Randomized Controlled Trial

The Effect of Erector Spinae Plane Blockade on Prevention of Postherpetic Neuralgia in Elderly Patients: A Randomized Double-blind Placebo-controlled Trial

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Background: Postherpetic neuralgia (PHN) is the most common chronic complication following the onset of herpes zoster (HZ). Both the incidence of HZ and the proportion of patients with HZ who develop PHN rise with age. Ultrasound-guided erector spinae plane blockade (ESPB) has been reported to relieve neuropathic pain and PHN in elderly patients, but no randomized controlled trials have been conducted regarding the effect of ESPB on elderly patients with HZ in the acute or subacute phases.

Objectives: To evaluate the effect of repeated ESPB on the occurrence of PHN in elderly patients with acute or subacute HZ.

Study Design: A randomized double blind placebo-controlled trial with 2 parallel groups.

Setting: A university hospital in China.

Methods: Patients diagnosed with acute or subacute HZ were randomized to receive either ultrasound-guided ESPB (the ESPB group) or placebo subcutaneous injection (the control group) every 24 hours for 3 days. Patients were followed up at 12 weeks after the final treatment. The primary end point was the incidence of PHN at 12 weeks.

Results: A total of 52 patients were enrolled and randomized; 50 completed 12 weeks of follow-up. The incidence of PHN at 12 weeks was significantly lower in the ESPB group (15.4% [4/26]) than in the control group (41.7% [10/24]); relative risk 0.37, 95% confidence interval 0.13-1.02, $P = 0.039$. At 12 weeks, the VAS scores at rest and the total scores from the Short-Form McGill Pain Questionnaire-2 were significantly decreased in the ESPB group ($P = 0.046$ and $P = 0.001$, respectively). The incidence of neuropathic pain, sleep disturbance, and anxiety/depression were significantly reduced in the ESPB group ($P = 0.002$, $P = 0.002$, and $P = 0.025$, respectively). Patients using tramadol and hypnotics as well as total complications with oral medicines were remarkably decreased in the ESPB group ($P = 0.008$, $P = 0.002$, and $P = 0.042$ respectively). The adverse events during or after the procedure were comparable between the groups.

Limitations: This trial was carried out in a single center with a 12-week follow-up. Nearly 8% of patients in the control group were lost to follow-up.

Conclusions: For elderly patients suffering acute or subacute HZ, ESPB reduces the incidence of PHN at 12 weeks after treatment; it also decreases the occurrence of neuropathic pain, sleep disturbance, and anxiety/depression.

Key words: Erector spinae plane blockade, herpes zoster, postherpetic neuralgia, neuropathic pain, sleep quality, hospital anxiety and depression

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Herpetic zoster (HZ) is caused by the reactivation of the varicella-zoster virus, which is latent in the sensory ganglia of the cranial and spinal nerves (1,2). Postherpetic neuralgia (PHN) is the most common chronic complication of HZ; more than 30% of patients with zoster aged ≥ 50 years have PHN 3 months after zoster onset (3,4). Treatment of PHN is challenging although topical and systemic agents are available. Moreover, less than 50% of patients receive significant pain relief (> 50%) despite the most effective management (5,6). Hence, preventing the development of PHN may be as equally significant as seeking novel or more efficacious management therapies.

There is substantial evidence for the efficacy of the zoster vaccine for reducing the risk of HZ and PHN in elderly patients abroad (7). However, the benefit from the vaccine takes time to emerge since its recent approval and clinical use in China. Not being covered by health insurance may also limit the inoculation of the vaccine. Antiviral medicine inhibits replication of the varicella zoster virus, thus attenuating the severity of acute HZ infection, which protects patients with HZ from developing PHN (8). Nevertheless, 20% of patients suffer from persistent pain even 6 months after HZ onset in spite of antiviral treatment (9). Supplementary therapies may be necessary to further decrease the incidence of PHN. Various interventional techniques (such as epidural, intrathecal, somatic, and sympathetic blocks) are found to provide effective analgesia during the acute phase of HZ infection and prevent PHN (8,9). But the potential risk of mechanical complications of these interventions, such as nerve damage, pleural puncture, or vessel puncture, has limited widespread application in patients with pain associated with HZ and PHN. Additional interventional techniques that are both effective and safe are therefore needed.

The ultrasound-guided erector spinae plane blockade (ESPB), which was first described by Forero in 2016 (10), provided excellent perioperative analgesia with minimal side effect in patients undergoing rib fractures, thoracic, breast and spine surgeries (11). As one of the interfacial plane blocks that target the dorsal and ventral rami of the spinal nerves, it is thought to work with the diffusion of local anesthetic into the paravertebral and intercostal spaces, which can spread in the cephalic and caudal direction and lead to analgesia from C7-T9 (12,13). An ESPB is technically easier to perform without multiple injections performed in the paravertebral and intercostal nerves (13). The complications of ESPB were lower and slighter than epidural and paravertebral blocks (11,13). Given the effectiveness and safety of this technique, it is suitable for outpatient care. It was reported that ultrasound-guided ESPB combined with gabapentin can relieve neuropathic pain and PHN in elderly patients (14), but there was only a case report describing ESPB for HZ in acute or subacute episode (15). Therefore, we performed this trial to evaluate the effect of ESPB on PHN in elderly Chinese patients with HZ in the acute or subacute phase in China.

