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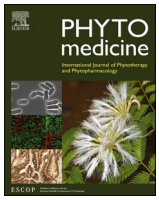

Original Article

Efficacy and safety of Pien Tze Huang capsules in patients with herpes zoster: A multicenter, randomized, double-blinded, and placebo-controlled trial

Wenfeng Wu [a,k], Dingquan Yang [b], Daoshun Sui [c], Minghua Zhu [d], Guangpu Luo [e], Zhonghui Yang [f], Yongfeng Wang [g], Hong Luo [h,l], Li Ling [i], Zexin Zhang [a], Yanmei Wu [j], Guoming Feng [j], Hongyi Li [k,*]

[a] The Second Clinical School of Guangzhou University of Chinese Medicine, Guangzhou, PR China
[b] Department of Dermatology, CHINA-JAPAN Friendship Hospital, Beijing, PR China
[c] Department of Dermatology, The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Guangzhou, PR China
[d] Department of Dermatology, The Guangdong Second Provincial Traditional Chinese Medicine Hospital, Guangzhou, PR China
[e] Department of Dermatology, The Dermatology Hospital of Southern Medical University, Guangzhou, PR China
[f] Department of Dermatology, The Jiangmen Wuyi Hospital of Traditional Chinese Medicine, Jiangmen, PR China
[g] Department of Dermatology, The Affiliated Hospital of Shanxi University of Chinese Medicine, Xianyang, PR China
[h] Department of Dermatology, The First Hospital of Changsha, Changsha, PR China
[i] Department of Medical Statistics, School of Public Health, Sun Yat-sen University, Guangzhou, PR China
[j] Guangzhou Evidence-Based Medicine Tech Co. Ltd, Guangzhou, PR China
[k] Department of Dermatology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangdong Provincial Hospital of Chinese Medicine), Guangzhou, PR China
[l] Department of Dermatology, The Third People's Hospital of Shenzhen, Shenzhen, PR China

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ABSTRACT

Background: Herpes zoster (HZ) is a common medical condition accompanied by several distressing symptoms, including acute pain. Pien Tze Huang (PZH) is a well-known traditional Chinese medicine (TCM) with numerous pharmacological effects, including antiviral properties, neuroprotection, and immunity regulation.
Purpose: To investigate the efficacy and safety of PZH capsules in patients with HZ.
Study design: A multicenter, double-blinded, randomized, and placebo-controlled trial from 8 hospitals in 5 cities of China.
Methods: Eligible participants were randomly assigned to the PZH capsule and placebo group at a 1:1 ratio. Treatment was conducted for 14 days with a window period of no more than 2 days. For the first 7 days, participants received antiviral drugs combined with PZH capsules (0.6 g/time, 3 times a day) or placebos. For the remaining 7 days, they were only treated with PZH capsules (0.6 g/time, 3 times a day) or placebos.
Results: We included 222 patients in the full analysis set (FAS), and 187 patients in the per protocol set (PPS). The change of numeric rating scale pain scores from baseline to the seventh day (±1 day) after treatment in the PZH capsule group was statistically superior to the placebo group (FAS: 2.33 *vs.* 1.71, 97.5%*CI*: 0.03 ~ 1.19; PPS: 2.29 *vs.* 1.51, 97.5%*CI*: 0.18 ~ 1.38). In the PPS, there was a significant difference in the time (days) of pain relief between the placebo group and the PZH capsule group (Mean (SD): 5.71 (3.76) *vs.* 4.69 (3.57), $p = 0.046$). On the seventh day (±1 day) after treatment, the level of CD8+ cells in the PZH capsule group were higher than those of the placebo group (FAS: Mean (SD): 24.08 (6.81) *vs.* 21.93 (8.19), $p = 0.007$; PPS: Mean (SD): 24.26 (6.93) *vs.* 22.15 (8.51), $p = 0.012$). The level of cytotoxic lymphocyte cells found similar results on the seventh

Abbreviations: AEs, adverse events; AIDS, acquired immune deficiency syndrome; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CI, confidence intervals; CTL, cytotoxic lymphocyte; FAS, full analysis set; GZMB, granzyme B; HZ, herpes zoster; IL-2, Interleukin-2; IL-6, Interleukin-6; Max, maximum; Min, minimum; NRS, numeric rating scale; NSAIDs, Non-steroidal anti-inflammatory drugs; PHN, postherpetic neuralgia; PPS, per protocol set; PZH, Pien Tze Huang; Q1, lower quartile; Q3, upper quartile; SD, standard deviation; SVV, simian varicella virus; TCM, traditional Chinese medicine; TNF-α, tumor necrosis factor alpha; VZV, varicella-zoster virus.

* Corresponding author.
E-mail address: lihongyi@gzucm.edu.can (H. Li).

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day (±1 day) (FAS: Mean (SD): 12.17 (4.65) *vs.* 10.55 (4.15), $p = 0.018$; PPS: Mean (SD): 12.25 (4.65) *vs.* 10.11 (3.93), $p = 0.002$). No serious adverse events were noted and PZH capsules were well tolerated.
Conclusion: PZH capsules confer therapeutic effects on HZ with the TCM symptom of stagnated heat of liver channel by substantially reducing the pain intensity, shortening the time of pain relief as well as regulating the immune function. On the basis of the efficacy and safety profiles, PZH capsules may be a promising complementary therapy for the treatment of HZ.

Introduction

Herpes zoster (HZ) manifests as a painful rash with a vesicular eruption that does not cross the midline, and healing occurs over approximately 2–4 weeks (Le and Rothberg, 2019). One of the most disturbing symptoms of HZ, burning or stabbing pain, which occurs in the majority of patients throughout the acute stage (He et al., 2022). After the rash has healed, it persists as postherpetic neuralgia (PHN) for an extended period of several months in approximately 20% of patients (Huang et al., 2004; Johnson and Rice, 2014). With an increasing incidence globally, herpes (including HZ) ranks among the top 10 most costly skin diseases according to the healthcare economic burden (Lim et al., 2017).

