Efficacy and Safety of PCA-assisted Continuous Paravertebral Block in Subacute Herpes Zoster-associated Pain: Study Protocol for a Randomized, Controlled, Double-blind Superiority Trial

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Research Article

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Abstract

Background

Pain management for herpes zoster-associated pain (ZAP) is essential to improve patients' daily lives and potentially intervene in the chronicity. Long-lasting, repetitive painful stimuli might lead to central sensitization and neuropathic pain generation. The subacute phase is the main period for ZAP patients to seek medical attention, and it is also a critical treatment time window for the transformation of ZAP to chronic pathological changes. Although there is still a lack of rigorous considerable sample evidence, the pain degree of ZAP and the incidence of postherpetic neuralgia (PHN) may decrease accordingly with increasing adequate analgesia. Compared to repeated paravertebral nerve block (PVB), Patient-controlled analgesia (PCA) -assisted continuous PVB provides more prolonged and comprehensive pain relief according to patient needs. Given this, we intend to test the hypothesis that PCA-assisted continuous PVB delivers a safe and better analgesic effect and reduces PHN incidence in subacute ZAP patients.

Methods

A total of 82 eligible subacute herpes zoster (SHZ) patients will be recruited and randomly assigned to the PCA-assisted continuous PVB group (Group PCA) and the repeated PVB group (Group rPVB) at a 1:1 ratio. All enrolled patients will undergo thoracic paravertebral space (TPVS) catheterization and receive similar doses of medication for seven days. The main intervention factor lies in the different drug administration manners. PCA-assisted continuous PVB treatment will be achieved by pumping, while repeated PVB treatment will be conducted by injecting other therapeutic solutions. The participants and investigators will be both blinded to group allocation. The primary outcome is the VAS scores one month after treatment. The secondary outcomes include the incidence of PHN and the adverse events during treatment and follow-up.

Discussion

The results from this study will provide clinical evidence on the efficacy and safety of PCA-assisted continuous PVB for subacute ZAP patients.

Trial registration

Chinese Clinical Trial Registry: ChiCTR2300068158. Registered on 9 February 2023. https://www.chictr.org.cn/searchproj.html

Administrative Information

Note: The numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

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Name and contact information for the trial sponsor {5b}	Investigator initiated clinical trial; Nan Gu (Principal Investigator) gunn818@126.com
Role of sponsor {5c}	This is an investigator initiated clinical trial. No sponsor played any part in the study design, collection, analysis, and interpretation of data and in the decision to write and submit the manuscript for publication.

Introduction

Background and rationale {6a}

Herpes zosters (HZ) patients frequently experience moderate-to-severe pain and considerable suffering[1, 2]. Herpes Zoster-associated pain (ZAP) is the acute or chronic pain caused by the reactivation of latent varicella zoster virus multiplies within sensory ganglion, which walking along the affected nerve innervated skin segments and may manifest as paresthesia, dysesthesia, allodynia, or hyperesthesia[3]. In large observational trials, the pain preceded the rash of HZ in 84% of patients and presented during the acute exanthem phase in 89%[4], and the incidence of pain over one month after the onset still exceeded 55%[5]. In some patients, especially those older than 50, ZAP can persist for months or even years after the skin lesions have disappeared[3, 6]. It is well known that long-lasting, repetitive painful stimuli might lead to central sensitization and neuropathic pain generation[7]. Persistent ZAP can also lead to depression, anxiety, insomnia, and inability to work and live normally, seriously affecting patients' quality of life and emotional functioning[8].

Pain management for ZAP is essential to improve patients' daily lives and potentially intervene in the chronicity of pain. Scholars mostly believe that early control of herpes zoster neuralgia is closely related to its chronic transformation, and adequate early analgesia tends to reduce the occurrence of postherpetic neuralgia (PHN)[9, 10]. However, there is still a lack of rigorous evidence. Nerve blocks have been used to relieve acute ZAP for several decades. With the advancement and popularization of ultrasound guide techniques, paravertebral block (PVB) has become simple, safe, and easy to perform, making it one of the most popular interventional techniques for controlling thoracic ZAP in clinical practice[11, 12]. The PINE study[13] reported that using a single epidural block with steroids within one week of the eruption has the advantage of short-term pain relief, while not effective for preventing long-term postherpetic neuralgia. On the other hand, several other studies[14-18] found that epidural catheters or repeated paravertebral injections could relieve pain and might reduce PHN incidence. The above studies suggest that the severity of pain and the incidence of PHN may decrease accordingly with increasing frequency and duration of nerve block treatment.

The subacute phase is a critical period for ZAP chronic transformation. Due to insufficient patient awareness and existing primary healthcare providers' medical services, many patients still have moderate-to-severe subacute ZAP at 30-90 days and seek medical help. Screening more effective therapies for subacute herpes zoster (SHZ) to prevent chronic pain has therefore become a vital trial topic.

