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CANCER PAIN & PALLIATIVE CARE SECTION

Thoracic Paravertebral Blockade Reduces Chronic Postsurgical Pain in Breast Cancer Patients: A Randomized Controlled Trial

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Abstract

Objective. To evaluate the effect of multilevel single-shot thoracic paravertebral blockade (PVB) on the occurrence of chronic postsurgical pain (CPSP) in patients undergoing breast cancer surgery. **Design**. A randomized controlled trial with two parallel groups. **Setting**. A tertiary hospital. **Methods**. Patients scheduled for breast cancer surgery were randomized to receive either ultrasound-guided multilevel single-shot PVB from T2 to T5 (the PVB group) or nothing (the control group). Surgery was then performed under general anesthesia. Patients were followed up for 12 months after surgery. The primary end point was incidence of CPSP at six months after surgery. **Results**. A total of 218 patients were enrolled and randomized; of these, 208 and 204 completed six- and 12-month follow-up, respectively. The incidence of CPSP at six months was significantly lower in the PVB group (12.5% [13/104]) than in the control group (24.0% [25/104], relative risk = 0.52, 95% CI = 0.28–0.96, $P = 0.031$). Pain scores within 48 hours both at rest and with movement were lower in the PVB group than the control group ($P = 0.006$ and $P < 0.001$, respectively). The percentages of patients with neuropathic pain were also lower in the PVB group than the control group at both six and 12 months after surgery ($P = 0.016$ and 0.028, respectively). Adverse events did not differ between groups. **Conclusions**. For patients undergoing breast cancer surgery, multilevel single-shot PVB reduces the incidence of CPSP at six months; it also improves early postoperative analgesia and reduces neuropathic pain at six and 12 months after surgery.

Key Words: Breast Cancer; Surgery; Thoracic Paravertebral Blockade; Chronic Postsurgical Pain; Neuropathic Pain

Introduction

Surgery is an important treatment for breast cancer. However, even microinvasive surgery such as lumpectomy or sentinel node biopsy may produce chronic neuropathic pain [1]. Acute pain is an independent risk factor for persistent pain after surgery [2]. Chronic postsurgical pain (CPSP), defined as pain persisting or recurring longer than three months after surgery [3], has an incidence of up to 60% in patients after breast cancer surgery [4]. The occurrence of CPSP seriously affects patients' physiological and psychological function, as well as quality of life [5]. It also consumes significant health care resources and increases economic expenditure [6].

Ultrasound-guided thoracic paravertebral block (PVB) provided excellent perioperative analgesia in patients

undergoing breast cancer surgery [7]. However, studies investigating the effects of PVB on chronic pain have reported inconsistent results [6–10]. A recent meta-analysis showed that in patients undergoing breast cancer surgery, multilevel single-shot PVB may be protective against CPSP at six months, but methodological limitations are present and well-organized large sample size trials are required to confirm the effects of PVB [8]. We therefore performed this trial to reevaluate the impact of PVB on CPSP following breast cancer surgery.

Methods

Study Design

This randomized controlled trial with two parallel arms was conducted at Peking University First Hospital. The study protocol was approved by the local ethics committee (2016-1098) and registered prospectively at the Chinese Clinical Trial Registry (http://www.chictr.org.cn; trial identifier ChiCTR-IPR-16008127) on March 22, 2016. Written informed consent was obtained from all participants.

Participants

Adult patients who were scheduled to undergo surgery for primary unilateral breast cancer were screened. Exclusion criteria were the following: previous thoracic surgery with an incision of >2 cm; allergy to ropivacaine; any contraindications to thoracic PVB, including intrathoracic infection, infection at the puncture site, cancer invasion of the puncture site, severe spinal deformity, history of spinal surgery, and severe coagulopathy; and American Society of Anesthesiologists (ASA) classification of 4 or higher.

Baseline data were collected after obtaining consent and included demographic characteristics, current diagnosis, comorbidities, ASA classification, history of surgery, and adjuvant therapy of breast cancer. The day before surgery, baseline assessments were performed by a trained and qualified research nurse (Chun-Li Shao) and included the following: chronic pain (defined as persistent pain for at least three months before surgery), neuropathic pain (assessed with the ID-pain scale [11, 12]), anxiety/depression (assessed with the Hospital Anxiety and Depression Scale [HADS] [13, 14]), and pain intensity and interference (assessed with the Brief Pain Inventory–Short Form (BPI) [15]) (Supplementary Data).

Before the study period, all investigators were trained to follow the study protocol and to use the above instruments according to the instructions or user guides.