Currently, the standard treatment of HZ mainly uses antiviral drugs, such as oral valaciclovir and acyclovir. The oral administration of valacyclovir provides the benefit of a three-to fivefold enhancement in acyclovir bioavailability. Both acyclovir and valacyclovir undergo processing into nucleoside analogs, which selectively inhibit viral DNA replication in impacted cells. The objective of HZ vaccines is to thwart the activation of HZ and the occurrence of PHN (Patil et al., 2022). The antiviral treatment period for HZ is generally 7 days, and can be extended to 10 to 14 days in special circumstances. Although antiviral drugs are essential for the treatment of HZ, their relief of accompanying acute pain symptoms is limited. Owing to the efficacy in alleviating pain, non-steroidal anti-inflammatory drugs (NSAIDs) are widely utilized to combined with antiviral drugs in cases of HZ and PHN. In spite of their therapeutic utility, these drugs also come with safety concerns. The rising occurrence of nephrotoxicity associated with antiviral drugs can often be attributed to the combination of potent antiviral medications with potentially toxic drugs in complex patient cases (Leowattana, 2019). Additionally, NSAIDs are notorious for severe side effects, including cardiovascular risks, gastrointestinal toxicities, and hepatotoxicity (Bindu et al., 2020). Consequently, alternative therapeutic strategies for HZ, especially in terms of pain relief, are still largely unexplored (Johnson, 2007).

Chinese medicine has substantial benefits for relieving pain and improving the cure rate of HZ (Jiang et al., 2022; Wu et al., 2022). Pien Tze Huang (PZH), a renowned traditional Chinese medicine (TCM), possesses diverse pharmacological activities, including immunoregulatory, anti-virus, and neuroprotective effects (Huang et al., 2021; Lin et al., 2022; Qiu et al., 2018). Mainly composed of Calculus bovis, Snake gall, Panax notoginseng roots, and Musk, PZH has been used for hundreds of years in Asian countries and recorded as “first grade” nationally protected TCMs in China (Chen, 2021). PZH clears heat-toxin, promotes blood circulation, and relieves pain based on TCM theory (Huang et al., 2019). Lately, dammarane-type triterpenoid saponins, which are the active components derived from Panax notoginseng roots, have demonstrated both anti-inflammatory and antiviral properties (Zheng et al., 2022). Moreover, the Calculus bovis has pharmacological effects in relieving pain and anti-inflammation (Du et al., 2022). Musk can protect against inflammation and immune system disorders (Lv et al., 2022). Hence, PZH capsules maybe beneficial in HZ treatment.

HZ can affect individuals of any age, especially those above 50 years or with suppressed immunity due to pills or diseases. The reactivation of the varicella-zoster virus (VZV) in individuals with compromised immune systems is responsible for the onset of HZ (Cheng et al., 2017). Therefore, the immune function of the patient plays an integral part in resistance to VZV.

To investigate the efficacy and safety of PZH capsules in HZ, we conducted a multicenter, randomized, double-blinded, and placebo-controlled trial. More importantly, we assessed the immune function and inflammatory cytokines to clarify the potential mechanism.

Methods

Study oversight

In this randomized, double-blinded, placebo-controlled, and multicenter clinical trial, we recruited patients with HZ from 8 hospitals in China. The research protocol received approval from the ethics committee of Guangdong Provincial Hospital of Chinese Medicine (BF2018–016–03) and was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered with the Chinese Clinical Trial Registry (www.chictr.org/cn/, NO.ChiCTR-1,800,016,441). All participants signed written informed consent.

Participants

Participants were eligible for inclusion if they:1) aged 18 to 75 years old; 2) diagnosed with HZ according to the criteria of Guidelines for the Treatment of Herpes Zoster in China 3) had TCM syndrome of stagnated heat of liver channel according to the criteria of TCM Diagnostic Criteria for Disease and Syndrome (ZY/T001.1–94); 4) numeric rating scale (NRS) pain scores $\geq$ 4; 5) skin lesions area $\leq$ 2% according to palm method for estimation of burn surface area; 6) HZ on the trunk (including limbs); 7) skin lesions occurred within 72 h; and 8) voluntarily participated in the trial and signed the informed consent form. The diagnosed criteria of HZ and TCM syndrome of stagnated heat of liver channel are listed in Appendix. When our trial was initially designed with skin lesions occurred within 72 h inclusion criterion, we faced challenges due to the limited number of eligible patients, making the experiment difficult to carry out. Therefore, a mid-course protocol amendment was made to change the inclusion criterion to skin lesions occurred within 5 days, and this change was approved through hospital ethics review, specifically on October 18, 2019. The physicians at each hospital were highly qualified and uniformly trained to ensure that the diagnosis was performed smoothly and with consistent diagnostic criteria.

Participants were excluded if they met any of the following criteria: 1) HZ occurred in particular sites (*i.e.*, craniofacial, genital and perianal); 2) skin lesions with pustules, erosions, ulcerations, necroses or serious infections; 3) used medication other than valacyclovir hydrochloride tablets, mecobalamin tablets, acyclovir cream, ibuprofen extended-release capsules, systemic glucocorticoids or immunosuppressive agents for the treatment of HZ within a week before enrollment; 4) had an allergic constitution or were allergic to the experimental medications; 5) had a peptic ulcer, digestive tract hemorrhage, or asthma patients are allergic to aspirin; 6) combined with cancer, acquired immune deficiency syndrome(AIDS), or other serious disease, the liver function (alanine aminotransferase(ALT), aspartate aminotransferase(AST)) exceeding 1.5 times than normal limit, the kidney function (Cr) exceeding the normal limit, or those who suffered from impaired immunity disease; 7) women planning for pregnancy, pregnant or

lactating; 8) participating in other clinical trials currently, or participated in any other clinical treatment within 3 months prior to screening; and 9) considered not suitable for the trial judged by the researchers.

