varying effects on different degrees of chronic postmastectomy pain. Despite this constraint, our study holds implications. Future research can enhance the comprehensiveness and specificity of postoperative weekly follow-ups, enabling us to map out the trajectory of changes in chronic postmastectomy pain.[33] Such an approach could greatly contribute to preventing and treating this condition.

The present study was limited to a single-center setting and lacked the inclusion of a multicenter large-sample cohort. Furthermore, the follow-up period was restricted to only 12 weeks post surgery, precluding any assessment of long-term effects. In addition, at the 12th-week evaluation, only NRS scores were utilized without comprehensive collection of data regarding pain location and characteristics in patients, thereby limiting an accurate reflection of pain nature. Future investigations should aim for more comprehensive and robust methodologies to address these aforementioned limitations.

Conclusions

The findings of our study suggest that PecS II blockade can effectively reduce the incidence of chronic postmastectomy pain following radical mastectomy, decrease intraoperative and postoperative opioid consumption, enhance analgesic efficacy, and ameliorate patients' levels of anxiety and depression.

Data availability

The datasets used and analyzed during the current study are not publicly available due to ethical reasons but are available from the corresponding author upon reasonable request.

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Author contributions

Conceptualization, H. H.; Data curation, Z. L. and T.W.; Methodology, H.H. and B.L.; Formal analysis, H.H, Z.L, B.L, and T.W. Investigation, Z.L. and T.W; Software, T.W. and B.L.; Writing-original draft preparation, H.H. and Z.L.; Writing- review and editing, B.L. and X.S.; Visualization, T.W, T.W.and X.S; Project administration, B.L., T.W. and X.S. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

This prospective, randomized single-center trial was approved by the Institutional Review Board, General Hospital of Central Theater Command of People's Liberation Army, Wuhan, China (reference number: [2022]046 − 01) and registered in the Chinese Clinical Trial Registry (ChiCTR2200066968, 22/12/2022,). All methods were carried out in accordance

with relevant guidelines and regulations. Written informed consent was obtained from all participants. All participants gave written informed consent.

Consent for publication
Not applicable.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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