Methods

This randomized double-blind placebo-controlled trial with 2 parallel arms was conducted in Peking University First Hospital in Beijing, China. The study protocol was approved by the local Ethics Committee (2019-90) and registered prospectively at the Chinese Clinical Trial Registry (http://www.chictr.org.cn; trial identifier ChiCTR1900023765) on June 11, 2019. Written informed consent was obtained from all patients.

Patients

Patients who were diagnosed as having acute or subacute HZ were screened. Inclusion criteria were the following: aged greater than 60 years; a zoster rash not healing or healed less than one month; location of the zoster rash in the unilateral thoracic region (C7-T9); a visual analog scale (VAS, 100 mm unmarked line, with anchors: 0 = no pain and 100 mm = worst pain imaginable) score ≥ 40 mm. Exclusion criteria were the following: an administered nerve blockade intervention within one week; allergy to ropivacaine; any contraindication to ESPB, including intrathoracic infection, infection at the puncture site, cancer invasion of the puncture site, severe spinal deformity, history of spinal surgery, and severe coagulopathy; a previous history of chronic pain or long-term intake of analgesic medicines; an American Society of Anesthesiologists (ASA) classification of 4 or higher.

Baseline data were collected after obtaining consent, including demographic characteristics, current diagnosis, comorbidities, history of surgery, ASA class, herpes location, distribution area, duration of time since zoster rash onset, current medication (including antiviral, anticonvulsant, antidepressant, analgesic, neurotrophic medicine) and Chinese medicine therapy (herbal medicine, acupuncture and cupping therapy). Assessments of pain on baseline were performed by a trained and qualified research nurse (NY) and contained the following aspects: neuropathic pain by the

ID pain scale (16,17), anxiety/depression by the Hospital Anxiety and Depression Scale (HADS) (18,19), sleep situation by the Pittsburgh Sleep Quality Index (PSQI) (20-22), and pain intensity using the VAS and the revised Short-Form of the McGill Pain Questionnaire, SF-MPQ-2 (23,24) (Supplemental Table 1).

Randomization and Intervention

Randomization numbers were generated by an investigator (JHM) in a 1:1 ratio using the SAS 9.3 statistical package (SAS Institute, Inc., Cary, NC). The generated numbers were then concealed in sequentially numbered envelopes. During the trial, the envelopes were selected according to the sequence of patient recruitment and were opened immediately before the ESPB procedure by the investigator (FZ) who performed the procedure in a clinic treatment room. In this way the enrolled patients were divided into the ESPB group and the control group.

Routine monitoring included electrocardiography, noninvasive blood pressure, and pulse oximetry. Based upon the rash area and pain dermatome, the involved spinal nerve was determined and the level of ESPB or subcutaneous injection selected. An 80 mm, 21-gauge insulated needle (Stimuplex D, B. Braun, Melsungen, Germany) was used for the procedure in the ESPB group. After confirming the correct position of the needle tip under real-time ultrasound visualization, a single-shot ESPB with 25 mL 0.4% ropivacaine (Naropine, AstraZeneca PLC, AB, Sweden) was performed according to the standardized technique (10). For the control group, a subcutaneous injection of 2 mL saline served as placebo. After 30 minutes, by observation of vital signs and ruling out complications of the procedure, all patients were permitted to leave the hospital. Tramadol was provided in case of need for rescue analgesia. The above procedures were repeated every 24 hours for 3 days in both groups. No additional nerve blockade or invasive therapy (acupuncture and cupping therapy) were performed during the 12-week follow-up.

All patients were admitted for the standard oral medicines (1000 mg valacyclovir 3 times daily for 7 days, 0.5 mg mecobalamin 3 times daily for 4 weeks). The rescue analgesics included acetaminophen (650 mg per tablet, up to 3 tablets daily) and tramadol (100 mg per tablet, up to 4 tablets daily). Other medicines including anticonvulsants, antidepressants, and hypnotics were administrated according to clinical requirement. All patients were instructed to record their VAS scores and medications by pain diaries.

Blinding

Patients and investigators who were in charge of follow-up and data collecting were unaware of the randomization, while an investigator (FZ) who performed the ESPB was aware of the group assignment and prohibited from communicating with either patients or other investigators regarding group assignment.

Data Collection and Outcome Assessments

Peri-procedure data including heart rate, blood pressure, pulse oximetry saturation, and time of procedure was collected by a registered nurse (NY). Potential complications of ESPB, either requiring an intervention or not, that occurred during or within 24 hours after the procedure were recorded as adverse events.