Study medications

The major ingredients of PZH consisted of ginsenoside Rb1, Rg1, Rg3, notoginsenoside R1, cholic acid, hyodeoxycholic acid, chenodeoxycholic acid, sodium taurochenodeoxycholate, deoxycholic acid, ursodesoxycholic acid, muscone, and sodium tauroursodeoxycholate (Huang et al., 2013). PZH capsules (Drug approval number: Z35020242) and placebos were supplied by Zhangzhou Pien Tze Huang Pharmaceutical Co., Ltd (Fujian, China).

Randomization and allocation concealment

This trial used the method of stratified block randomization with the center as the stratified factor, and block randomization was carried out in each center. The patients were randomly assigned in a 1:1 ratio to PZH capsule or placebo group according to random codes generated by the SAS9.4 software (SAS Institute, Cary, North Carolina). The drug blinding was performed by statisticians independent of this trial. The blinding process was recorded in written form and signed by all blinding personnel. The blinding record was sealed and stamped on the spot after the drugs were packed, and one copy was kept by the clinical research unit and the sponsor. The PZH capsules and placebos had no differences in appearance and were packaged identically with a randomization number as the only identifier. The allocation of groups and treatment were concealed from all patients, investigators, outcome assessors, and statisticians.

Intervention

Eligible patients were randomly divided into the PZH capsule or placebo group in a 1:1 ratio. Treatment was conducted for 14 days with a window period of no more than 2 days. For the first 7 days, participants received antiviral drugs combined with PZH capsules (0.6 g/time, 3 times a day) or placebos (0.6 g/time, 3 times a day). The antiviral drugs including valacyclovir hydrochloride tablets (0.3 g/time, twice a day), mecobalamin tablets (0.5 mg/time, three times a day), and acyclovir cream (topical, four times a day). For the remaining 7 days, they were only treated with PZH capsules (0.6 g/time, 3 times a day) or placebos (0.6 g/time, 3 times a day). Ibuprofen sustained-release capsules (0.3 g/time, $\leq$ 2 times a day) were taken as needed when the pain scores were $\geq$ 7 and the patient could not tolerate it.

Outcome measures

The primary outcome was the change in NRS pain scores on the seventh day (±1 day) after treatment compared with that of the baseline. NRS pain scores are the widely used instrument for measuring pain intensity, with scores ranging from 0 (no pain) to 10 (pain as bad as you can imagine) (Giudice et al., 2022).

Secondary outcomes included: 1) evaluation of TCM syndrome; 2) evaluation of clinical efficacy; 3) pain assessment after treatment; 4) the number of analgesics consumed; 5) herpes evaluation; 6) immune function and cytokines; 7) incidence of PHN. More details of each evaluation standard were supplied in the Appendix.

There were 4 visits, specifically at baseline, the fourth day (± 1 day), the seventh day (± 1 day), and the 14th day (± 2 days) after treatment. The evaluation of TCM syndrome, clinical efficacy, and pain assessment were conducted at 4 visits; the number of analgesics consumed and herpes evaluation were assessed at 3 visits, not the baseline; the immune function and cytokines were analyzed at baseline, on the seventh day (± 1 day), and the 14th day (± 2 days). The telephone follow-up visits afterwards were conducted at the fourth week (± 2 days), 12th week (± 2 days), and 24th week (± 2 days) after the end of treatment to evaluate the incidence of PHN.

Safety assessment

The safety indices included the vital signs (body temperature, heart rate, respiration, and blood pressure), blood routine, urine routine, urine pregnancy test, stool routine, stool occult blood, kidney and liver function, as well as electrocardiogram. The safety indices were measured at baseline and after treatment. Any possible adverse symptoms or events, especially skin irritation, were recorded during the whole trial and the causality of adverse events was assessed by the study clinicians.

Sample size calculation

In accordance with the preceding research (Tang, 2016), the mean difference of the change in NRS pain scores on the seventh day after treatment compared with baseline between treatment and control group were 6.8 and 5.3, respectively. The standard deviation (SD) in two groups were 3.7 and 3.4, respectively. According to the ratio of the PZH capsule group: placebo group = 1:1. Set type I error α as 0.025 (one sided), type II error β as 0.2, and the superiority test (Δ) as 0; 89 patients were needed in each group. Considering the dropout rate as 20% and block size, the sample size was calculated as at least 112 patients in each group, and 224 patients in total.

Statistical analysis

All statistical analysis was two-sided (unless specially mentioned) and $p < 0.05$ was considered statistically significant (unless specifically noted). Patients who received at least one treatment and provided evaluable data for effectiveness were included in the full analysis set (FAS). The FAS was the main data set for the efficacy evaluation of primary and secondary outcomes. However, patients with significant protocol deviation were excluded from the per protocol set (PPS). The safety set (SS) included patients who were randomized, had accessible safety evaluation data and received at least one dose of the trial drugs.

Numerical data was presented with mean value, standard deviation (SD), median, minimum (Min) and maximum (Max), and lower quartile (Q1) and upper quartile (Q3). Categorical data was described by the number of cases and percentage. The *t*-test, χ^2 test, Fisher exact test or rank-sum test were used for homogeneity comparison between two groups. SAS9.4 (SAS Institute Inc, North Carolina, USA) was used for statistical analysis.

As for the primary outcome, the consistency among all study centers was evaluated using the general linear model, considering the interaction effects between study centers and groups. If there were no interaction effects, the superiority test would be conducted to compare the primary scores between two groups, including the NRS scores of each center and that at baseline as covariates. The difference was presented with one-sided 97.5% confidence intervals (*CI*).

As for the secondary outcome, the center effect was evaluated using Cochran-Mental-Haenszel (CMH) test and the comparison of homogeneity between study centers was performed using the Breslow-Day test. The effective rate of the two groups was compared by χ^2 test. The difference was presented with 97.5%*CI*.