Patient-controlled analgesia (PCA)-assisted continuous PVB is an advanced new clinical analgesic technology that can provide more prolonged and comprehensive pain relief according to patient needs. It has been used in perioperative analgesia and other clinical scenarios[19, 20]. However, whether PCA-assisted continuous PVB could provide a safe and better analgesic effect in subacute ZAP patients and reduce PHN incidence has not been investigated. We designed a single-center, randomized, controlled, double-blind superiority trial to investigate the efficacy and safety of PCA-assisted continuous paravertebral block in subacute ZAP.

Objectives {7}

The primary aim of this trial is to determine whether PCA-assisted continuous PVB is superior to repeated PVB in reducing pain intensity at one month post-treatment in subacute ZAP patients, measured by the visual analog scale (VAS) score[21]. The secondary objectives of the study include the incidence of PHN at two months post-treatment, VAS scores, levels of anxiety and depression, sleep status, analgesic drug dosage before treatment, and at 1, 2, and 3 weeks, 1 and 2 months after treatment, and adverse events during treatment and follow-up.

Trial design {8}

This single-center parallel randomized, controlled, double-blind clinical trial will be conducted with 82 eligible SHZ patients who signed informed consent. Participants will be randomly assigned to receive PCA-assisted continuous PVB or repeated PVB at a 1:1 ratio. All participants will accept a 1-week treatment through a thoracic paravertebral space (TPVS) catheter and about two months of the same oral drug analgesic

regimen. A 2-month follow-up will be conducted on pain relief, PHN incidence, sleep quality, anxiety/depression, etc (Fig. 1).

Methods: Participants, interventions and outcomes

Study setting {9}

Patients will be recruited in the Pain Medicine Center at the First Affiliated Hospital of the Fourth Military Medical University (Xijing Hospital, Xi'an, China). Patients will be considered for inclusion if they meet the criteria outlined below.

Eligibility criteria {10}

Inclusion criteria

Patients must meet the following criteria to be eligible for the study:

1. Patients meeting the diagnostic criteria of HZ and VAS score ≥40 points

2. Age ≥18 years old, ≤85 years old

3. Skin lesions range within the thoracic spinal nerve innervation area, involving segments ≤4

4. The course of disease within 30-90 days (after the onset of the rash)

5. No nerve block or other interventional therapy was received before enrolment

6. Voluntary participation and provision of written informed consent

Exclusion criteria

Participants will be excluded from the study if any of the following conditions are reported:

1. Patients with severe cardiopulmonary insufficiency, severe hepatic and renal insufficiency and hematological diseases

2. Severe skin lesions or local infections at the puncture site

3. Diabetic patients with poor glycemic control (fasting blood glucose ≥ 10.0mmol/L)

4. Patients with abnormal coagulation function

5. Patients who are allergic to drugs such as local anesthetics used in this study or unsuitable for performing nerve blocks

6. Pregnancy or breastfeeding status

7. Patients with mental illness or cognitive dysfunction who cannot fully understand the research scale

8. Patients with a history of sleep disorders

9. Patients with a history of opioid addiction or abuse

Who will take informed consent? {26a}

The researchers will explain the trial's purpose to eligible subjects, the possible benefits and risks, and educate them about PVB therapy and PCA devices before the test. All those who agree to participate in the trial will sign an informed consent form.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

No other consent provisions are applicable; no biological specimens are collected.

Interventions

Explanation for the choice of comparators {6b}

The two comparators are the PCA-assisted continuous PVB group (Group PCA) and the repeated PVB group (Group rPVB, control group). The control group receives repeated PVB, which is a mainstream treatment for thoracic ZAP[14, 15].

Intervention description {11a}

Ultrasound-guided TPVS catheterization

Two senior pain physicians, who have performed over 20 TPVS catheterization procedures with years of experience in ultrasound-guided nerve block, will place all the TVPS catheters. The method of TPVS catheterization has been described previously by Matinian et al. [22]. Firstly, the injured nerves should be determined before catheterization treatment according to the patient's painful nerve segments and pigmented or scarred skin area. Then the TPVS catheterization level will be selected. The patients lie prone. Blood pressure (BP), electrocardiogram (ECG), and oxygen saturation (SpO2) will be continuously monitored. After routine aseptic skin preparation, a 2-5 MHz convex array probe (C5-2S, TE7, Mindray Inc., Shenzhen, China) inside a sterile sheath will be used to localize the target thoracic segment. Fine-tune the position of the ultrasound probe to optimize TVPS imaging for easy catheter placement. Next, a 20-gauge Braunula-type needle KIT (Contiplex D, B. Braun, Melsungen, Germany) will be inserted and advanced using the in-plane approach. At the T4-T12 segment, the in-plane puncture will usually be performed from the lateral to medial end, while the puncture will usually be performed from the Caudal side to the Cephalic side at the T1-T3 segment. After needle penetration into the TPVS, 5–10mL saline will be injected, and ventral movement of the parietal pleura will be confirmed to identify the needle tip position. Subsequently, withdraw the puncture needle and retain the outer tube. An 18-gauge continuous nerve block catheter will be inserted 3-4 cm beyond the tube tip and left in place. A small amount of air-mixed saline will be injected through the catheter to confirm that it produced a bubble inside the TPVS, without air or blood aspiration (Fig. 2). The injection will always be followed by verification of the disappearance of pain in the relevant dermatome. Finally, the catheter will be fixed to the skin with a suture.