Follow-up data were collected by investigators (HFW and ZML) through face-to-face or telephone interviews at one-, 4- and 12-weeks after the final intervention. The VAS at rest and with movement were inquired at every interview. In addition, at 12-week follow-up, the dosage of analgesics, as well as an assessment with ID pain scale(16,17), PSQI, HADS and SF-MPQ-2 were recorded. Posttreatment complications, which were defined as newly occurred medical events that were harmful to the patient's recovery and required a therapeutic intervention, i.e., grade II or higher on the Clavien-Dindo Classification (25,26), were monitored until 12 weeks posttreatment.

The primary outcome was the incidence of PHN at 12 weeks posttreatment, which was defined as persistent dermatomal pain after the appearance of the acute HZ rash, with a score of 40 or higher on the VAS (27,28). The secondary outcomes included the VAS score at one-, 4- and 12-week posttreatment, the percentage of patients with neuropathic pain (defined as the score of ID pain more than 2), poor quality of sleep (defined as a PSQI score more than 5) and anxiety/depression (defined as an anxiety/depression subscale score of HADS more than 7), the scores of SF-MPQ-2, daily dosage consuming of analgesics and other medicines at 12 weeks posttreatment, as well as the occurrence of complications within 12 weeks.

Statistical Analysis

Sample Size Estimation

Previous studies reported an incidence of PHN at 3 months from 38.4% - 42.7% in patients aged ≥ 50 years (29,30). In a prospective study of paravertebral blockade, which has similar effectiveness as ESPB, it

was reported that the incidence of PHN was 7.0 % at 3 months in the intervention group (31). We approximately presumed that ESPB could reduce the incidence of PHN from 40.0% to 7.0% at 3 months posttreatment. With the significance set at 0.05 (2-sided) and 80% power, the sample size required to detect differences was 46 patients. Considering a drop-out rate of approximately 10%, we planned to enroll 52 patients. The sample size calculation was performed with PASS 15.0 software (NCSS LLC, Kaysville, UT).

Outcome Analyses

The primary outcome, i.e., the incidence of PHN at 12 weeks posttreatment, was compared by χ^2 tests, with differences between groups expressed as a relative risk (RR) and 95% confidence interval (CI). Missing data were not replaced. Regarding other outcomes, normally distributed continuous variables were compared using a 2-tailed Student's t test. Nonnormally 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 by the χ^2 analysis or Fisher's 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, 2-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).

Results

Patient Population

From June 12, 2019 to December 29, 2019, 83 patients who were diagnosed with HZ were screened for eligibility; of these, 52 patients gave consent and were randomized into the study. During the study period, 2 patients were lost at the end of follow-ups. As a result, 52 patients were included in the intention-to-treat and safety analyses; 52, 52 and 50 patients were included in the one-, 4- and 12-week analyses, respectively (Fig. 1).

Demographic and baseline characteristics were well matched between the 2 groups (Table 1 and Supplemental Table 1).

Effectiveness Analysis

The incidence of PHN at 12 weeks was significantly lower in the ESPB group than in the control group (15.4% [4/26] in the ESPB group vs 41.7% [10/24] in the control group; RR 0.37, 95% CI 0.13 - 1.02; *P* = 0.039) (Table 2).

The VAS scores at one- and 12-week posttreatment were significantly lower in the ESPB group than in the control group (Fig. 2). At the 12 week follow-up, the percentage of patients with neuralgia pain, poor sleep, and anxiety/depression were significantly lower in the ESPB group than in the control group (*P* = 0.002, *P* = 0.002, and *P* = 0.025, respectively). The total scores, scores of continuous pain and affective descriptors of SF-MPQ-2 were significantly decreased in the ESPB group than in the control group (*P* = 0.001, *P* = 0.020, and *P* < 0.001, respectively). Patients using tramadol and hypnotics, as well as the daily dosage of tramadol were significantly reduced in the ESPB group (*P* = 0.008, *P* = 0.002, and *P* = 0.001, respectively) (Table 2).

The total complications at 12 weeks were significantly reduced in the ESPB group (*P* = 0.042) (Table 2).

Safety Analysis

ESPB was performed successfully in in the ESPB group. There were no significant differences regarding other adverse events between the 2 groups (Table 3).

Discussion

The results of this trial confirmed that in elderly patients with an acute or subacute episode of HZ, sequential ESPB for 3 days reduced the incidence of PHN at 12 weeks; the treatment also improved analgesia at one week and 12 weeks posttreatment and reduced the incidence of neuropathic pain, poor sleep, and anxiety/depression at 12 weeks posttreatment.

Previous studies and a meta-analysis reported that PHN occurred in 40% of elderly patients after 3 months at the affected sites (3,4,29,30). The risk factors included aging, severe lesions in the acute episode of HZ, severe pain, and insufficient function of immune system (32). Our results revealed that the incidence of PHN in elderly patients was 41.7% at 12 weeks in the control group; it was lower than the previously reported incidence which may be explained by the administration of medication therapy (such as an antiviral, an anticonvulsant, and analgesics).

