Clinical Research on the Effect of Salvia Miltiorrhiza Injection into Jiaji Points and Its Influence on Postherpetic Neuralgia Incidence

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Abstract: Objective: To determine whether Huatuo Jiaji point injection with *Salvia miltiorrhiza (SM)* for acute herpes zoster (AHZ) would reduce pain and incidence of PHN. Methods: 105 patients over 50 years old were randomized to receive Huatuo Jiaji Point acupuncture (Group A, n=35) or Huatuo Jiaji Point Injection of either saline (Group B, n=35) or *SM* (Group PI, n=35). The treatment was started at patient's first visit and performed twice every 7 days for 3 weeks. VAS and analgesics were recorded at the initial visit (basal), the 7th, 14th, 28th, 90th, 180th day after injection. PHN was identified using the DN4 Questions on the 90th, 180th day after onset. Patient's satisfaction evaluated by SF-36 was also recorded 90th, 180th day after onset. The levels of beta-endorphin in peripheral blood were measured before treatment and 90 and 180 days after treatment. Results: The VAS scores in Group PI were lower than that in Group A and B throughout the study period. The Group PI displayed a significantly lower incidence of PHN than Group A and B after 90 days and 180 days. According to SF-36 index scores, the magnitude of improvement was significantly greater in Group PI than that at Group A and B after 90 and 180 days. The plasma beta-endorphin in PI group were higher than those in Group A and B at 90 and 180 days after treatment. Conclusion: Huatuo Jiaji PI with SM can quickly relieve HZ-related pain, reduce incidence of PHN and improve quality of patients' life.

Keywords: Huatuo Jiaji Points; *Salvia miltiorrhiza*; Herpes Zoster; Post-herpetic Neuralgia; Prevention

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1 Introduction

Acute Herpes zoster (AHZ), also known as shingles, is a common disease characterized by a painful blistering skin eruption in a dermatomal distribution that is caused by reactivation of a latent varicella zoster virus (VZV) within the dorsal root or cranial nerve ganglia. Postherpetic neuralgia (PHN) refers to a chronic pain syndrome that persists after the skin lesion subsides. The American Academy of Neurology (AAN) defines PHN as pain after the skin lesion subsides for more than three months. PHN is a neuropathic pain, the most common and refractory complication of HZ. It could last for a few months, or several years, even for a lifetime [1]. The risk of developing into PHN increases with age. The incidence of

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PHN among the HZ patients aged 60 and over is more than 65%, and it would rise up to 75% among the patients ages 70 and over. PHN has a substantial effect on the quality of life; many patients develop severe physical, occupational, social, and psychosocial disabilities as a result of the unceasing pain [2, 3]. In recent years, scholars have made relevant research on the treatment of PHN. Drug therapy, nerve block, and acupuncture are the main treatments of PHN. But so far, there is no ideal method to cure PHN effectively, which can only relieve pain. How to treat PHN effectively is still a serious challenge. A number of trails indicated that early intervention is crucial to reduce the incidence of PHN. However, up till now, there is no disease-modifying therapy available in this area. In description of Traditional Chinese Medicine (TCM), this disease is mostly due to incomplete heat and damp clearing in liver and spleen meridians, qi and toxic pathogens stagnation, accumulation of yin (blood stagnation in microcapillary), internal fire, and heat and obstruction of meridians [4]. Point injection (PI) works based on the eradication of wind, clearing of heat, and destroying of damp by regulating qi and blood movement [5]. Several points, such as Huatuo Jiaji point, have been used in treatment of PHN. Salvia Miltiorrhiza (SM) is a Chinese medicinal herb with diverse pharmacological property to improve circulation and stasis. However, whether application of SM to Huatuo Jiaji point has a potential to prevent PHN, hasn't been studied. Therefore, we designed this randomized, double-blinded trail to determine whether early Huatuo Jiaji PI with *SM* for AHZ would reduce pain and incidence of PHN.

2 Materials and Methods

2.1 Study Design

This double-blind randomized clinical trial was conducted in the Pain Clinic of Shanghai Ruijin Hospital Luwan Brunch from February 2018 to February 2021. The study was approved by the Ethics Committee of Ruijin Hospital Luwan Branch, Shanghai Jiao Tong University School of Medicine. A written informed consent was obtained from each participant.

2.2 Inclusion Criteria and Exclusion Criteria

Inclusion criteria included patients (1) who had a herpetic eruption of less than 1 week; (2) VAS >3; (3) aged over 50 years; and (4) without any other treatments except appropriate antiviral therapy. Exclusion criteria included patients with (1) rash localized on face and head; (2) an eruption of more than 1 week duration; (3) infection at the site of injection; (4) a history of renal or hepatic diseases or coagulopathy, diabetes, and patients with malignancies; (5) patients with any diagnosed immune dysfunction.