One-week therapeutic intervention

After TPVS catheterization, all eligible patients will receive similar doses of medication for seven days via the catheters. The main intervention factor will lie in the different drug administration manners (Fig. 3). More specifically, the treatment consists of continuous pumping for seven days and three intermittent injections.

1. All the patients in both groups will receive continuous liquid pumping via an electronic Patient-controlled analgesia pump (AM230/350, ACE MEDICAL Co, Ltd, Seoul, South Korea). The patients in Group PCA will be continuously pumped with an anti-inflammatory analgesic solution (AAS, 250ml), while the placebo solution will be used in Group rPVB. The parameters of the PCA pump are set as follows: total volume 250ml, background dose 3ml/h, bonus dose 6ml/time, lock time 30 minutes.

2. As for the three intermittent injections, all the patients will receive the first PVB injection (injected with 20ml AAS) just before connection to the PCA pump. Group rPVB patients will receive the second and third PVB injections (20 ml AAS) on days 3 and 7, respectively, while Group PCA patients will get 20 ml of 0.9% saline simultaneously.

3. The formula of the therapeutic solutions is described as follows: 1) 250ml AAS: 0.1875% ropivacaine (AstraZeneca AB, 100mg 10ml) + Diprospan 1.0ml (Compound Betamethasone Injection, Schering-Plough Labo N.V. 5mg/2mg 1ml) + cobamamide 6.0mg (Chongqing Yaoyou Pharmaceutical Co. LTD, 1.5mg) + saline, dilute to 250ml; 2) 250ml placebo solution: cobamamide 6.0mg + saline, dilute to 250ml; 3) 20ml AAS: 0.1875% ropivacaine + Diprospan 0.5ml + saline, dilute to 20ml. Because of cobamamide, the colors of the 250ml AAS and placebo solutions appear indistinguishable.

An assigned nurse will prepare the therapeutic solutions according to grouping and then hand them to the treatment staff but will not be involved in the specific treatment and follow-up. So that, the participants and investigators will be blind to the interventions. After completing all PVB treatments, the staff will carefully withdraw the catheter and reconfirm its integrity.

The oral analgesic regimens

The oral analgesics regimen will be consistent within the two groups of patients during treatment and follow-up, including 1) Pregabalin Capsules (Pfizer Manufacturing Deutschland GmbH, Betriebsstatte Freiburg, 75mg): the initial dose is 75mg Bid, the dosage is determined according to the pain degree, and the maximum dose is 300mg/ day. When VAS $\leq$30, the pregabalin dosage will be gradually reduced until finally stopped. If the VAS is above 30 again, the dosage will be increased accordingly. 2) Paracetamol and Tramadol Hydrochloride Capsules (Good Doctor Pharmaceutical Co., LTD, China, 37.5mg: 325mg): as a remedial analgesic to suppress eruptive pain, when the VAS score is $\geq$60; maximum daily dose is six tablets per day.

Criteria for discontinuing or modifying allocated interventions {11b}

Patients can withdraw from the study for any reason without any consequences. The patient data that has been collected up to that point will be included in the analysis. Suppose patients experience severe adverse

events (SEAs) during the course of the study, such as infection and catheter dislodgement during the intervention period, or require alternative treatment measures due to complications or changes in their medical condition. In that case, the study will be terminated early.

Strategies to improve adherence to interventions {11c}

Throughout the entire week-long treatment intervention, a designated physician is responsible for the specific treatment of patients, providing guidance and response to treatment-related consultations and reminding patients of their scheduled appointment dates. During the 2-month follow-up period after the treatment, an investigator who is unaware of the patient's grouping and not involved in the treatment is responsible for the follow-up. Patients are required to attend regular follow-up appointments at the clinic or communicate through various channels, such as telephone calls or WeChat (https://weixin.qq.com, Tencent Computer System Co., LTD, Shenzhen, China), to ensure the successful completion of the follow-up process.

Relevant concomitant care permitted or prohibited during the trial {11d}

The analgesic drug regimen for both groups is identical. During the study period, the use of analgesic medications and invasive therapeutic protocols, other than those specified in this study, will be strictly prohibited.

Provisions for post-trial care {30}

Based on previous research and clinical practice, the risk of SEAs associated with the intervention measures in this study is extremely low. During the intervention period, the puncture procedures will be strictly standardized by an experienced pain physician under ultrasound guidance. Additionally, we have excellent medical emergency setups in place to minimize the occurrence of any adverse reactions or associated risks. If any SEAs related to this study occur during the treatment, we will provide active treatment to the patient and waive the treatment costs.