Randomization, Intervention, and Masking

Randomization numbers were generated by a biostatistician (Xue-Ying Li) in a 1:1 ratio using the SAS 9.3 statistical package (SAS Institute, Cary, NC, USA). The generated numbers were then concealed in sequentially numbered envelopes. During the study period, the envelopes were selected according to the sequence of patient recruitment and were opened immediately before surgery by the attending anesthesiologist, who performed PVB according to the randomization results. In this way, the enrolled patients were divided into two groups, that is, the PVB group and the control group.

The standard monitoring included electrocardiography, noninvasive blood pressure, pulse oximetry, and bispectral index (BIS). For patients in the PVB group, PVB was performed under ultrasound guidance before anesthesia by two senior anesthesiologists (Zeng-Mao Lin and Feng Zhang) with the patients in a seated position. After confirming the correct position of the needle tip (80 mm, Stimuplex D, B. Braun, Melsungen, AG, Germany), single-shot PVB was performed at the T2–T5 levels according to the standardized technique [9]. Under real-time ultrasound visualization, each level was injected with 5 mL of 0.5% ropivacaine (Naropine, AstraZeneca plc, AB, Sodertalje, Sweden), with a total volume of 20 mL. The success of PVB was confirmed by testing cold sensation with an alcohol swab 15 minutes later.

General anesthesia was performed for all patients. Anesthesia was induced with midazolam, sufentanil, propofol, and rocuronium and maintained with propofol infusion or sevoflurane inhalation, as well as sufentanil and rocuronium when necessary. A laryngeal mask or endotracheal tube was used for airway management. The BIS value was maintained between 40 and 60. Flurbiprofen axetil (50 mg) and tropisetron (5 mg) were administered before the end of surgery. Postoperative analgesia was provided with oral paracetamol (650 mg bid) during the whole postoperative hospital stay. Intravenous morphine was administered in case of breakthrough pain in the postanesthesia care unit (PACU) and the general ward.

Patients and anesthesiologists were aware of the group assignment. Investigators who performed the postoperative (Mu-Han Li and Xue Li) and long-term (Chun-Li Shao) follow-ups did not participate in anesthesia and perioperative care, were unaware of randomization, and were prohibited from communicating with either patients or anesthesiologists regarding group assignment. The PACU and ward staff were also unaware of randomization.

Data Collection and Outcome Assessments

Intraoperative data were collected by anesthesiologists and included duration of anesthesia, types and doses of anesthetic drugs, type of surgery, and fluid balance. Any unfavorable events, either that required or did not require intervention, that occurred from the start of PVB or anesthesia until 24 hours after surgery were recorded as adverse events. Potential complications of PVB were recorded. Failure of blockade was defined as a sensatory block of less than two dermatomes at 15 minutes after PVB.

Postoperative pain was assessed with the numeric rating scale (NRS; an 11-point scale where 0 = no pain and 10 = the worst pain) at rest and with movement (ipsilateral arm raised to a 90° abduction position) at one, six, 12, 24, 36, and 48 hours after surgery. Use of rescue analgesics (in addition to oral paracetamol) and length of hospital stay were recorded. Postoperative complications, which were defined as newly occurred medical events that were harmful to patients' recovery and required therapeutic intervention, that is, grade II or higher on the Clavien-Dindo Classification [16, 17], were monitored until 30 days after surgery.

Long-term follow-up was performed through face-to-face or telephone interviews at six and 12 months after surgery. CPSP was defined as pain persisting for at least three months after surgery that was not present before surgery or that had different characteristics, and other possible causes of pain were excluded (e.g., cancer recurrence, infection) (Supplementary Data) [3, 18]. Assessments with the ID-pain scale, HADS, and BPI were completed. Outcomes of breast cancer were also recorded and included the following: 1) local recurrence within one year, including recurrence of breast cancer in the ipsilateral breast, thoracic wall, and axillary tissue, with pathological confirmation; 2) distant metastasis within one year, including the occurrence of breast cancer in the contralateral breast or any other remote organs with pathological confirmation, or multiple lesions consistent with metastases on imaging examination; and 3) death from breast cancer.

The primary outcome was incidence of CPSP at six months after breast cancer surgery. The secondary outcomes included NRS pain scores within 48 hours, length of stay in hospital, occurrence of complications within 30 days, and incidence of CPSP at 12 months after surgery, as well as percentage of patients with neuropathic pain, percentage of patients with anxiety/depression, and pain intensity and interference at six and 12 months after surgery. Other predefined end points included outcomes of breast cancer within one year after surgery.