Results

Patient characteristics

A total of 224 eligible patients were screened from 8 hospitals in 5 cities of China from November 12, 2018 to May 24, 2021. 2 patients were excluded from the study for different reasons: one declined participation, while the other met one exclusion criteria but was

mistakenly enrolled. Therefore, 222 patients were included in the FAS (111 in each group) and 223 patients were included in the SS (112 in the placebo group and 111 in the PZH capsule group). 35 patients were excluded from the PPS for multiple reasons: 2 patients experienced adverse events; 4 patients concomitantly used of other medications for HZ; 17 patients were poor adherence; 6 patients were unwilling to continue;4 patients were lack of efficacy; and 2 patients considerably exceeded the designated window period. Thus, 187 patients were included in the PPS (94 in the placebo group and 93 in the PZH capsule group). The study workflow is presented in Fig. 1.

At baseline, there were 102 males (45.9%) and 120 females (54.1%). The demographic and clinical characteristics of patients in the FAS were comparable between two groups ($p > 0.05$) (Table 1), including the vital signs, sex, age, NRS pain scores, comorbidities/symptoms, previous medical history/complications, TCM syndrome scores, clinical efficacy scores, immune function and cytokines.

Primary outcome

The result of the general linear model showed that there was no interaction between centers and groups. After adjusting the NRS pain scores of centers and baseline, the least square method was used to test for superiority. The results revealed that the change of NRS pain scores from baseline to the seventh day (±1 day) after treatment in the PZH capsule group was statistically superior to the placebo group (FAS: 2.33 *vs.* 1.71, 97.5%*CI*: 0.03 ~ 1.19; PPS: 2.29 *vs.* 1.51, 97.5%*CI*: 0.18 ~ 1.38) (Table 2). Furthermore, the pain scores on the seventh day (±1 day) after treatment of the PZH capsule group was reduced significantly as compared with the placebo group (FAS: Mean (SD): 2.51 (2.15) *vs.* 3.29 (2.43), $p = 0.025$; PPS: Mean (SD): 2.49 (2.10) *vs.* 3.31 (2.30), $p = 0.019$) (Table 2).

Secondary outcomes

Evaluation of TCM syndrome

The results of TCM syndrome evaluation in the FAS and PPS were listed in Tables S1 and S2, respectively. No significant difference was observed in the TCM syndrome scores, TCM efficacy index, and the total effective rate at baseline, on the fourth day (±1 day), the seventh day (±1 day), and 14th day (±2 days) after the treatment ($p > 0.05$) (Tables S1 and S2). The superiority test showed that the total effective rate of PZH capsule group at 4 visits could not be considered superior to placebo group (FAS: 63% *vs.* 57%, 97.5%*CI*: −19%~8%; PPS: 61% *vs.* 55%, 97.5%*CI*: −20%~8%).

Evaluation of clinical efficacy

Tables S1 and S2 summarized the clinical efficacy evaluation in the FAS and PPS collected at 4 visits. No statistically significant difference was found at each visit. Similar results were also found in the clinical efficacy index and total effective rate ($p > 0.05$) (Tables S1 and S2). According to the superiority test, the mean of total effective rate at 4 visits in the PZH capsule group could not be considered higher than that of the placebo group (FAS: 73% *vs.* 71 %, 97.5%*CI*: −14%~10%; PPS: 72% *vs.* 71%, 97.5%*CI*: −14%~12%).

Pain assessment after treatment

In the FAS, no significant difference was detected in the time(days) of pain relief and disappearance between the placebo group and the PZH capsule group (Mean (SD): 5.46(3.67) *vs.* 4.67(3.52), $p = 0.104$; 9.36 (3.46) *vs.* 8.59(3.23), $p = 0.239$) (Table 3).

In the PPS, the difference between the placebo and PZH capsule group in the time (days) of pain relief was significant (Mean (SD): 5.71 (3.76) *vs.* 4.69 (3.57), $p = 0.046$) (Table 3). However, no significant difference was detected in the time (days) of pain disappearance (Mean (SD): 9.58 (3.47) *vs.* 8.61 (3.24), $p = 0.164$) (Table 3).

There was no significant difference in NRS pain scores at baseline, on the fourth day (±1 day) and 14th day (± 2 days) between the two groups in the FAS and PPS ($p > 0.05$) (Table S3). No statistical difference was detected in the change of NRS pain scores from baseline to the fourth day (±1 day) and 14th day (± 2 days) ($p > 0.05$) (Table S3).

Number of analgesics consumed

The consumption of analgesics, the total dosage of analgesics, and daily analgesic consumption did not differ significantly between the two groups at 4 visits in the FAS and PPS ($p > 0.05$) (Tables S1 and S2).

Herpes evaluation

PZH capsule group showed no improvement as compared with the placebo group in the time of blisters beginning to shrivel (days), the time of herpes beginning to scab (days), and the time of all herpes scabbed (days) in the FAS and PPS ($p > 0.05$) (Table S4).