The most important mechanism of PHN is considered to be the central sensitization of the nociceptive system, which might be caused by repetitive painful

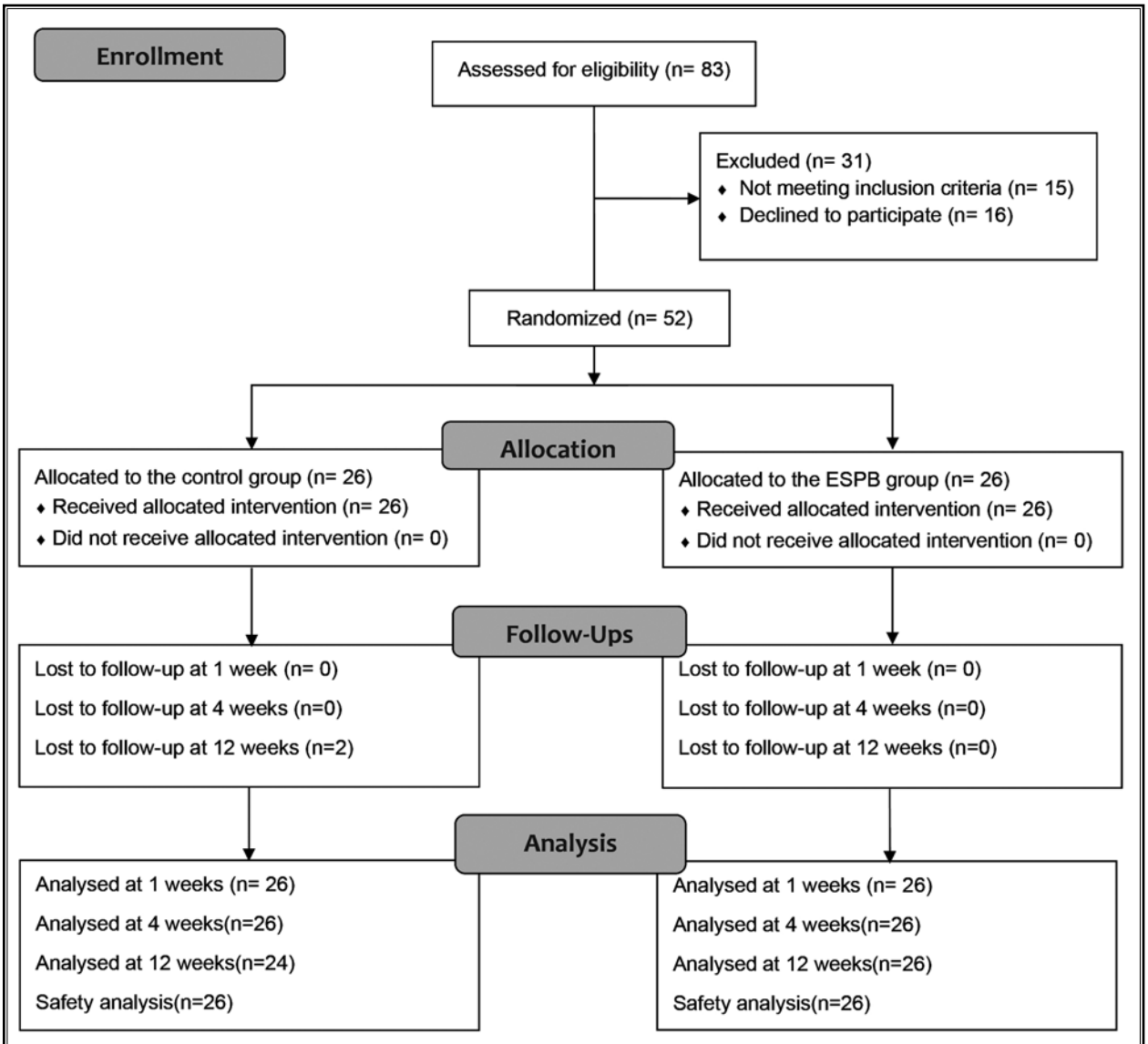

Fig. 1. *Flow Diagram of the study. ESPB, erector spinae plane blockade.*

stimuli (4,5,8). Interventions that block repetitive painful stimuli during the acute phase of HZ may attenuate central sensitization and substantially reduce the incidence of chronic pain (5,8,9). Ultrasound-guided ESPB significantly decreased the incidence of PHN in our study's ESPB group (15.4%). Meanwhile, pain intensity was also reduced in the ESPB group at one- and 12-weeks after treatment. The pain relief in the acute and subacute periods by ESPB could contribute to controlling acute HZ-related pain, as well as reducing the occurrence of PHN at 12 weeks.

In our study, neuropathic pain was assessed by the ID pain and the neuropathic pain descriptors of SF-MPQ-2. Ultrasound-guided ESPB not only reduced the occurrence of neuropathic pain, but also decreased the score of neuropathic pain in SF-MPQ-2. Both acute HZ-related pain and PHN severely injure patients' sleep and emotion (4,14). During the acute or subacute period of HZ, the percentage of sleep disturbance reached 69% (36/52) in this study. After routine medication therapy, the incidence of poor sleep was 62.5% in the control group; by comaprison, ESPB significantly reduced the incidence to 19.2%. The results were consistent with regard to the requirement for hypnotic medicines

Table 1. *Demographic and baseline characteristics*.