Statistical Analysis

Sample Size Estimation

Previous studies reported an incidence of CPSP from 25% to 60% [4, 19–22]. In a prospective observational study of 80 patients, Gacio et al. [23] reported that the incidence of chronic pain at six months after breast cancer surgery was 9.4% (3/32) in the PVB group. We presumed that PVB could reduce the incidence of CPSP from 25% to 10% at six months after breast cancer surgery. With the significance and power set at 0.05 (two-sided) and 80%, respectively, the sample size required to detect differences was 196 patients. Considering a dropout rate of ~10%, we planned to enroll 218 patients. The sample size calculation was performed with PASS 11.0 software (Stata Corp. LP, College Station, TX, USA).

Outcome Analyses

The primary outcome, that is, the incidence of CPSP at six months after surgery, was compared with chi-square tests, with differences between groups expressed as relative risks (RRs; with 95% CIs). Missing data were not replaced. As the development of CPSP in breast cancer patients is known to be caused by a variety of factors [2, 5] and the outcome (CPSP: no or yes) is categorical, the interactions between treatment effect and predefined factors were assessed separately with logistic regression models.

Regarding other outcomes, normally distributed continuous variables were compared using a two-tailed Student *t* test. Non–normally distributed continuous variables and ordinal data were analyzed using the Mann-Whitney *U* test. Differences (and 95% CIs) between medians were calculated with Hodges-Lehmann estimators. Categorical variables were compared with chi-square analysis or the Fisher exact test. Repeatedly measured data were analyzed using nonlinear mixed-effects models. Missing data were not replaced. Outcome and safety data were analyzed in the intent-to-treat population. For all hypotheses, two-tailed *P* values <0.05 were considered statistically significant. For the interactions between treatment effect and predefined factors, *P* values <0.10 were considered statistically significant. Statistical analyses were performed with the SPSS statistical package, version 25.0 (IBM Corp. Armonk, NY, USA).

Results

Patient Population

From May 1, 2016, to January 20, 2017, 283 female patients who were scheduled for primary breast cancer surgery were screened for eligibility; of these, 218 patients gave consent and were randomized into the study. During the study period, four patients withdrew consent, three died within six months, two more died within 12 months, three were lost at six-month follow-up, and two more were lost at 12-month follow-up. As a result, 214 patients were included in the intention-to-treat and safety analyses; 208 and 204 patients were included in the six- and 12-month analyses, respectively (Figure 1).

Demographic and baseline characteristics were well matched between the two groups (Table 1). During anesthesia, PVB produced a median sensory blockade (interquartile range) of six dermatome segments (5–6) with coverage from T2 to T6 in all patients. As expected, intraoperative sufentanil consumption ($P<0.001$) and postoperative requirement of rescue analgesia within three days ($P=0.027$) were significantly lower in the PVB group than in the control group. Other perioperative variables did not differ significantly between the two groups (Table 2).