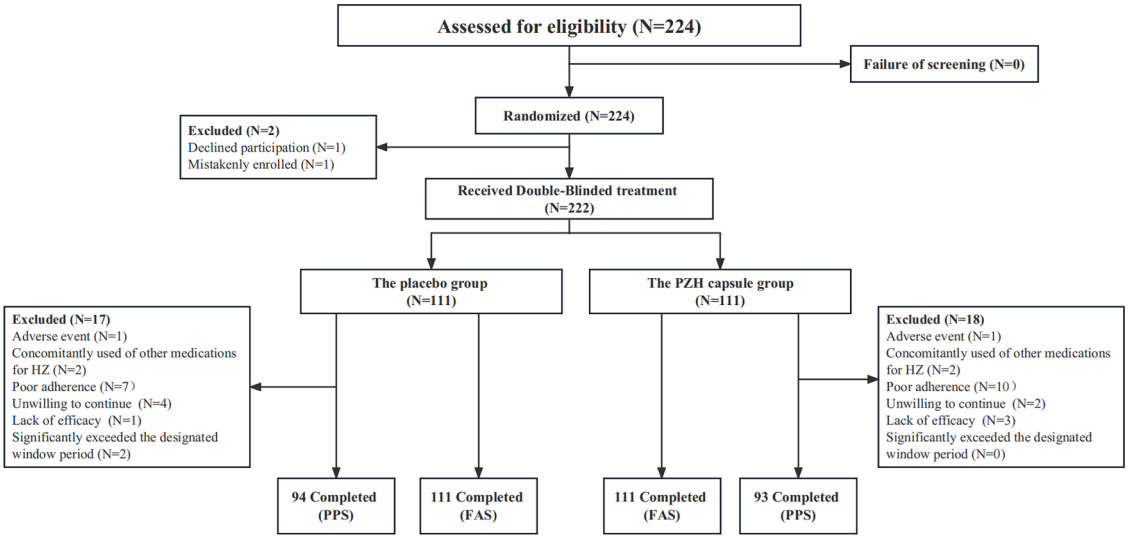

Fig. 1. Study workflow diagram.

Table 1
Baseline demographic and clinical characteristic of patients including in the FAS.

Characteristics	Placebo	N (nmiss)	PZH capsule	N (nmiss)	*p* value
Sex, n (%)		111(0)		111(0)	1.000
Male	51 (45.9)		51 (45.9)		
Female	60 (54.1)		60 (54.1)		
Age in years, median (Q1, Q3)	48.0 (33.0, 59.0)	111(0)	46.0 (31.0, 57.0)	111(0)	0.354
Temperature °C, Mean (SD)	36.4 (0.3)	111(0)	36.4 (0.3)	110(1)	0.789
Systolic blood pressure, mmHg, Mean (SD)	120.6 (15.2)	111(0)	119.8 (14.7)	111(0)	0.592
Diastolic blood pressure, mmHg, Mean (SD)	77.9 (11.5)	111(0)	76.1 (9.4)	111(0)	0.232
Heart rate, bmp, Mean (SD)	77.1 (11.7)	111(0)	76.5 (10.1)	111(0)	0.967
Respiratory rate, bmp, Mean (SD)	19.2 (1.5)	111(0)	19.1 (1.3)	111(0)	0.296
Comorbidities/ symptoms, n (%)		111(0)		109(2)	0.471
Yes	65 (58.6)		69 (63.3)		
No	46 (41.4)		40 (36.7)		
Previous medical history/ complications, n (%)		111(0)		110(1)	0.196
Yes	54 (48.7)		44 (40.0)		
No	57 (51.3)		66 (60.0)		
NRS pain score, Mean (SD)	4.91 (1.09)	111(0)	4.74 (1.06)	111(0)	0.142
TCM syndrome score, Mean (SD)	8.77 (1.79)	111(0)	8.44 (1.71)	110(1)	0.170
Clinical efficacy score, Mean (SD)	15.43 (2.62)	111(0)	15.69 (3.43)	111(0)	0.718
Immune function					
NK cell, Mean (SD)	14.94 (7.60)	111(0)	13.61 (7.35)	111(0)	0.122
CD3+, Mean (SD)	51.97 (13.43)	111(0)	53.76 (11.59)	111(0)	0.502
CD4+, Mean (SD)	25.46 (9.54)	111(0)	27.18 (8.88)	111(0)	0.183
CD8+, Mean (SD)	20.48 (8.64)	111(0)	21.10 (7.39)	111(0)	0.318
CD4+/CD8+ ratio, Mean (SD)	1.49 (0.83)	111(0)	1.49 (0.83)	111(0)	0.987
CD8+CD28+(CTL cell) , Mean(SD)	9.13 (4.34)	111(0)	9.71 (4.37)	110(1)	0.369
CD4+CD25+CD127- (Treg cell) , Mean(SD)	7.35 (2.99)	111(0)	7.26 (3.10)	111(0)	0.594
Cytokines					
IL-6, Mean (SD)	23.51 (3.09)	111(0)	22.98 (3.18)	111(0)	0.207
TNF-α, Mean (SD)	482.90 (58.25)	111(0)	472.20 (59.13)	111(0)	0.176
IL-2, Mean (SD)	996.43 (369.16)	111(0)	998.22 (361.93)	111(0)	0.715

Abbreviations: SD, standard deviation; Q1, lower quartile; Q3, upper quartile; NRS, numeric rating scale; TCM, traditional chinese medicine; IL-6, Interleukin-6; IL-2, Interleukin-2; TNF-α, tumor necrosis factor alpha; NK, natural killer.

Immune function and cytokines

On the seventh day (± 1 day), the level of CD8+ cell in the PZH capsule group was higher than those of the placebo group (FAS: Mean (SD): 24.08 (6.81) *vs.* 21.93 (8.19), $p = 0.007$; PPS: Mean (SD): 24.26 (6.93) *vs.* 22.15 (8.51), $p = 0.012$) (Table 4). The level of cytotoxic lymphocyte (CTL) cell on the seventh day (± 1 day) in the PZH capsule group was higher as compared with the placebo group (FAS: Mean (SD): 12.17 (4.65) *vs.* 10.55 (4.15), $p = 0.018$; PPS: Mean (SD): 12.25 (4.65) *vs.* 10.11 (3.93), $p = 0.002$) (Table 4). Moreover, similar result was detected in the change from baseline to the seventh day (± 1 day) in the PPS (Mean (SD): 2.50 (3.63) *vs.* 1.36 (3.30), $p = 0.036$) (Table 4). On the 14th day (± 2 days), no increase in the level of CD8+ and CTL cells (Table 4). No significant difference between the two groups was observed in other immune cells (NK cells, CD3+, CD4+, CD4 +/CD8 + ratio, Treg cells) and cytokines (IL-6, TNF-α, IL-2) in the FAS and PPS ($p > 0.05$) (Table S5 and S6).