	Control group (n = 26)	ESPB group (n = 26)	*P* value
Age, years	65.2 ± 9.7	68.2 ± 9.8	0.272
Male gender	13 (50.0%)	12 (46.2%)	0.781
BMI, kg/m^2	24.0 ± 1.9	24.9 ± 2.9	0.182
Comorbidities			
Stoke	7 (26.9%)	7 (26.9%)	> 0.999
Hypertension	12 (46.2%)	13 (50.0%)	0.781
Coronary artery disease	6 (23.1%)	4 (15.4%)	0.482
Diabetes mellitus	14 (53.8%)	10 (38.5%)	0.266
Asthma/COPD	3 (11.5%)	1 (3.8%)	0.288
Tumor/ autoimmune disease	7 (26.9%)	5 (19.2%)	0.510
History of surgery	8 (30.8%)	9 (34.6%)	0.768
ASA class			0.373
I	6 (23.1%)	9 (34.6%)	
II	14 (53.8%)	9 (34.6%)	
III	6 (23.1%)	8 (30.8%)	
Left Side rash	13 (50.0%)	14 (53.8%)	0.781
Location of rash			0.784
C7-T2	6 (23.1%)	8 (30.8%)	
T3-T5	11 (42.3%)	9 (34.6%)	
T6-T9	9 (34.6%)	9 (34.6%)	
Area of rash, %BSA	3.7 ± 1.1	4.1 ± 0.9	0.117
Time since rash onset, day	10 (8, 15)	9 (7, 14)	0.221
Medication treatment			
Antiviral	14 (53.8%)	15 (57.7%)	0.780
Anticonvulsant	18 (69.2%)	16(61.5%)	0.560
Antidepressant	1 (3.8%)	2 (7.7%)	0.548
Acetaminophen/ NSAIDSs	5 (19.2%)	9 (34.6%)	0.211
Tramadol	4 (15.4%)	7 (26.9%)	0.308
Mecobalamin	15 (57.7%)	20 (76.9%)	0.139
Chinese herbal medicine	4 (15.4%)	6 (23.1%)	0.482
Acupuncture and/or cupping therapy	7 (26.9%)	4 (15.4%)	0.308

Table 1 (cont.). *Demographic and baseline characteristics*.

	Control group (n = 26)	ESPB group (n = 26)	*P* value
VAS on baseline, mm			
At rest	60.0 (51.0, 70.0)	70.0 (55.0, 80.0)	0.166
With movement	70.0 (60.0, 80.0)	77.5 (65.0, 86.0)	0.579
Neuropathic pain [a]	23 (88.5%)	26 (100.0%)	0.235
Poor sleeper [b]	21 (80.8%)	15 (57.5%)	0.071
Anxiety/ Depression [c]	7 (26.9%)	6 (23.1%)	0.749
SF-MPQ-2 on baseline			
Total score [d]	37.5 (20.3, 48.3)	38.5 (28.8, 54.5)	0.400
Continuous pain [e]	15.0 (8.0, 18.5)	13.0 (9.5, 18.5)	0.956
Intermittent pain [f]	8.0 (4.8, 14.3)	10.0 (8.0, 19.3)	0.066
Neuropathic pain [g]	5.0 (3.0, 7.5)	5.0 (3.0, 9.3)	0.818
Affective descriptors [h]	8.0 (5.0, 10.8)	10.0 (5.0, 18.0)	0.138

The results are presented as the mean ± standard deviation, median (interquartile range) or number (%).
ESPB, erector spinae plain blockade; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, America Society of Anesthesiologists; BSA, body surface area; NSAIDs, nonsteroidal anti-inflammatory drugs; VAS, visual analog scale; SF-MPQ-2, the revised Short-Form McGill Pain Questionnaire.
a Defined as the score of ID pain (Supplemental Table 2) ≥ 2;
b Defined as the score of the Pittsburgh Sleep Quality Index (Supplemental Table 2) ≥ 6;
c Defined as the anxiety/depressive subscale score of the Hospital Anxiety and Depression Scale (Supplemental Table 2) ≥ 8;
d Calculated by summating the values for all 22 items of SF-MPQ-2 (Supplemental Table 2);
e Summarized 6 items of continuous pain descriptors (throbbing, cramping, gnawing, aching, heavy pain, and tender) in SF-MPQ-2 (Supplemental Table 2);
f Summarized 6 items of intermittent pain descriptors (shooting, stabbing, sharp, splitting, electric-shock pain, and piercing) in SF-MPQ-2 (Supplemental Table 2);
g Summarized 6 items of predominantly neuropathic pain descriptors (hot-burning and cold-freezing pain, pain caused by light touch, itching, tingling or pins and needles, and numbness) in SF-MPQ-2 (Supplemental Table 2);
h Summarized 4 items of affective descriptors (tiring–exhausting, sickening, fearful, and punishing–cruel) in SF-MPQ-2 (Supplemental Table 2).