2.3 Sample Size Calculation

The sample size calculation was determined assuming that the expected incidence of PHN in patients above 50 years old in the control group was 20%, according to a previous study by Lapolla et al. on the "Incidence of postherpetic neuralgia after combination treatment with Gabapentin and valacyclovir in patients with acute herpes zoster: open-label study" [6]. Our aim was to lower the incidence to less than 5% at a 95% confidence interval (CI) and power of study 80% ($\alpha = 0.05$, $\beta = 0.1$). A calculated sample size of 32 patients in each group was needed. Allowing for 10% loss of follow-up, 105 patients were included.

2.4 Procedure

In the first pain clinic visit, after analyzing the medical history and going through clinical examination, we explained the study procedures (injections and follow-up) for the patient and then written, informed consent was obtained. Pain duration, severity and localization of the rash, and quality of life (QoL, measured by the Medical Outcomes Study Short-Form 36) were recorded. The time of the first injection (the day on which the patient received the first Jiaji point injection in relation to appearance of the rash and confirmation of the diagnosis of acute herpes zoster) was recorded. The patients were randomly assigned using a computer-generated random number assignment to different groups. The patients in Group A received Huatuo Jiaji point acupuncture. The patients in Group B received Huatuo Jiaji PI with saline. The patients in Group PI received Huatuo Jiaji PI with *SM*.

Huatuo Jiaji points locate at half an inch (1.3 cm) apart from the lower spinous process of spine and at the vertebral level. Appropriate points must be selected corresponding to the location of the involved dermatomal of herpes zoster (plus 1-2 dermatomes above and below the vertebral level of lesion) [4-7]. After local disinfection, a No. 7 puncture tip was pierced vertically from skin until the needlepoint reached lamina (depth is about 3-4 cm). Then the patient feels acid, numbness and distension.

Confirmed the tip was not in the blood vessel, inject medicine or saline. Medicine was prepared with 4 ml *SM* diluted to 20 ml with normal saline. 1-3 ml was injected at each point with a total of no more than 20 ml. Medicine was prepared with 4 ml *SM* diluted to 20 ml with normal saline. 1-3 ml was injected at each point with a total of no more than 20 ml. The treatment was started at patient's first visit and performed twice every 7 days for 3 weeks. All patients received 300mg valacyclovir one time daily for 7 days (initially within 72h of the onset of symptoms) and gabapentin initially in a dose of 300 mg three times daily that would be gradually increased to a maximum of 1800 mg/day. Tramadol was available as needed. Once a patient reported mild pain (VAS ≤ 3), 300mg Gabapentin was reduced every other day provided the pain score remained less than 3 with each reduction. All patients received 1000 mg caplets of valacyclovir three times daily for 7 days (initially within 72h of the onset of symptoms) and gabapentin initially in a dose of 300 mg three times daily that would be gradually increased to a maximum of 1800 mg/day.

2.5 Assessments

Pain VAS: VAS evaluated for the severity of zoster-associated pain (ZAP). 10 was the severest, 0 was no pain, 3 or less was mild pain, 4 to 6 was moderate pain, 7 or higher was severe pain. VAS evaluations were made at the initial visit (basal), the 7^{th}, 14^{th}, 28^{th}, 90^{th}, 180^{th} day after injection (approximately 8-10 AM each day).

The incidence of PHN: Patients were assessed changes in neuropathic pain according to the changes from baseline to the end of the study in the Douleur Neuropathique in 4 Questions (DN4 questionnaire). This scale includes the items, with "yes" response scored as 1, and is subdivided into descriptors (seven items) and signs relating to the sensory examination (three items). A score above 4 indicates neuropathic pain. This questionnaire has been validated previously [8-10]. PHN was identified using the DN4 questionnaire on the 90^{th}, 180^{th} day after onset.

Total dosage of medication: At each assessment visit, the amount of on-request analgesia and Gabapentin used was recorded. Once a patient reported mild pain (VAS ≤ 3), 300mg Gabapentin was reduced every other day provided the pain score remained less than 3 with each reduction.

Quality of life: The Medical Outcomes Study Short-Form 36 (SF-36) [11] is a 36-item self-report survey containing eight subscales designed to assess general health-related quality of life (HRQL): physical functional (PF: 10 items), role physical (RP: 4 items), bodily pain (BP; 2 items), general health (GH: 5 items), vitality (VT, 4 items), social functioning (SF, 2 items), role emotional (RE, 3 items), and mental health (MH, 5 items). The scores for the 8 scales ranged from 0 (worst QoL) to 100 (best QoL). The remaining category concerns the experience of change in general health during the previous years. SF-36 scores were assessed prior to the treatment and at 90^{th}, 180^{th} day after rash onset. (Table 7)

The levels of beta-endorphin in peripheral blood: The levels of beta-endorphin in peripheral blood were measured before treatment and 90 and 180 days after treatment.