Incidence of PHN

PZH capsules did not decrease the incidence of PHN as compared with placebos in the FAS and PPS at the fourth week (±2 days), 12th week (±2 days), and 24th week (±2 days) after end of treatment ($p > 0.05$) (Table S7).

Safety profile and adverse events

In the SS, a total of 64 adverse events (AEs) were reported in 42 participants and the incidence of AE was 18.8%. No differences between the two groups in the rate of AEs (PZH: 20.7%; Placebo: 17.0%; $p = 0.473$). 14 of the AEs in 7 participants were considered to be related to the treatment with a 3.1% incidence rate (Table 5) and no differences in the rate of AEs (PZH: 3.6%; Placebo: 2.7%; $p = 0.692$). No serious AEs were reported. No significant change in the results of the body temperature, systolic blood pressure, respiration, heart rate, and diastolic blood pressure between the two groups at 4 visits after the treatment ($p > 0.05$). There were no statistical differences in blood, urine, and stool + occult blood examination, as well as corrected Q-T interval and heart rate, at baseline and the 14th day (± 2 days) ($p > 0.05$). No significant difference in liver and kidney function was found between the two groups at baseline ($p > 0.05$). On the 14th day (± 2 days), the levels of ALT, AST, and urea was reduced in PZH capsule group as compared with placebo ($p < 0.05$) (Table S8), but the mean values were within reference ranges and had no clinically meaningful change.

Discussion

The acute pain of HZ is the most distressing symptom, causing a broad impact on physical and emotional function (Katz et al., 2004). Chinese medicine can attenuate pain symptoms in acute HZ as adjuvant therapy (Zhang et al., 2022). To date, this is the first double-blinded, multicenter randomized clinical trial that illustrates the safety and efficacy of PZH capsules, a product of Chinese medicine, in patients with HZ. Overall, the PZH capsule group resulted in a considerably higher change of NRS pain scores from baseline to the seventh day (±1 day) after treatment as compared with that of the placebo group. Moreover, the pain scores after the seventh day (±1 day) treatment of the PZH capsule group was reduced substantially compared with the placebo group. Another promising finding was that PZH capsules combined with antiviral drugs were observed to relieve the pain earlier than when antiviral drugs combined with placebos were used.

Compound PZH ointment combined with valaciclovir in the treatment of HZ effectively alleviated the symptoms, improved the quality of life as well as regulated the levels of pain mediators, such as substance P, prostaglandin E2, and nerve growth factor-induced protein (Zhang and Han, 2021). Furthermore, compound PZH ointment combined with valaciclovir resulted in the time of pain relief earlier than oral valaciclovir (Mean(SD):4.83(0.42) *vs.* 6.35(0.48), $p < 0.05$) , and the present trial demonstrated a similar result in the time of pain relief (4.69 (3.57) *vs.* 5.71 (3.76), $p < 0.05$). Notably, the present study had a lower risk of bias and the result was more convincing through using larger sample sizes, double-blinded, multicenter, and randomization. A study on guinea pig reported that PZH could substantially decrease the acetic acid-induced writhing response, showing an analgesic effect (Li et al., 2019). Muscone, a key component of PZH, alleviates inflammatory pain by suppressing microglial activation-induced inflammatory responses. This suppression occurs through the inhibition of the NLRP3 inflammasome and the NOX4/JAK2-STAT3 pathway (Yu et al., 2020). Ginsenoside Rg3, an active compound of PZH, has also been reported central and peripheral analgesic effects via modulating pain-related amino acids and inflammatory factors (Sun et al., 2019).

Table 2
Primary outcome: The change of NRS pain score from baseline to the seventh day after treatment.

Visits	Baseline		The seventh day (±1 day)		Change from baseline to the seventh day (±1 day)		*Change from baseline to the seventh day (±1 day)	
	Placebo	PZH capsule	Placebo	PZH capsule	Placebo	PZH capsule	Placebo	PZH capsule
In the FAS								
N(nmiss)	111 (0)	111 (0)	106 (5)	102 (9)	106 (5)	102 (9)		
Mean(SD)	4.91 (1.09)	4.74 (1.06)	3.29 (2.43)	2.51 (2.15)	1.62 (2.23)	2.24 (2.19)	1.71	2.33
Median (Q1,Q3)	5.00 (4.00, 5.00)	4.00 (4.00, 5.00)	3.00 (1.00, 5.00)	2.00 (1.00, 4.00)	2.00 (0.00, 4.00)	3.00 (1.00, 4.00)		
Min, Max	4.00, 8.00	4.00, 9.00	0.00, 9.00	0.00, 8.00	−3.00, 6.00	−3.00, 7.00		
p value	0.142		0.025		0.065			
97.5 %*CI*							0.03 ~ 1.19	
In the PPS								
N(nmiss)	94 (0)	93 (0)	94 (0)	92 (1)	94 (0)	92 (1)		
Mean(SD)	4.82 (1.04)	4.77 (1.10)	3.31 (2.30)	2.49 (2.10)	1.51 (2.18)	2.29 (2.12)	1.51	2.29
Median (Q1,Q3)	5.00 (4.00, 5.00)	4.00 (4.00, 5.00)	3.00 (2.00, 5.00)	2.00 (1.00, 4.00)	2.00 (0.00, 3.00)	3.00 (1.00, 4.00)		
Min, Max	4.00, 8.00	4.00, 9.00	0.00, 7.00	0.00, 8.00	−3.00, 5.00	−3.00, 7.00		
p value	0.494		0.019		0.025			
97.5 %*CI*							0.18 ~1.38	

*The results were adjusted for center and NRS pain scores baseline using least squares method.
Abbreviations: FAS, full analysis set; PPS, per protocol set; PZH, Pien Tze Huang; NRS, numeric rating scale; *CI*, confidence intervals.