Outcomes {12}

Primary outcome

The primary outcome is the visual analog scale for pain at one month after the treatment. The VAS scale is an unscaled 100 mm line, with one end representing "no pain at all" and the other representing "the most severe pain imaginable"; it means a score from 0 to 100. Patients are asked to mark the appropriate point on the line (with a dot or a "×") to represent the pain level they are experiencing at that time; the distance to the marked point is measured with a straightedge to describe the current pain score.

Secondary outcomes

The secondary outcomes include the incidence of PHN at two months post-treatment; changes in VAS scores, levels of anxiety and depression, and sleep status within 2-month follow-up, as well as the analgesic drug dosage and adverse events during treatment and follow-up. Details are as follows:

1. Incidence of PHN at two months after treatment. PHN is defined as persistent pain that continues for three months or longer after the onset of a shingles (herpes zoster) rash, with a VAS score exceeding 40. The investigator will contact patients two months after treatment and determine whether PHN has developed; PHN incidence is calculated: P= n(PHN) /N×100%.

2. The number of PCA pressing (including effective and total pressing numbers) during treatment.

3. Changes in VAS scores, the Pittsburgh Sleep Quality Index (PSQI)[23] scores, the Patient Health Questionnaire-9 (PHQ-9)[24] scores, and the Generalized Anxiety Disorder-7 (GAD-7)[25] scores before treatment, 1, 2, 3 weeks, 1 and 2 months after treatment.

4. The amounts of analgesic drugs and remedial drugs. The total amount of oral analgesic drug pregabalin capsules (mg) and remedial analgesic drug paracetamol and tramadol hydrochloride capsules (mg) will be recorded during treatment and follow-up.

5. The occurrence of adverse events and SEAs during treatment and follow-up, including but not limited to PVB treatment-related hypotension, bleeding, hematoma, motor and sensory disorders, catheter loss, and skin infection; treatment measures taken due to complications or disease changes that render continued study participation unsuitable. Severe adverse events refer to pneumothorax, local anesthetic poisoning, respiratory depression, hypoxia, cardiac arrest, new arrhythmias, sustained hypotension, bradycardia, etc.

Participant timeline {13}

The participant timeline of enrolment, randomization, assessments, and follow-up are summarised in Fig. 3 and Table 1.

Table 1 Schedule of enrolment, interventions, and outcome assessment

Action/timepoint	Study period						
	Enrolment	Intervention phase	Follow-up				
			1 week	2weeks	3 weeks	1 month	2months
Enrolment							
Eligibility screen	▯						
Informed consent	▯						
Basic information	▯						
Herpes related information	▯	▯					
Examination and Laboratory Tests	▯						
Randomization	▯						
Interventions							
vital signs	▯	▯					
Therapeutic information		▯					
Assessment							
VAS	▯	▯	▯	▯	▯	▯	▯
PSQI	▯		▯	▯	▯	▯	▯
PHQ-9	▯		▯	▯	▯	▯	▯
GAD-7	▯		▯	▯	▯	▯	▯
Adverse events/SEAs		▯	▯	▯	▯	▯	▯
Dosage of Analgesic drug		▯	▯	▯	▯	▯	▯

VAS the Visual Analog Scale, PSQI the Pittsburgh Sleep Quality Index, PHQ-9 the Patient Health Questionnaire-9, GAD-7 the Generalized Anxiety Disorder-7, SEAs Serious Adverse Events

Sample size {14}

The primary outcome is pain degree (VAS score) 1 month after treatment. According to a clinical study published by Liu et al. [26] in 2021, the VAS score of SHZ patients treated with repeated PVB after one month is 32±9. It is considered that the mean VAS score of patients receiving PCA-assisted continuous PVB treatment after one month decreased by 10 points or more than that receiving repeated PVB treatment will have a clinical significance. Using the PASS 15.0.5 software (NCSS, Kaysville, Utah, USA) and the superiority test of two independent means, at least 37 patients per group will be required for 80% power to identify a

difference at the α=0.025 (unilateral test) level of significance. Considering a drop-out rate of 10%, a minimum of 82 patients (41 per group) will be required.

Recruitment {15}

Patients will be recruited at the pain clinic of Xijing Hospital from February 2023 to June 2024, where there are many HZ patients. In case the recruitment process is slower than anticipated, we will disseminate clinical trial information by placing recruitment posters in the outpatient area and on Xijing Hospital's official WeChat account.

Assignment of interventions: allocation

Sequence generation {16a}

The study adopts the method of stratified blocked randomization. A 1:1 randomization sequence with block sizes of 2 and 4 will be generated using the R software (The R Foundation for Statistical Computing, Vienna, Austria). According to the enrolment order, eligible participants will be randomized to the PCA group and rPVB group.

Concealment mechanism {16b}

The generated sequences will be placed in sequentially numbered, opaque, sealed envelopes to ensure the concealment of allocation from the participants, investigators, and data analysts.