Side effects: Every reported adverse event would be recorded, including type of event, time of onset, duration, and severity.

2.6 Ethical Statement

Permission to conduct this study was obtained from the Ethics Committee of the Shanghai Ruijin Hospital Luwan Brunch (LWEC201608).

2.7 Statistical Analysis

A statistical analysis was carried out using SPSS version 16 (SPSS Inc., Chicago, IL). The descriptions of data were done in the form of mean (+/-) standard error for quantitative data. Data analysis was done to test statistically significant differences between the groups. For quantitative data, Student's t-test was used to compare the 2 groups. For qualitative data, chi-square test was used. *P* value was considered significant if ≤ 0.05 at 95% CI.

3. Results

182 patients with pain and diagnosis of AHZ were assessed for eligibility. 75 patients did not meet the criteria to enter the study, and 2 patients declined to participate in the study. A total of 105 adult patients were randomly assigned into three groups (with 35 in each). 3 patients in Group A, 4 patients in Group B and 4 patients in Group PI were excluded from the study because they were unavailable for follow up (Figure 1). The baseline demographic characteristics weren't significantly different between the three groups (P>0.05) (Table 1).

Pain VAS: Regarding the severity of pain, the VAS scores in three groups were all significantly reduction at follow-up time points (*P*<0.01), while the VAS scores in

Group PI were lower than that in the Group A and Group B throughout the study period (P<0.01). There were no significant difference between group A and group B *(P*>0.05) (Table 2).

Table 1 Demographic data comparison of three groups (mean ± SE) and (%)

Groups	Group A	Group B	Group PI
Age (years)	66.0±2.56	67.5±2.16	67.3±1.55
Sex (male/ female)	18/15	16/15	14/17
Duration of pain after rash onset (days)	3.84±0.37	3.72±0.29	3.61±0.31
VAS (min)	7.65±0.17	7.87±0.15	7.51±0.20
Localization			
Cervical region	6 (10%)	7 (23%)	7 (23%)
Thoracic region	17 (55%)	16 (52%)	15 (48%)
Lumbar region	9 (35%)	8 (25%)	9 (29%)

Notes: Group A: Jiaji Point Acupuncture. Group B: Jiaji Point Injection using saline. Group PI: Jiaji Point Injection using *Salvia miltiorrhiza*.

Table 2 Pain VAS before and after treatment of three groups (mean ± SE)

	A (32)	B (31)	PI (31)	F	P
Basal	7.65±0.17	7.87±0.15	7.51±0.20	1.043	0.357
7d	3.68±0.24$^{\#}$	3.81±0.16$^{\#}$	2.97±0.09$^{\#}$*	6.571	0.002*
14d	2.72±0.14$^{\#}$	2.39±0.13$^{\#}$	2.0±0.66$^{\#}$*	9.797	0.000*
28d	2.28±0.25$^{\#}$	2.32±0.18$^{\#}$	0.71±0.12$^{\#}$*	23.129	0.000*
90d	2.06±0.21$^{\#}$	2.19±0.18$^{\#}$	0.65±0.11$^{\#}$*	24.914	0.000*
180d	2.13±0.22$^{\#}$	2.19±0.18$^{\#}$	0.74±0.11$^{\#}$*	21.535	0.000*
F	108.293	190.077	468.764		
P	<0.001	<0.001	<0.001		

Notes: Group A: Jiaji Point Acupuncture. Group B: Jiaji Point Injection using saline. Group PI: Jiaji Point Injection using *Salvia miltiorrhiza*.
*P<0.001 vs. Group A and Group B. $^{\#}P$<0.001 vs. Pre-treatment

The incidence of PHN: The Group PI displayed a significantly lower incidence of PHN than Group A and Group B after 90days (6.45% vs 18.75% vs 19.35%, P< 0.05) and 180days (3.23% vs 15.63% vs 16.13%, *P*< 0.05) (Table 3).