Table 3
The time(days) of pain relief and disappearance.

Data sets	In the FAS		In the PPS	
	Placebo	PZH capsule	Placebo	PZH capsule
The time(days) of pain relief				
N(nmiss)	94 (17)	98 (13)	84 (10)	90 (3)
Mean(SD)	5.46 (3.67)	4.67 (3.52)	5.71 (3.76)	4.69 (3.57)
Median (Q1, Q3)	4.00(3.00, 8.00)	4.00(2.00, 6.00)	4.00(3.00, 9.00)	4.00 (2.00, 6.00)
Min, Max	1.00, 17.00	0.00, 15.00	1.00, 17.00	1.00, 15.00
p value	0.104		0.046	
The time(days) of pain disappearance				
N(nmiss)	50 (61)	56 (55)	43 (51)	51 (42)
Mean(SD)	9.36 (3.46)	8.59 (3.23)	9.58 (3.47)	8.61 (3.24)
Median (Q1, Q3)	10.00(7.00, 12.00)	8.50(6.00, 11.50)	10.00(7.00, 12.00)	9.00 (6.00, 12.00)
Min, Max	2.00, 17.00	2.00, 15.00	2.00, 17.00	2.00, 15.00
p value	0.239		0.164	

Abbreviations: SD, standard deviation; Q1, lower quartile; Q3, upper quartile; FAS, full analysis set; PPS, per protocol set; PZH, Pien Tze Huang;.

HZ results from the reactivation of VZV when the immunity of individuals is decreased. Consequently, the regulation of immune function is of great importance for HZ treatment. Our results demonstrated that the level of CD8+ and CTL cells on the seventh day (±1 day) in the PZH capsule group were considerably higher than those of the placebo group. The immune system plays a vital role in the context of VZV infection. T cell-mediated responses are crucial in host defense against VZV. The onset of HZ is related to a decrease in VZV-specific T cell-mediated immunity (Asada, 2019). VZV-specific T cell-mediated immune response demonstrates a substantial negative correlation with the incidence and severity of HZ, as well as acute pain and the risk of developing PHN (Weinberg and Levin, 2010). The reactivation of subclinical simian varicella virus (SVV), the counterpart of human VZV, in rhesus monkeys with thymectomy and depletion of CD8+ *T* cells (Arnold et al., 2017; Traina-Dorge et al., 2019). Additionally, the rate of CD8+ was negatively correlated with pain scores in HZ (Zhao et al., 2021). CTL cells also showed a potential role in VZV-infection. Typically, the CTLs can directly secrete granzyme B (GZMB) and perforin to kill the virus-infected target cell (Gerada et al., 2019). In the case of VZV infection, CTL cells were detected within the ganglia of patients afflicted with HZ (Gowrishankar et al., 2010). Furthermore, CTL cells that expressed GZMB were found in close proximity to VZV-infected dorsal root neurons (Steain et al., 2014). In summary, these discoveries implied that the PZH capsules can relieve the pain of patients with HZ through regulating the immune function, especially the level of CD8+ and CTL cells.

It is widely acknowledged that the core principle of TCM, which involves syndrome differentiation and treatment, is pivotal in clinical practice to achieve its optimal therapeutic outcomes (Cheng et al., 2017) . The efficacy of PZH capsules is grounded in this fundamental therapeutic principle. According to TCM theory, PZH exerts its effects by clearing heat-toxins, promoting blood circulation and relieving pain (Huang et al., 2019) . Patients enrolled for this trial had HZ and a diagnostic syndrome of stagnated heat of liver channel confirmed by the nationally accepted criteria. Hence, this trial was consistent with the principles of TCM theory, making our findings applicable for daily clinical practice of Chinese medicine.

In this study, we included patients from 18 to 75 years old, and more than half of them had comorbidities. One critical aspect of PZH capsules was their safety profiles. This study demonstrated that the incidence of AEs was similar between the two groups. Correspondently, no severe adverse events were found, supporting the fact that the PZH capsules exhibited an excellent safety profile for the treatment of HZ.

However, the study design also had limitations. The trial was conducted across 8 hospitals in China, and it remains uncertain whether these findings can be extrapolated to different regions or populations. Further research is needed to identify the optimal therapeutic dose and treatment duration in order to elicit substantial change in evaluation of clinical efficacy and the incidence of PHN.

Conclusion

PZH capsules confer therapeutic effects on HZ with the TCM symptom of stagnated heat of liver channel by considerably reducing the pain intensity, shortening the time of pain relief, as well as regulating the immune function. On the basis of the efficacy and safety profiles, PZH capsules may be a promising complementary therapy for the treatment of HZ.

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CRediT authorship contribution statement

Wenfeng Wu: Writing – original draft, Visualization, Investigation. **Dingquan Yang:** Supervision, Investigation. **Daoshun Sui:** Supervision, Investigation. **Minghua Zhu:** Supervision, Investigation. **Guangpu Luo:**

Table 4
The level of CD8+ cells and CD8+CD28+ (CTL) cells between two groups.