Implementation {16c}

The attending doctor will screen and record the patients in the outpatient department, and obtain the written informed consent of all eligible patients with a detailed explanation. Eligible patients will be randomly assigned to one of the study arms, and a specific nurse will conduct allocation according to the generated sequences.

Assignment of interventions: Blinding

Who will be blinded {17a}

The experimental blinding method is one of the highlights of this study. Given that pain is a subjective sensory and emotional experience, we have ingeniously designed the trail to make all the patients appear to receive the treatment similarly and try our best to avoid the participants' personal bias (Fig. 4). Specifically, all enrolled patients will undergo TPVS catheterization and receive similar doses of medication for seven days. The main intervention factor lies in the different drug administration manners (Fig. 3). Placing catheters in Group rPVB patients will also reduce the discomfort and damage caused by repeated punctures. An exceptional specific duty nurse will be set up to implement blindness, who will open each envelope before intervention and prepare the therapeutic solutions accordingly but will not be involved in the specific treatment and follow-up. The participants, investigators, and data analysts will be blind to the interventions.

Procedure for unblinding if needed {17b}

Unblinding will only be allowed under emergencies, such as SEAs. No other procedure for unblinding will be needed as all data analyses are performed after the trial is closed.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All data from this study will be collected using the case report form (CRF). After enrolment, a researcher will collect data on participants' demographic characteristics (height, weight, age, sex (male/female), history of smoking/alcohol consumption and co-morbidities, etc.), herpes-related conditions (herpes site, pain degree in acute phase, severity of herpes, prodrome pain, herpes area, and nature of pain, etc.), relevant laboratory results and treatment history, through patient interviews and electronic medical records. Patient's vital signs, target nerve segments, catheterization/puncture depth, number of PCA compressions, adverse reactions, and SEAs will be recorded during treatment. At the end of treatment, a 2-month follow-up will be performed to record the patients' VAS score, PSQI score, PHQ-9 score, GAD-7 score, the amounts of analgesic drugs used, and drug-related adverse reactions.

Plans to promote participant retention and complete follow-up {18b}

The patients will receive comprehensive information about the trial's setup and requirements during the study. The importance of completing the follow-up will be emphasized. We will provide patients with a two-month follow-up schedule and encourage them to visit the clinic for face-to-face follow-up on the assigned date. Two days before the follow-up date, the investigator in charge of the follow-up will proactively contact and remind the patients via phone, WeChat, or other means. If patients cannot complete the offline follow-up, they will be asked to complete the scales using an online Questionnaire Star software (Ranxing Information Technology Co., Ltd, Changsha, China). Therefore, patients can do this at any convenient moment. Throughout the follow-up period, the researchers will check responses and if necessary, contact patients for completion of their follow-up.

Data management {19}

The paper version of CRF of patient data will be appropriately stored as the raw materials for the study. Two data managers, supervised by an independent quality monitor, will be responsible for entering all CRF data into the Electronic Data Capture System (EDC). Any entries, modifications, deletions, and other actions made in the EDC will be recorded in a log, indicating the individuals who made the changes and the corresponding timestamps. All research material will be maintained on a secure server or locked in file cabinets.

Confidentiality {27}

Research data will be stored using a unique study identification code assigned to each participant. The key to the identification code list will be accessible only to the research team during the study and will be

documented and securely stored by the principal investigator in accordance with research guidelines upon completion of the study. No patient identification details will be included in any publications.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

This trial does not involve the collection, laboratory evaluation, or storage of biological specimens for genetic or molecular analysis.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

All statistical analysis will be conducted using R software. Descriptive statistical analysis will be performed to compare the patients' baseline data between groups. For Continuous variables, the Shapiro-Wilk test will be used to assess normality, and the Levene test will be utilized to examine the homogeneity of variance. Normally distributed data will be presented as mean ± standard deviation (SD) and compared using Student's t-test. Non-normally distributed data will be expressed as medians with interquartile range [median (IQR)] and compared using the Wilcoxon rank-sum test. Classification or categorical data will be reported as frequencies with percentages or ratios [N (%)] and compared using the 2-tailed $\chi 2$ test or Fisher's exact test. Additionally, repeated measures will be analyzed using a logistic mixed-effects model to assess data at multiple time points. For time-to-event data, Kaplan-Meier survival curves will be generated, and a Log-rank test will be performed.

Interim analyses {21b}

There are no interim analyses planned.

Methods for additional analyses (e.g., subgroup analyses) {20b}

For primary outcome, a sensitivity analysis will be performed using a linear mixed-effect model, adjusting variables for baseline VAS score, age, sex, rash severity, acute pain degree, prodromal pain. Any differential effects will be assessed by adding the variable for the interaction of the subgroup with the treatment group to the models.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The primary outcome analysis will be conducted on an intention-to-treat (ITT) basis[27]. Missing data will be reduced to a minimum by using the appropriate measures described above. A complete case analysis will be performed if the outcome data is missing for less than 5% of the study population during the entire study period. However, if the missing data exceeds 5% of the participants, multiple imputation will be used[28].