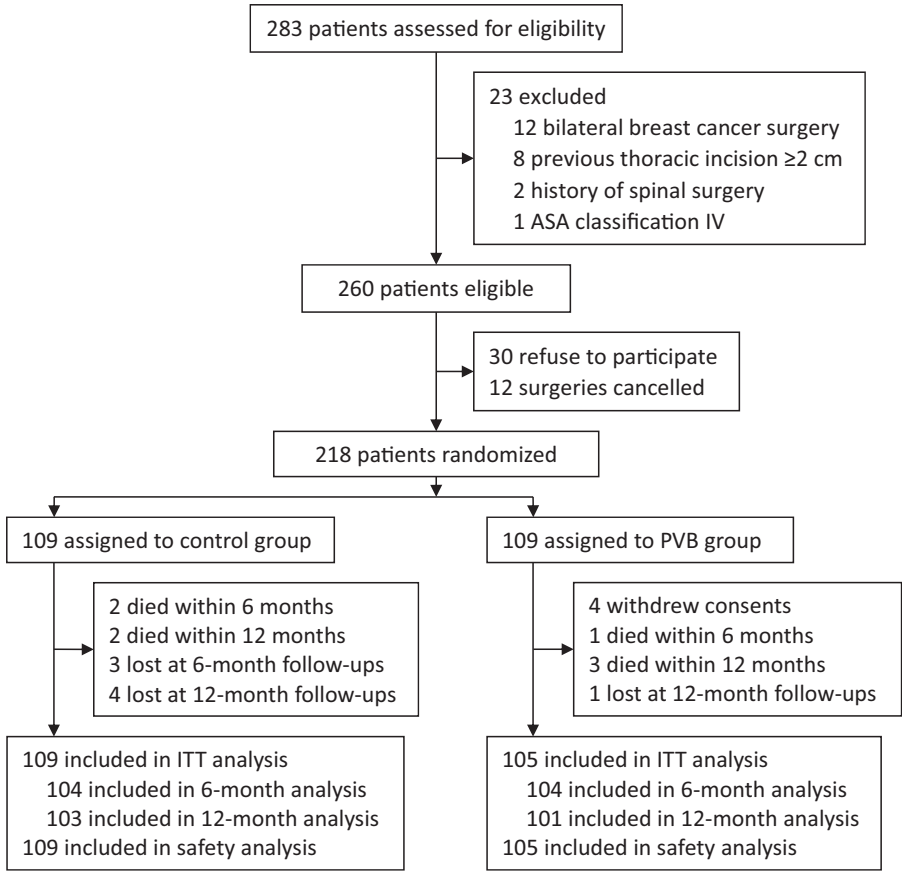

Figure 1. Flowchart of the study. ASA = American Society of Anesthesiologists; ITT = intention-to-treat; PVB = paravertebral block.

Table 1. Demographic and baseline characteristics

	Control Group (N = 109)	PVB Group (N = 105)	*P* Value
Age, y	55.0 ± 10.0	54.6 ± 10.5	0.770
Body mass index, kg/m^2	24.3 ± 3.6	24.7 ± 3.1	0.449
Comorbidities			
Stoke	0 (0.0)	1 (1.0)	0.232
Hypertension	30 (27.5)	23 (21.9)	0.341
Coronary artery disease	5 (4.6)	9 (8.6)	0.239
Diabetes mellitus	7 (6.4)	14 (13.3)	0.089
Asthma/COPD	0 (0.0)	2 (1.9)	0.090
ASA class			0.711
I	65 (59.6)	59 (56.2)	
II	35 (32.1)	39 (37.1)	
III	9 (8.3)	7 (6.7)	
History of nonthoracic surgery	15 (13.8)	19 (18.1)	0.386
Neo-adjuvant chemotherapy	19 (17.4)	17 (16.2)	0.808
Chronic pain*	14 (12.8)	17 (16.2)	0.487
Neuropathy pain†	4 (3.7)	3 (2.9)	0.738
Anxiety‡	1 (0.9)	3 (2.9)	0.285
Depression§	1 (0.9)	3 (2.9)	0.285
Pain severity¶	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.559
Pain interference‖	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.706

Data are mean ± SD, number (%), or median (interquartile range).
ASA = America Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; PVB = paravertebral block.
*Defined as persistent pain for at least three months (Supplementary Data).
†Defined as a score of ≥2 on the ID-pain scale (Supplementary Data).
‡Defined as a score of ≥8 on the anxiety subscale of the Hospital Anxiety and Depression Scale (Supplementary Data).
§Defined as a score of ≥8 on the depression subscale of the Hospital Anxiety and Depression Scale (Supplementary Data).
¶Average score of pain severity on the Brief Pain Inventory–Short Form (Supplementary Data).
‖Average score of pain interference on the Brief Pain Inventory–Short Form (Supplementary Data).

Table 2. Intra- and postoperative data

	Control Group (N = 109)	PVB Group (N = 105)	*P* Value
Dermatomes of sensory block	–	6 (5–6)	–
Duration of anesthesia, min	137 (120–163)	139 (120–168)	0.357
Maintenance of anesthesia			0.441
Intravenous	48 (44.0)	48 (45.7)	
Inhalational	14 (12.8)	19 (18.1)	
Combined	47 (43.1)	38 (36.2)	
Intraoperative medication			
Midazolam, mg	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.619
Propofol, mg	420 (125–572)	335 (130–550)	0.275
Rocuronium, mg	50 (50–60)	55 (50–60)	0.535
Dexamethasone	98 (89.9)	92 (87.6)	0.596
Dexamethasone, mg	10 (5–10)	10 (10–10)	0.564
Flurbiprofen axetil	93 (85.3)	89 (84.8)	0.909
Flurbiprofen axetil, mg	50 (50–50)	50 (50–50)	0.909
Sufentanil, μg	40.4 ± 15.9	22.2 ± 14.2	<0.001
Fluid balance			
Total fluid infusion, mL	1,000 (600–1,000)	1,000 (500–1,000)	0.772
Estimated blood loss, mL	0 (0–0)	0 (0–0)	0.951
Duration of surgery, min	85 (68–101)	83 (71–110)	0.482
Type of breast surgery			0.067
Mastectomy	66 (60.6)	76 (72.4)	
Lumpectomy	43 (39.4)	29 (27.6)	
Management of ALNs			0.650
Dissection of ALNs	38 (34.9)	43 (41.0)	
Sentinel node biopsy	69 (63.3)	60 (57.1)	
None	2 (1.8)	2 (1.9)	
Rescue analgesia within 3 d	9 (8.3)	1 (1.0)	0.027
Postoperative chemotherapy	73 (67.0)	67 (63.8)	0.627
Postoperative radiotherapy	61 (56.5)	50 (47.6)	0.196
Postoperative hormone therapy	77 (70.6)	83 (79.0)	0.157

Data are median (interquartile range), number (%), or mean ± SD.
ALNs = axillary lymph nodes; PVB = paravertebral block.