between the 2 groups. A cohort study by Yamada et al (33) revealed that sleep shortage was associated with an increased risk for PHN; acute pain intensity appeared to exacerbate this association. Therefore, in our opinion, ESPB might reduce the incidence of PHN by improving sleep quality associated with immediate

Table 2. *Effectiveness outcomes at 12 weeks follow-up.*

	Control group (n = 24)	ESPB Group (n = 26)	Estimated effects (95% CI) [a]	*P* value
Primary outcome				
Postherpetic neuralgia [b]	10 (41.7%)	4 (15.4%)	RR = 0.37 (0.13, 1.02)	0.039
Secondary outcomes				
Neuropathic pain [c]	17 (70.8%)	7 (26.9%)	RR = 0.38 (0.19, 0.75)	0.002
Poor sleeper [d]	15 (62.5%)	5 (19.2%)	RR = 0.31 (0.13, 0.72)	0.002
Anxiety/ Depression [e]	15 (62.5%)	8 (30.8%)	RR = 0.49 (0.26, 0.95)	0.025
SF-MPQ-2				
Total score [f]	19.0 (7.3, 28.8)	3.0 (0.7, 28.8)	Median D = -10.0 (-20.0, -5.0)	0.001
Continuous pain [g]	3.5 (0.0, 8.0)	0.0 (0.0, 1.3)	Median D = -2.0 (-5.0, 0.0)	0.020
Intermittent pain [h]	2.5 (0.0, 6.0)	0.0 (0.0, 2.0)	Median D = 0.0 (-3.0, 0.0)	0.054
Neuropathic pain [i]	3.0 (1.0, 5.5)	1.0 (0.0, 2.3)	Median D = -1.0 (-3.0, 0.0)	0.068
Affective descriptors [j]	7.0 (4.0, 8.8)	1.0 (0.0, 3.0)	Median D=-5.0 (-7.0, -3.0)	< 0.001
Analgesics				
Acetaminophen	18 (75.0%)	17 (65.4%)	RR = 0.87 (0.61, 1.25)	0.459
Acetaminophen, mg	1300 (325, 1300)	650 (0, 1300)	Median D = -325 (-650, 0)	0.058
Tramadol	19 (79.2%)	11 (43.3%)	RR = 0.53 (0.33, 0.88)	0.008
Tramadol, mg	200 (125, 400)	0 (0, 100)	Median D = -200 (-300, -100)	0.001
Others medicines				
Anticonvulsant	23 (95.8%)	21 (80.8%)	RR = 0.84 (0.69, 1.04)	0.192
Antidepressant	9 (37.5%)	5 (19.2%)	RR = 0.51 (0.20, 1.32)	0.151
Hypnotic	15 (62.5%)	5 (19.2%)	RR = 0.31 (0.13, 0.72)	0.002
Complications within 12 weeks				
Dizziness	11 (45.8%)	6 (23.1%)	RR = 0.50 (0.22, 1.15)	0.090
Drowsiness	8 (33.3%)	5 (19.2%)	RR = 0.58 (0.22, 1.52)	0.256
Nausea	5 (20.8%)	2 (7.7%)	RR = 0.50 (0.22, 1.15)	0.090
Vomiting	1 (4.2%)	0 (0.0%)	--	0.480
Lower extremity edema	1 (4.2%)	2 (7.7%)	RR = 1.85 (0.18, 19.08)	> 0.999
Others [k]	1 (4.2%)	1 (3.8%)	RR = 0.92 (0.06, 13.95)	> 0.999
Total	17 (70.8%)	11 (42.3%)	RR = 0.60 (0.36, 1.00)	0.042

The results are presented as the median (interquartile range) or number (%).
a Calculated as Group ESPB vs or minus Group C;
b Defined as persistent dermatomal pain after the appearance of acute herpes zoster rash, with a score of 40 or higher on the VAS
c Defined as the score of ID pain (Supplemental Table 2) ≥ 2;
d Defined as the score of the Pittsburgh Sleep Quality Index (Supplemental Table 2) ≥ 6;
e Defined as the anxiety/depressive subscale score of the Hospital Anxiety and Depression Scale (Supplemental Table 1) ≥ 8;
f Calculated by summating the values for all 22 items of SF-MPQ-2 (Supplemental Table 2);
g Summarized 6 items of continuous pain descriptors (throbbing, cramping, gnawing, aching, heavy pain, and tender) in SF-MPQ-2 (Supplemental Table 2);
h Summarized 6 items of intermittent pain descriptors (shooting, stabbing, sharp, splitting, electric-shock pain, and piercing) in SF-MPQ-2 (Supplemental Table 2);
i Summarized 6 items of predominantly neuropathic pain descriptors (hot-burning and cold-freezing pain, pain caused by light touch, itching, tingling or pins and needles, and numbness) in SF-MPQ-2 (Supplemental Table 2);
j Summarized 4 items of affective descriptors (tiring–exhausting, sickening, fearful, and punishing–cruel) in SF-MPQ-2 (Supplemental Table 2);
k Including one patient with mild alopecia in the ESPB group and one patient with perioral numbness in the control group.

pain relief. Furthermore, HADS depression is associated with acute pain intensity, which is an independent risk factor for PHN (34). Our study indicates that pain catastrophizing may bring increased HADS scores, which could be relieved by ESPB.