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The full protocol, de-identified datasets, and statistical code may be made available from the corresponding author upon reasonable request and appropriate resources after the final publication of results.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

This single-center study is conducted at the Pain Medicine Center of Xijing Hospital, Fourth Military Medical University. Daily support for the trial is provided by:

Principal investigator: supervises the trial and is responsible for the medical responsibility of the patients.

Data manager: organizes data capture, safeguards quality and data.

Study coordinator: trial registration, coordinate study visits, annual safety reports.

Study physician: identifies potential recruits, takes informed consent, ensures follow-up according to protocol.

The study team meets biweekly. There is no trial steering committee or stakeholder and public involvement group.

Composition of the data monitoring committee, its role and reporting structure {21a}

The data monitoring committee is set up by the Xijing Hospital of Fourth Military Medical University, and its members have no interest relationship with the sponsor. The members should have professional knowledge of medicine, pharmacy, health statistics, and be familiar with relevant laws and regulations of clinical trials. The committee monitors the eligibility, integrity, safety, and effectiveness of data through EDC system and question the problem data, which can be directly marked in EDC and generate a verification log. The data monitoring committee will meet once a year to review and monitor the trial data, including recruitment quality, data quality, protocol compliance, and adverse events. And it is independent of the sponsor and competing interests.

Adverse event reporting and harms {22}

The safety of the participants will be monitored for the duration of the 1-week intervention and 2-month follow-up period. Adverse events and SEAs reported by the subject or observed by the investigators should be recorded. When an adverse event or SEAs occurs, the investigator should provide an adequate treatment immediately and follow it up until recovery or remission is confirmed. SAEs data will be reported at regular Data Safety and Monitoring Committee meetings.

Frequency and plans for auditing trial conduct {23}

The research group convenes on a monthly basis to review the progress of the trial and address any potential issues that may arise. Furthermore, an independent monitor will annually verify the presence and

integrity of the trail documentation, which include informed consent, inclusion and exclusion criteria, as well as source data collection.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Any significant amendments to the protocol must receive a favorable opinion from the Medical Ethics Committee of Xijing Hospital before implementation. All modifications to the protocol need to be communicated to all participating investigators in the research. Any modification that alters participant coverage or affects the benefits, risks, and limitations of the study will require a new information sheet and consent form. All protocol amendments will undergo review and approval.

Dissemination plans {31a}

The findings of this research will be fully disclosed in international peer-reviewed journals. This includes the reporting of both positive and negative results.

Discussion

Finding more efficient and safe treatment methods to relieve ZAP and prevent the occurrence of PHN has always been a hot and challenging research topic among pain specialists[29]. Patient-controlled analgesia, a new personalized analgesic technology developed and introduced into pain treatment recently[30], provides more prolonged and comprehensive pain relief according to patient needs. PCA-assisted continuous PVB technology significantly overcomes the shortcomings of traditional medication, such as untimely, slow onset, incomplete analgesia, and noticeable adverse reactions[31, 32]. Based on the above, we have designed this clinical trial and expect that PCA-assisted continuous PVB for seven days could provide a better and safer analgesic effect in subacute ZAP patients one month after the treatment. The main focus of this study is whether it can provide more effective analgesic effects compared to the repeated PVB.

Postherpetic neuralgia, a classic neuropathic pain over 90 days, is one of the most unbearable severe complications of herpes zoster. The skin herpes of HZ heals gradually around two weeks; however, the ZAP accompanying the entire course of the disease is considerable suffering. As the disease progresses, treating PHN becomes increasingly challenging[33]. In clinical trials of available therapies, fewer than half of patients with PHN have a 50% or more significant reduction in pain[5].

Prevention is likely the best strategy to deal with PHN. Just as HZ vaccination can significantly reduce the incidence of both herpes zoster and PHN[34], the available clinical evidence suggests that repeated nerve blocks show better therapeutic outcomes and a lower incidence of PHN than single block within one week of eruption[15]. However, under clinical conditions, it is not common for HZ patients to receive specialized pain treatment, such as a nerve block, within seven days. Due to insufficient patient awareness and existing primary healthcare providers' medical services, many patients still have moderate-to-severe subacute ZAP at 30–90 days and seek medical help[35]. The subacute phase is the main period for ZAP patients to seek

medical attention, and it is also a critical treatment time window for the transformation of herpes zoster related pain to chronic pathological changes. However, there is still a lack of rigorous evidence on whether adequate analgesia of subacute herpes zoster neuralgia is closely related to ZAP chronic transformation. The secondary focus of this study is the incidence of PHN (pain persisting at two months after treatment, VAS ≥ 40). Our trial findings will to some extent test our hypothesis and help us screen more effective therapies for subacute herpes zoster.