Effectiveness Analysis

The incidence of CPSP at six months was significantly lower in the PVB group than in the control group (12.5% [13/104] in the PVB group vs 24.0% [25/104] in the control group, RR = 0.52, 95% CI = 0.28–0.96, $P = 0.031$) (Table 3). Post hoc subgroup analyses found significant interactions for the occurrence of CPSP between treatment group and body mass index (<25 kg/m^2 vs ≥ 25 kg/m^2, $P = 0.060$) and type of breast surgery (mastectomy vs lumpectomy, $P = 0.032$). PVB was more beneficial in women with a body mass index <25 kg/m^2 and in those undergoing mastectomy (Figure 2).

The NRS pain scores both at rest and with movement within 48 hours were significantly lower in the PVB group than in the control group ($P = 0.006$ and $P < 0.001$, respectively) (Figure 3). Regarding long-term outcomes, the percentage with neuropathic pain at both six months (10.6% [11/104] vs 23.1% [24/104], RR = 0.46, 95% CI = 0.24–0.89, $P = 0.016$) and 12 months after surgery (10.9% [11/101] vs 22.3% [23/103], RR = 0.49, 95% CI = 0.25–0.95, $P = 0.028$) was significantly lower in the PVB group than in the control group. Other parameters did not differ significantly between the two groups (Table 3).

Safety Analysis

Thoracic PVB was performed successfully in all patients. There were no significant differences regarding other adverse events between the two groups (Table 4).

Discussion

The results of this trial confirmed that, in patients undergoing breast cancer surgery, a multilevel single-shot PVB significantly reduced the incidence of CPSP at six months; this treatment also improved postoperative analgesia and reduced the incidence of neuropathic pain at six and 12 months without increasing adverse events.

Previous studies reported that chronic pain occurred in 25–60% of patients after breast cancer surgery [4, 19–22]. However, the definition of chronic pain varied among these studies. In the present study, we adopted the strict definition of CPSP proposed by the International Association for the Study of Pain [3] and Werner's [18] update. Our results showed that the incidence of CPSP was 24.0% at six months and 19.4% at 12 months in the control group, well within the previously reported incidences.

In a recent meta-analysis, the use of PVB reduced the incidence of CPSP at six months, but not at three months,

Table 3. Effectiveness outcomes

	Control Group (N = 109)	PVB Group (N = 105)	RR, Median Difference, or HR (95% CI)*	*P* Value
Primary outcome				
CPSP at 6 mo†	25 (24.0) (N = 104)	13 (12.5) (N = 104)	RR = 0.52 (0.28–0.96)	0.031
Secondary outcomes				
LOS in hospital after surgery, d	6 (5–8)	7 (5–9)	Median D = 0.0 (0.0–1.0)	0.156
Complications within 30 d‡	10 (9.2)	10 (9.5)	RR = 1.04 (0.45–2.39)	0.930
CPSP at 12 mo†	20 (19.4) (N = 103)	10 (9.9) (N = 101)	RR = 0.51 (0.25–1.04)	0.055
Neuropathic pain§				
At 6 mo	24 (23.1) (N = 104)	11 (10.6) (N = 104)	RR = 0.46 (0.24–0.89)	0.016
At 12 mo	23 (22.3) (N = 103)	11 (10.9) (N = 101)	RR = 0.49 (0.25–0.95)	0.028
Anxiety¶				
At 6 mo	4 (3.8) (N = 104)	4 (3.8) (N = 104)	RR = 1.00 (0.26–3.89)	>0.999
At 12 mo	4 (3.9) (N = 103)	4 (4.0) (N = 101)	RR = 1.02 (0.26–3.97)	>0.999
Depression‖				
At 6 mo	6 (5.8) (N = 104)	4 (3.8) (N = 104)	RR = 0.67 (0.19–2.29)	0.517
At 12 mo	8 (7.8) (N = 103)	4 (4.0) (N = 101)	RR = 0.51 (0.16–1.64)	0.248
Pain severity‖‖				
At 6 mo	0.0 (0.0–0.8) (N = 104)	0.0 (0.0–0.0) (N = 104)	Median D = 0.0 (0.0–0.0)	0.087
At 12 mo	0.0 (0.0–0.2) (N = 103)	0.0 (0.0–0.0) (N = 101)	Median D = 0.0 (0.0–0.0)	0.063
Pain interference**				
At 6 mo	0.0 (0.0–0.1) (N = 104)	0.0 (0.0–0.0) (N = 104)	Median D = 0.0 (0.0–0.0)	0.183
At 12 mo	0.0 (0.0–0.0) (N = 103)	0.0 (0.0–0.0) (N = 101)	Median D = 0.0 (0.0–0.0)	0.365
Exploratory analyses				
Local recurrence within 1 y††	6 (5.7) (N = 105)	2 (1.9) (N = 104)	HR = 0.33 (0.07–1.62)	0.170
Distant metastasis within 1 y‡‡	9 (8.6) (N = 105)	8 (7.7) (N = 104)	HR = 0.92 (0.35–2.39)	0.862
Death within 1 y	2 (1.9) (N = 105)	3 (2.9) (N = 104)	HR = 1.53 (0.26–9.15)	0.642