Analgesics for acute/subacute HZ-related pain including acetaminophen, and tramadol and other opioids, but they do not provide excellent analgesic efficacy (4,6). In clinical practice, anticonvulsants and tricyclic antidepressants are the first-line medicines for PHN (34).

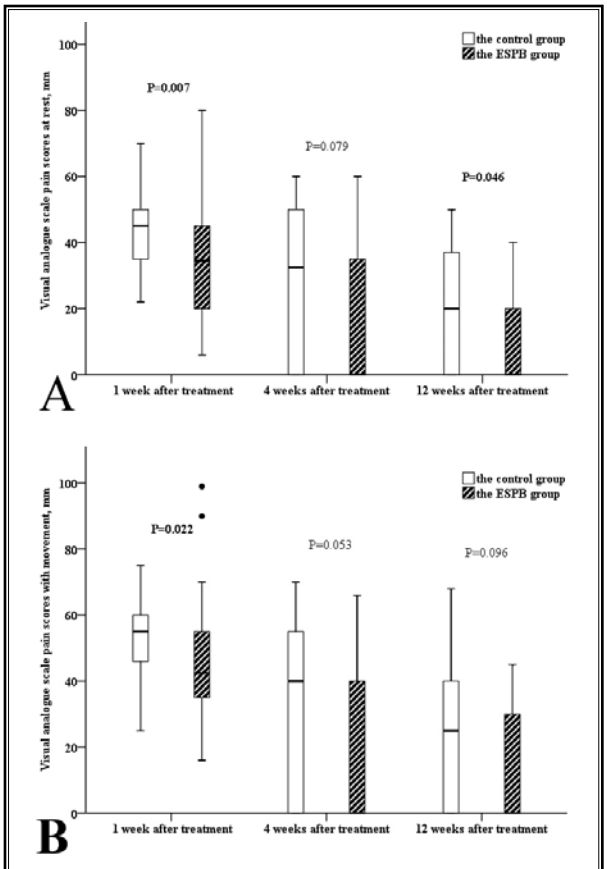

Fig. 2. *The VAS pain scores at rest (A) and with movement (B) at different time-points after treatment. At one week the pain scores at rest and with movement and at 12 weeks the pain score at rest were significantly lower in the ESPB group than in the control group (P = 0.007, P = 0.022, P = 0.046). Data analyzed using nonlinear mixed effects models. The box plots show medians and interquartile ranges and individual points are mild outliers (o, which are outside 1.5 times of interquartile range). VAS, visual analog scale.*

Table 3. *Adverse events during and within 24 hours after the procedure.*

	Control group (n = 26)	ESPB group (n = 26)	*P* value
Hematoma	1 (3.8%)	1 (3.8%)	> 0.999
Dizziness	5 (19.2%)	2 (7.7%)	0.216
Limb weakness	0 (0.0%)	2 (7.7%)	0.091
Hypotension [a]	0 (0.0%)	0 (0.0%)	> 0.999
Bradycardia [b]	0 (0.0%)	0 (0.0%)	> 0.999

The results are presented as the number (%).
a A reduction of systolic blood pressure of more than 30% from prepuncture lasting for at least 15 minutes.
b Heart rate < 45 beats per minute or a decrease of more than 30% from prepuncture lasting for at least 5 minutes.

There remains a lack of effective and safe analgesics for the acute/subacute periods of HZ (6). Although ESPB did not reduce the requirements for anticonvulsants or antidepressants in this study, it significantly reduced the consumption of tramadol, which consequently decreased complications with oral medicines.

A few procedure-related complications occurred in our study, i.e., hematoma, dizziness, and limb weakness; however, the incidences of complications were comparable between the 2 groups. Therefore, ultrasound-guided ESPB appears to be an effective, feasible, and safe procedure for outpatients with HZ in the acute/subacute phases.

Limitations

There are several limitations of our study. Firstly, as a single-center trial, the generalization of the results might be influenced. Secondly, our study performed 12 weeks of follow-up to assess the occurrence of PHN; longer follow-up may be required for the complicated and latent appearance of PHN. Thirdly, 2 patients were lost to follow-up in the control group, which may slightly affect the results. But we considered this condition and explained the solution in the sample size estimation. Fourthly, prior to intervention, most of the patients were administrated several medications and physical treatments (such as antivirals, anticonvulsants, antidepressants, analgesics and Chinese medicine treatment). We found that the preintervention medications and treatments were comparable between the 2 groups (Table 1 and Supplemental Table 2). Therefore, it was acceptable that the treatments before enrollment were similar with both groups. For avoiding interference of treatment prior to intervention, a larger sample size and enrolling patients without any preintervention medications or treatments may be needed in further studies. Lastly, our study evaluated the interference of sleep and emotion at 12 weeks follow-up; however, we could not establish a standard prescription of hypnotics or antidepressants according to variable clinical practice and the patients' individual requirements. Therefore, the resulting bias cannot be excluded. However, those were not the primary outcome of our study, and we did find that ultrasound-guided ESPB reduced the incidence of PHN at 12 weeks for elderly patients with acute or subacute HZ.