Pain is a subjective sensory and emotional experience. One major strength of our trial is that we have ingeniously designed it to make all the patients appear to receive a similar treatment. The double-masked design will give the best shot at reducing participant and researcher bias, making the study conclusions more accurate. Of course, this study is a randomized, controlled, double-blind trial, the best study design to reduce the risk of selection bias. However, there are also limitations in our study. Although the Xijing hospital is a top-level general hospital in China with high-level pain specialties, we also strive to optimize the blinding method, but selection bias may still exist. Regretfully, a single-center, small sample-size study design may limit the external validity and is not necessarily generalizable to a broader population. After the unblinding of this event, if the results are as we speculate, a multicenter, large-sample RCT study will be conducted soon.

Trial status

The current protocol is version 1.2 as of December 1, 2023. The trial was registered on February 9, 2023, and patient recruitment began on February 10, 2023. The study aims to include 82 subjects, and 51 patients have been enrolled. Patient recruitment is estimated to be completed by June 30, 2024.

Abbreviations

HZ
Herpes zoster
PHN
Postherpetic neuralgia
ZAP
herpes zoster-associated pain
PVB
paravertebral nerve block
PCA
patient-controlled analgesia
SHZ
Subacute herpes zoster
AHZ
Acute herpes zoster
TPVS
thoracic paravertebral space

BP
Blood pressure
ECG
electrocardiogram
SpO2
oxygen saturation
DRG
dorsal root ganglion
AAS
anti-inflammatory analgesic solution
CRF
Case Report Form
VAS
the Visual Analog Scale
PSQI
the Pittsburgh Sleep Quality Index
PHQ-9
the Patient Health Questionnaire-9
GAD-7
the Generalized Anxiety Disorder-7
SEAs
serious adverse events
PASS
Power Analysis and Sample Size
ITT
intention-to-treat
SD
standard deviation
IQR
interquartile range
EDC
electronic data capture system.

Declarations

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Authors' contributions {31b}

All authors made substantial contributions to the intellectual content of this paper. NG, BY conceived the study and drafted the manuscript. LL, JX, XH-S, YN-X, QW, JQ and ZJ-M helped with the design, patient recruitment and implementation. BY and NG will contribute to data analysis. YL and HL-D critically reviewed the manuscript for important intellectual content. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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Availability of data and materials {29}

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate {24}

This study has been approved by the Xijing Hospital Ethics Committee (KY20222269-X-1). Informed consent to participate will be obtained from all participants.

Consent for publication {32}

This manuscript does not contain individual personal data from patients. Model consent forms are available from the corresponding author upon request.

Competing interests {28}

The authors declare that they have no competing interests.