Data are number (%), median (interquartile range), or mean ± SD.

CPSP = chronic postsurgical pain; HR = hazard ratio; LOS = length of stay; PVB = paravertebral block; RR = relative risk.

*Calculated as the PVB group vs or minus the control group.

†Defined as recurrent or persistent pain for at least three months that was not present before surgery or that had different characteristics or increased intensity from preoperative pain, localized to the ipsilateral axilla, arm, shoulder, or chest wall, and other possible causes of the pain (such as infection or cancer recurrence) were excluded (Supplementary Data).

‡Included wound infection, wound dehiscence, hematoma, and effusion.

§Defined as a score of ≥2 on the ID-pain scale (Supplementary Data).

¶Defined as a score of ≥8 on the anxiety subscale of the Hospital Anxiety and Depression Scale (Supplementary Data).

‖Defined as a score of ≥8 on the depression subscale of the Hospital Anxiety and Depression Scale (Supplementary Data).

‖‖Average score of pain severity on the Brief Pain Inventory–Short Form (Supplementary Data).

**Average score of pain interference on the Brief Pain Inventory–Short Form (Supplementary Data).

††Recurrence of breast cancer in the ipsilateral breast, thoracic wall, and axillary tissue, with pathological confirmation.

‡‡Occurrence of breast cancer in the contralateral breast or any other remote organs with pathological confirmation or multiple lesions consistent with metastasis on imaging examination.

after breast cancer surgery [8]. However, neutral results were also reported in some earlier studies investigating the effects of thoracic PVB in preventing pain chronicity [9, 23–25]. Therefore, further studies are needed to clarify the problem. In the present study, we used a multilevel single-shot PVB method and adopted the incidence of CPSP at six months as the primary end point. Our results confirmed that PVB reduced the occurrence of CPSP at six months by 48%, further demonstrating the efficacy of PVB in preventing pain chronicity after breast cancer surgery. Our study also found that the effect of PVB in decreasing CPSP was more prominent in patients with a body mass index $<25\,kg/m^2$ and in those undergoing mastectomies. The underlying reasons are not totally clear but may be due to higher incidences of CPSP in these patients, which highlighted the effect of PVB. We did not find any significant interactions for the occurrence of CPSP between treatment group and postoperative oncologic therapy (i.e., chemotherapy, radiotherapy, and hormone therapy), which may be explained by unfinished treatment in the majority patients at six months postoperatively and limited sample size. Further studies are required to confirm these hypotheses.

The effect of PVB in relieving acute postoperative pain might be an important mechanism in preventing CPSP [5, 8]. In the present study, the success of PVB was verified before surgery; this was also confirmed by the facts that the consumption of intraoperative sufentanil, the requirement of rescue analgesics, and the severity of acute postoperative pain were significantly lower in patients who