Visits	Baseline		The seventh day (±1 day)		Change from baseline to the seventh day (±1 day)		The 14th day (±2 days)		Change from baseline to the 14th day (±2 days)	
	Placebo	PZH capsule	Placebo	PZH capsule	Placebo	PZH capsule	Placebo	PZH capsule	Placebo	PZH capsule
In the FAS CD8+ cells										
N(nmiss)	111 (0)	111 (0)	104 (7)	104 (7)	104 (7)	104 (7)	102 (9)	101 (10)	102 (9)	101 (10)
Mean(SD)	20.48 (8.64)	21.10 (7.39)	21.93 (8.19)	24.08 (6.81)	−0.20 (0.81)	−0.28 (0.61)	22.02 (7.85)	23.33 (7.40)	−0.17 (0.82)	−0.17 (0.64)
Median (Q1,Q3)	20.20 (14.15, 24.50)	21.00 (15.41, 26.51)	20.73 (16.60, 26.22)	23.42 (19.51, 29.08)	−0.08 (−0.48, 0.13)	−0.17 (−0.54, 0.07)	21.38 (16.23, 26.51)	21.90 (18.41, 28.20)	−0.16 (−0.46, 0.09)	−0.14 (−0.39, 0.09)
Min, Max	3.25, 52.43	7.15, 40.60	2.04, 55.91	7.82, 48.50	−3.37, 4.17	−2.64, 1.48	5.43, 49.50	3.32, 44.28	−2.62, 3.86	−2.85, 3.16
p value	0.318		0.007		0.408		0.187		0.736	
CD8+CD28+ (CTL) cells										
N(nmiss)	111 (0)	110 (1)	104 (7)	103 (8)	104 (7)	104 (7)	102 (9)	100 (11)	102 (9)	101 (10)
Mean(SD)	9.13 (4.34)	9.71 (4.37)	10.55 (4.15)	12.17 (4.65)	−0.94 (2.19)	−0.61 (2.54)	10.49 (4.51)	11.31 (4.78)	−0.66 (2.03)	−0.80 (2.92)
Median (Q1,Q3)	8.64(6.14, 11.67)	8.76(6.52, 12.90)	10.20(7.69, 13.23)	11.27(9.17, 14.81)	−1.00 (−1.98, 0.30)	−0.70 (−2.00, 0.70)	10.20(7.69, 13.23)	11.27(9.17, 14.81)	−0.51 (−1.67, 0.41)	−0.72 (−1.89, 0.65)
Min, Max	0.79, 24.77	0.33, 21.80	1.25, 20.93	5.08, 27.07	−8.11, 8.00	−10.77, 8.52	2.55, 25.68	3.30, 24.80	−6.69, 4.56	−15.27, 8.58
p value	0.369		0.018		0.315		0.288		0.807	
In the PPS CD8+ cells										
N(nmiss)	94 (0)	93 (0)	92 (2)	93 (0)	92 (2)	93 (0)	94 (0)	92 (1)	94 (0)	92 (1)
Mean(SD)	20.36 (9.03)	21.13 (7.71)	22.15 (8.51)	24.26 (6.93)	1.83 (6.62)	3.13 (6.40)	22.26 (8.01)	23.25 (7.22)	1.91 (7.77)	2.04 (6.92)
Median (Q1,Q3)	19.48 (14.03, 24.50)	21.35 (15.41, 26.67)	21.02 (16.04, 26.77)	23.95 (19.70, 29.18)	1.35 (−1.16, 5.39)	2.70 (0.20, 6.24)	21.71 (16.23, 26.60)	21.95 (18.46, 28.66)	2.26 (−0.62, 6.24)	1.75 (−1.47, 5.20)
Min, Max	3.25, 52.43	7.15, 40.60	2.04, 55.91	7.82, 48.50	−28.86, 22.56	−23.52, 18.28	5.43, 49.50	3.32, 44.28	−38.82, 21.58	−28.61, 22.67
p value	0.283		0.012		0.136		0.286		0.508	
CD8+CD28+ (CTL cells)										
N(nmiss)	94 (0)	92 (1)	92 (2)	92 (1)	92 (2)	92 (1)	94 (0)	91 (2)	94 (0)	91 (2)
Mean(SD)	8.69 (3.99)	9.75 (4.38)	10.11 (3.93)	12.25 (4.65)	1.36 (3.30)	2.50 (3.63)	10.24 (4.22)	11.34 (4.71)	1.55 (3.40)	1.57 (3.61)
Median (Q1,Q3)	8.30(6.04, 10.74)	8.79(6.08, 13.00)	9.44(7.24, 12.08)	11.35(9.26, 14.84)	1.36 (−0.51, 3.30)	2.17 (0.38, 4.88)	9.67 (7.10, 13.16)	10.41 (7.82, 14.60)	1.39 (−0.28, 3.33)	1.16 (−0.40, 2.52)
Min, Max	0.79, 20.68	0.33, 21.45	1.25, 19.29	5.08, 27.07	−7.67, 10.26	−7.50, 14.32	2.55, 19.95	3.30, 24.29	−8.02, 13.60	−6.87, 13.33
p value	0.149		0.002		0.036		0.170		0.552	

Abbreviations: SD, standard deviation; Q1, lower quartile; Q3, upper quartile; FAS, full analysis set; PPS, per protocol set; PZH, Pien Tze Huang;CTL,cytotoxic lymphocyte.

Table 5
Adverse events associated with the treatment in the safety set.

Type of adverse event	Placebo (No. of Cases)	PZH capsule (No. of Cases)
Mild abdominal distension	1	1
Chest distress	1	0
Tachycardia	2	0
Tachypnea	2	0
Cough	1	0
Diarrhea	1	1
Abdominal pain	1	1
Dry and astringent mouth	0	1
Skin allergy	0	1
Total	9	5

Abbreviations: PZH, Pien Tze Huang.

Supervision, Investigation. **Zhonghui Yang:** Supervision, Investigation. **Yongfeng Wang:** Supervision, Investigation. **Hong Luo:** Supervision, Investigation. **Li Ling:** Formal analysis. **Zexin Zhang:** Writing – review & editing. **Yanmei Wu:** Supervision, Project administration. **Guoming Feng:** Supervision, Project administration. **Hongyi Li:** Supervision, Methodology, Investigation, Conceptualization, Writing – review & editing.

Declaration of competing interest

We declare that we have no conflicts of interest associated with this publication. The medications were supplied by Zhangzhou Pien Tze Huang Pharmaceutical Co.,Ltd (Fujian, China), however Zhangzhou Pien Tze Huang Pharmaceutical was not involved in any aspect of this study including study design, collection, data analysis, interpretation of results, and manuscript preparation.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2024.155453.

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