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Figures

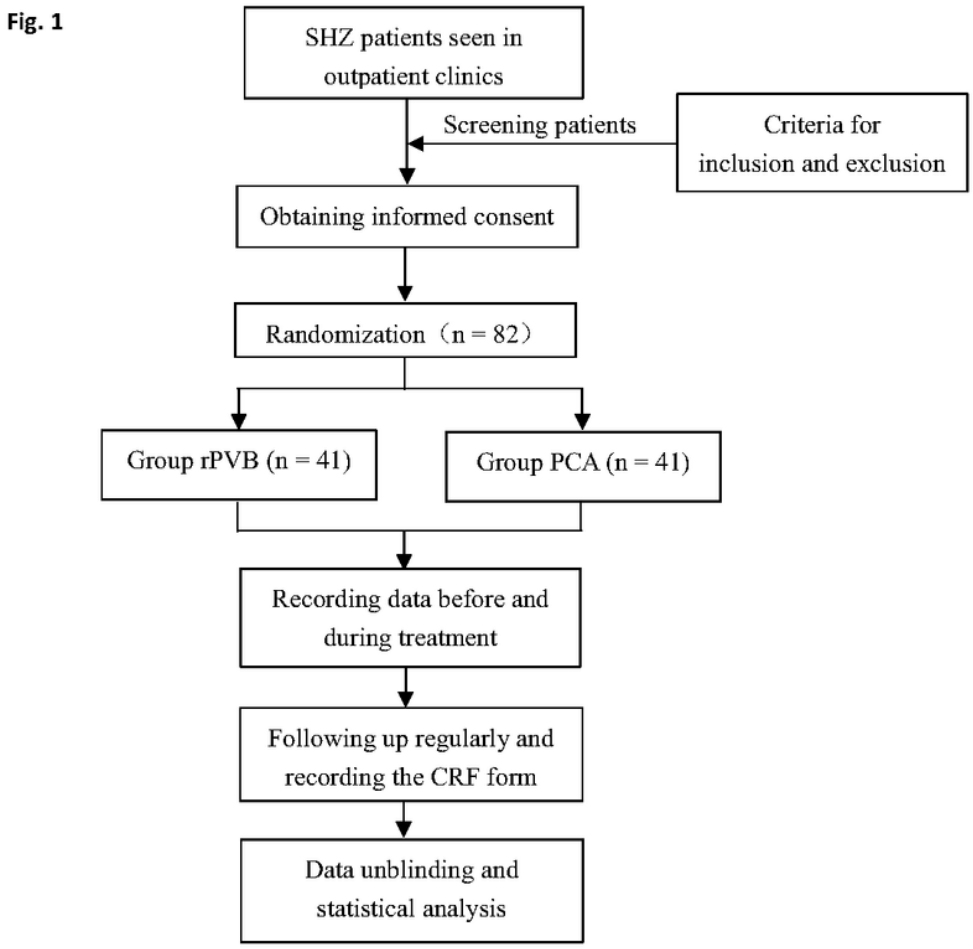

Figure 1

Flow of the trial. SHZ, Subacute Herpes Zoster; PVB, Paravertebral Block; CRF, Case Report Form; Group PCA, PCA-assisted Continuous PVB Group; Group rPVB, Repeated PVB Group.

Fig. 2

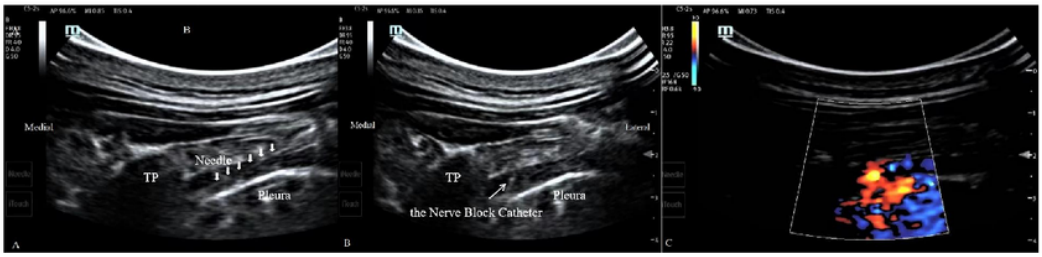

Figure 2

Ultrasound-guided TPVS catheterization. A. By ultrasound-guided puncture, the needle of Braunula-type needle KIT (Contiplex D, B. Braun, Melsungen, Germany) is penetrated the target TPVS, and the parietal pleura moved ventrally after saline injection. B. After withdrawing the puncture needle and retaining the outer tube, an 18-gauge catheter was inserted 3-4 cm beyond the tube tip and left in place. C. In the color Doppler mode, the liquid vortex was observed after injecting a small amount of air-mixed saline to ensure the proper placement of the catheter. TPVS, Thoracic Paravertebral Space; TP, Transverse process.

Fig. 3

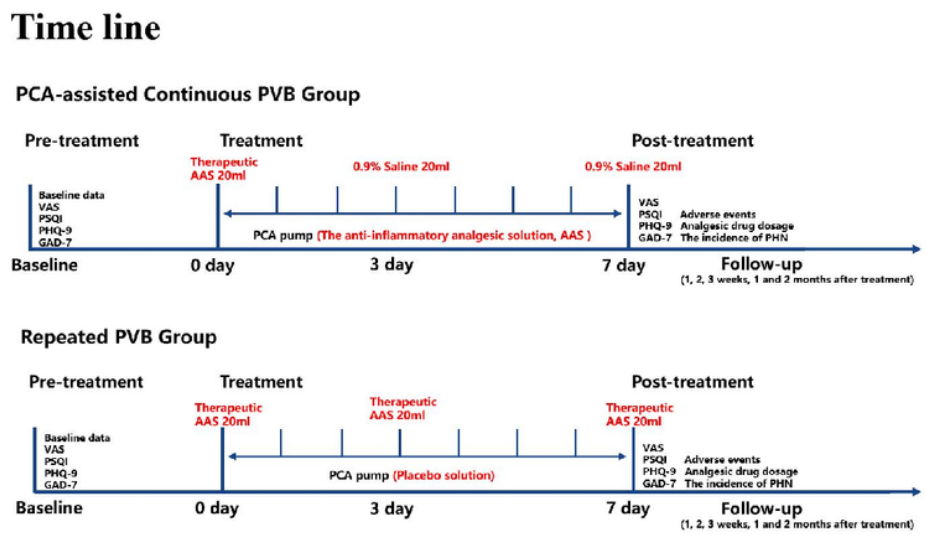

Figure 3

Schematic diagram showing the timeline of different drug administration manners in PCA-assisted continuous PVB group or repeated PVB group. The treatment consists of continuous pumping for seven days and three intermittent injections. The main intervention factor will lie in the different drug administration manners. AAS, anti-inflammatory analgesic solution; PVB, Paravertebral Block; PHN, Postherpetic Neuralgia; VAS, the Visual Analog Scale; PSQI, the Pittsburgh Sleep Quality Index; PHQ-9, the Patient Health Questionnaire-9; GAD-7, the Generalized Anxiety Disorder-7.

Fig. 4

Figure 4

Example appearance of the therapeutic solutions, which are indistinguishable in color.