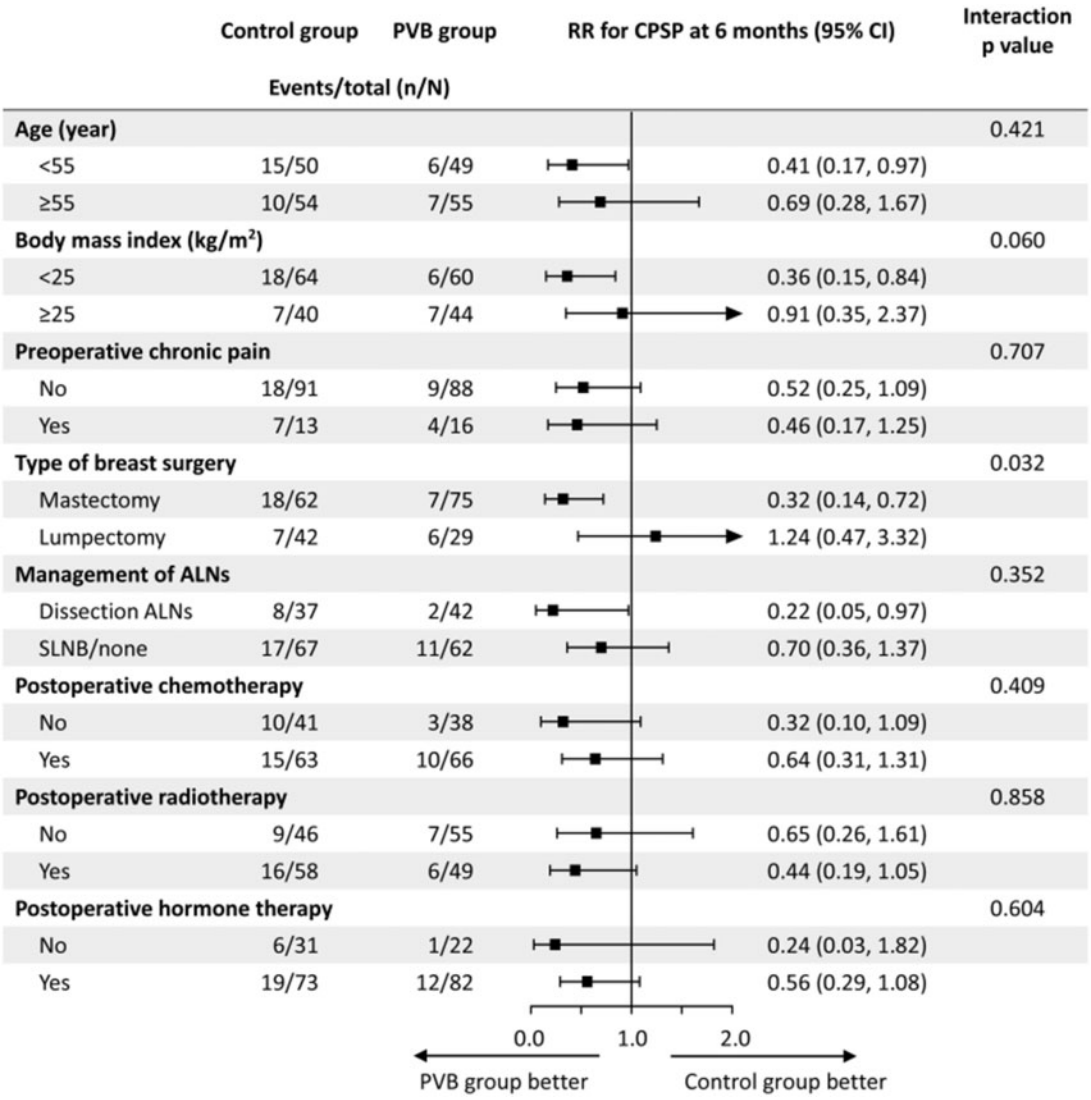

Figure 2. Forest plot assessing the effect of PVB on CPSP at six months in subgroups. Logistic models were applied for assessment of treatment-by-covariate interactions. Treatment-by-covariate interactions were assessed separately for each subgroup factor, including age, body mass index, preoperative chronic pain, type of breast surgery, management of ALNs, postoperative chemotherapy, postoperative radiotherapy, and postoperative hormone therapy. ALNs = axillary lymph nodes; CPSP = chronic postsurgical pain; PVB = paravertebral block; RR = relative risk; SLNB = sentinel lymph node biopsy.

received PVB. Consistent with the reduced incidence of CPSP, our results found that the incidence of neuropathic pain was also lower in patients with PVB than in those without at both six and 12 months after surgery (reduced by 54% and 51%, respectively). However, the severity of chronic pain, as assessed by the BPI severity items, did not differ significantly between the groups at six and 12 months after surgery, despite that the scores tended to be lower in the PVB group ($P = 0.087$ and 0.063, respectively). This might be explained by the fact that only a small proportion of patients developed CPSP (12.5–24.0% at six months and 9.9–19.4% at 12 months); thus, the majority of patients gave a "0" score for pain severity at the six- and 12-month assessments. This decreased the power to detect differences between groups when directly comparing pain severity scores. In the present study, we did not find differences between groups regarding psychological distress and daily life interference. Other factors including cancer therapy as well as social and economic problems might have interfered with these results.

In previous studies, procedure-related complications, including hemorrhage, hematoma, pneumothorax, block failure, and Horner's syndrome, were reported in 5.7% of patients [26]. However, these complications did not occur in our patients, confirming the safety of ultrasound-guided PVB performed by senior anesthesiologists.