Conclusion

This randomized controlled double-blinded trial confirmed that, for elderly patients with acute or subacute HZ, ultrasound-guided ESPB reduces the incidence of PHN at 12 weeks; it also decreases the oc-

currence of neuropathic pain, sleep disturbance, and anxiety/depression.

Authors' Contributions

Zeng-Mao Lin, MD: This author conceived and designed the study, collected data, performed data analysis, and drafted and revised the manuscript.

Hai-Feng Wang, MD: This author conceived and designed the study, collected data, performed data analysis, and drafted and revised the manuscript.

Feng Zhang, MD: This author performed the erector spinae plane blockades.

Jia-Hui Ma, MD, PhD: This author performed data collection and analyzed the data.

Ni Yan, RN: This author collected the baseline and periprocedure data and helped record follow-up data.

Xiu-Fen Liu, MD: This author participated in designing the study, reviewed and analyzed data, and revised the manuscript. She is the corresponding author.

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Ethics Approval and Consent to Participate

The research protocol was approved by the Biomedical Research Ethics Committee of Peking University First Hospital (Number: 2019-90). All participants signed written informed consent.

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Supplemental Table 1. *Assessment of pain on baseline.*

Items	Definition/methods
ID pain scale (16,17)	A 6-item self-administered questionnaire with a total score ranging from -1 to 5; a cut-off score of ≥ 2 was adopted for diagnosing neuropathic pain.
Hospital Anxiety and Depression Scale (HADS) (18,19)	Including 2 self-rating subscales for anxiety and depression, each with a total score ranging from 0 to 21; a cut-off score of ≥ 8 was adopted for diagnosing anxiety and/or depression.
The Pittsburgh Sleep Quality Index, PSQI (20-22)	A questionnaire consisted of 19 self-reported items, scores of each question range from 0 to 3, with higher scores indicating more acute sleep disturbances; a cut-off score of 6 for the global scale was adopted for identifying a poor sleeper.
The revised Short-Form of McGill Pain Questionnaire (SF-MPQ-2) (23,24)	A scale that was self-rated by patients according to the intensity of pain perceived on a 0–10 numeric scale (0 = no pain and 10 = the worst pain), is composed of 22 pain descriptors and 4 subscales. It includes 6 continuous pain descriptors (throbbing, cramping, gnawing, aching, heavy pain, and tender), 6 intermittent pain descriptors (shooting, stabbing, sharp, splitting, electric-shock pain, and piercing), 6 predominantly neuropathic pain descriptors (hot-burning and cold-freezing pain, pain caused by light touch, itching, tingling or pins and needles, and numbness), and 4 affective descriptors (tiring–exhausting, sickening, fearful, and punishing–cruel). The 4 subscale scores were calculated by summating the numerical values of each item, and the total scores represented the sum of values for all 22 items. Higher subscale or total scale scores indicated patients with more intense symptoms.

Supplemental Table 2. *Current medication and daily dose on baseline.*

	Control group (n = 26)	ESPB group (n = 26)	*P* value
Antiviral	14 (53.8%)	15 (57.7%)	0.780
Famciclovir	8 (30.8%)	9 (34.6%)	0.774
Famciclovir, mg	0.0 (0.0, 7.5)	0.0 (0.0, 9.0)	0.970
Valacyclovir	6 (23.1%)	6 (23.1%)	> 0.999
Valacyclovir, mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.970
Anticonvulsant	18 (69.2%)	16 (61.5%)	0.560
Gabapentin	14 (53.8%)	13 (50.0%)	0.781
Gabapentin, mg	1.7 (0.0, 7.5)	0.2 (0.0, 7.5)	0.822
Pregabalin	4 (15.4%)	3 (11.5%)	0.684
Pregabalin, mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.734
Antidepressant			
Doxepin	1 (3.8%)	2 (7.7%)	0.548
Doxepin, mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.526
Analgesics	5 (19.2%)	10 (38.5%)	0.126
Acetaminophen/NSAIDs	5 (19.2%)	9 (34.6%)	0.211
Acetaminophen	4 (15.4%)	7 (26.9%)	0.308
Acetaminophen, mg	0.0 (0.0, 0.0)	0.0 (0.0, 1300.0)	0.334
Celecoxib	1 (3.8%)	2 (7.7%)	0.548
Celecoxib, mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.556
Tramadol	4 (15.4%)	7 (26.9%)	0.308
Tramadol, mg	0.0 (0.0, 0.0)	0.0 (0.0, 200.0)	0.313

The results are presented as the median (interquartile range) or number (%).