There were several limitations of our study. First, as a single-center trial, the generalization of our results might

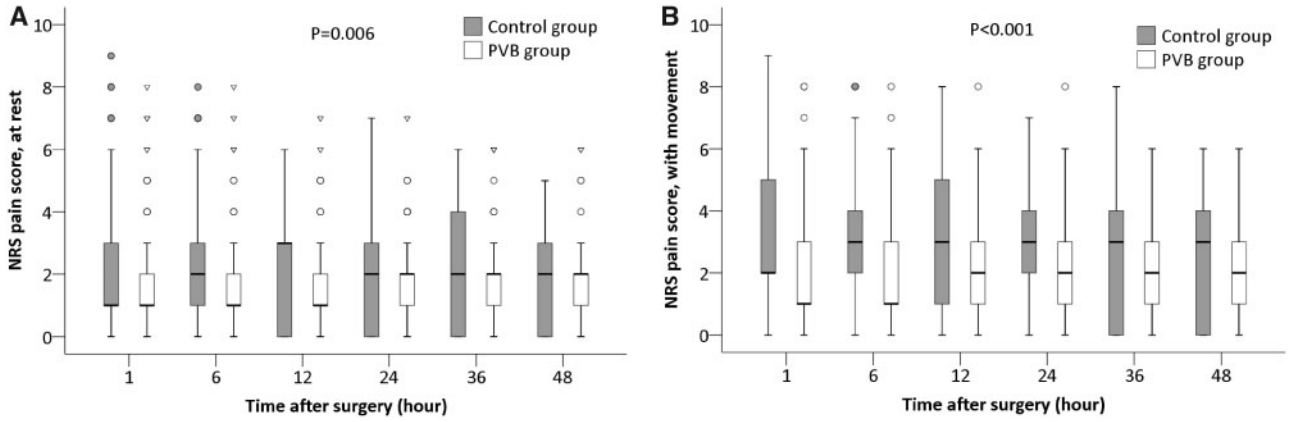

Figure 3. NRS pain scores at rest (A) and with movement (B) after surgery. Pain scores at rest and with movement at different time points were significantly lower in the PVB group than in the control group ($P = 0.006$ and $P < 0.001$, respectively). Data were analyzed using nonlinear mixed-effects models. The box plots show medians and interquartile ranges, and individual points are mild outliers (○, which are outside 1.5 times the interquartile range) and extreme outliers (▽, which are outside three times the interquartile range). NRS = numeric rating scale (an 11-point scale where 0 = no pain and 10 = the worst pain); PVB = paravertebral block.

Table 4. Safety outcomes

	Control Group (N = 109)	PVB Group (N = 105)	*P* Value
Complications of puncture*	–	0 (0.0)	–
Failure of blockade	–	0 (0.0)	–
Intraoperative hypotension†	29 (26.6)	35 (33.3)	0.261
Intraoperative bradycardia‡	3 (2.8)	2 (1.9)	0.680
Postoperative dizziness	7 (6.4)	7 (6.7)	0.942
Postoperative nausea and vomiting	30 (27.5)	19 (18.1)	0.101

Data are presented as number (%).
PVB = paravertebral block.
*Included hemorrhage, hematoma, pneumothorax, and Horner's syndrome.
†Systolic blood pressure >160 mmHg or a decrease of systolic blood pressure of >30% from baseline (average value in the ward).
‡Heart rate <45 beats per minute or a decrease of >30% from baseline (average value in the ward).

be limited. Second, due to ethical concerns, placebo injection was not performed in patients from the control group, and therefore the resulting bias could not be excluded. However, the investigator who performed long-term follow-up was not included in perioperative care and was not aware of the study group assignment.

Conclusions

Our results confirmed that, for patients undergoing breast cancer surgery, preoperative multilevel single-shot PVB reduces CPSP at six months; it also improves postoperative analgesia and reduces neuropathic pain within one year after surgery.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

Authors' Contributions

Zeng-Mao Lin, MD: This author designed the study, collected data, performed data analysis, and drafted and revised the manuscript. Mu-Han Li, MD, PhD: This author performed postoperative follow-ups and helped analyze data. Feng Zhang, MD: This author performed the paravertebral block and collected the intraoperative data. Xue Li, MD: This author performed postoperative follow-ups and helped analyze the data. Chun-Li Shao, RN: This author performed long-term follow-ups. Xue-Ying Li, MSc: This author helped perform statistical analysis. Dong-Xin Wang, MD, PhD: This author conceived and designed the study, reviewed and analyzed data, and revised the manuscript. He was the primary investigator and corresponding author.

Ethics Approval and Consent to Participate

The research protocol was approved by the Biomedical Research Ethics Committee of Peking University First

Hospital (Number: 2016-1098). All participants signed written informed consent.

Availability of Data and Materials

The detailed data sets are available from the corresponding author upon reasonable request.

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