Table 3 Incidence of PHN at various time points

	90 days	180 days
A (32)	6/32 (18.75%)$^{\#}$	5/32 (15.63%)$^{\#}$
B (31)	6/31 (19.35%)$^{\#}$	5/31 (16.13%)$^{\#}$
PI (31)	2/31 (6.45%)*	1/31 (3.23%)*

Notes: Group A: Jiaji Point Acupuncture. Group B: Jiaji Point Injection using saline. Group PI: Jiaji Point Injection using *Salvia miltiorrhiza*.
*P<0.001 Group PI vs. Group A and Group B. $^{\#}P$>0.05 Group A vs. Group B

Medication consumption: Concerning the medication consumption per week, there was less consumption of Gabapentin and Tramadol in 3 groups since the third week (P < 0.05). There was a significant reduction in the dose of Gabapentin and Tramadol taken by Group PI, compared with Group A and Group B (P < 0.05) (Tables 4, 5).

Table 4 Gabapentin dose in mg/week in the studied group (mean ± SE)

	A (32)	B (31)	PI (31)	F	P
7d	5400±0.0	5400±0.0	5400±0.0		
14d	5400±0.0	5400±0.0	5400±0.0		
28d	3571±232$^{\#}$	3280±300$^{\#}$	784±251$^{\#}$*	34.074	<0.001*
90d	1893±334$^{\#}$	1790±365$^{\#}$	271±188$^{\#}$*	8.760	<0.001*
180d	1106±366$^{\#}$	1209±363$^{\#}$	135±94$^{\#}$*	3.769	0.027
F	64.877	54.179	352.354		
P	<0.001	<0.001	<0.001		

Notes: Group A: Jiaji Point Acupuncture. Group B: Jiaji Point Injection using saline. Group PI: Jiaji Point Injection using *Salvia miltiorrhiza*.
*P<0.001 Group PI vs. Group A and Group B. $^{\#}P$<0.001 Intra-group

Table 5 Tramadol dose in mg/week in the studied group (mean ± SE)

	A (32)	B (31)	PI (31)	F	P
7d	1138±61	1152±61	768±82*	10.037	<0.001*
14d	613±69$^{\#}$	531±78$^{\#}$	23±23$^{\#}$*	27.057	<0.001*
28d	306±60$^{\#}$	135±42$^{\#}$	11±11$^{\#}$*	11.727	<0.001*
90d	55±28$^{\#}$	45±27$^{\#}$	0±0$^{\#}$	1.694	0.190
180d	33±24$^{\#}$	23±23$^{\#}$	0±0$^{\#}$	0.764	0.469
F	79.139	89.930	78.667		
P	0.000	0.000	0.000		

Notes: Group A: Jiaji Point Acupuncture. Group B: Jiaji Point Injection using saline. Group PI: Jiaji Point Injection using *Salvia miltiorrhiza*.
*P<0.001 Group PI vs. Group A and Group B. $^{\#}P$<0.001 Intra-group

Quality of life: According to SF-36 index scores, the magnitude of improvement was significantly greater in Group PI than that observed following treatment at Group A and B after 90 and 180 days (P < 0.05) (Figure 2).

Table 6 β-EP before and after treatment of three groups (mean ± SE, ng/L)

	Basal	90D	180D	F	P
A (32)	30.26±0.98	39.94±1.16$^{\#}$	41.25±1.12$^{\#}$	30.494	0.000
B (31)	31.23±0.94	41.26±1.12$^{\#}$	42.28±1.14$^{\#}$	30.560	0.000
PI (31)	31.45±1.0	49.50±1.54$^{\#}$*	50.38±1.51$^{\#}$*	60.557	0.000
F	.422	16.258	15.505		
P	.657	0.000	0.000		

Notes: Group A: Jiaji Point Acupuncture. Group B: Jiaji Point Injection using saline. Group PI: Jiaji Point Injection using *Salvia miltiorrhiza*.
*P<0.001 Group PI vs. Group A and Group B. $^{\#}P$<0.001 vs. Pre-treatment

The levels of beta-endorphin in peripheral blood: The plasma levels of beta-endorphin in PI group were higher than those in Group A and B ($P < 0.05$) at 90 and 180 days after treatment ($P < 0.05$) (Table 6).

No serious adverse effects were reported during the study period. The side effects of dizziness, sleepiness and nausea in PI group were significantly less than those in group A and B. After adjusting the oral dosage, the patient's symptoms improved without further treatment (Table 7).

Table 7 side effects in 3 groups (%)

	Dizzy	Drowsiness	Nausea
A (32)	5 (15.6%)	5 (15.6%)	3 (9.4%)
B (31)	6 (19.4%)	5 (16.1%)	3 (9.7%)
PI (31)	2 (6.5%)*	1 (3.2%)*	0 (0%)*

Notes: Group A: Jiaji Point Acupuncture. Group B: Jiaji Point Injection using saline. Group PI: Jiaji Point Injection using *Salvia miltiorrhiza*.
*P<0.05 Group PI vs. Group A and Group B.

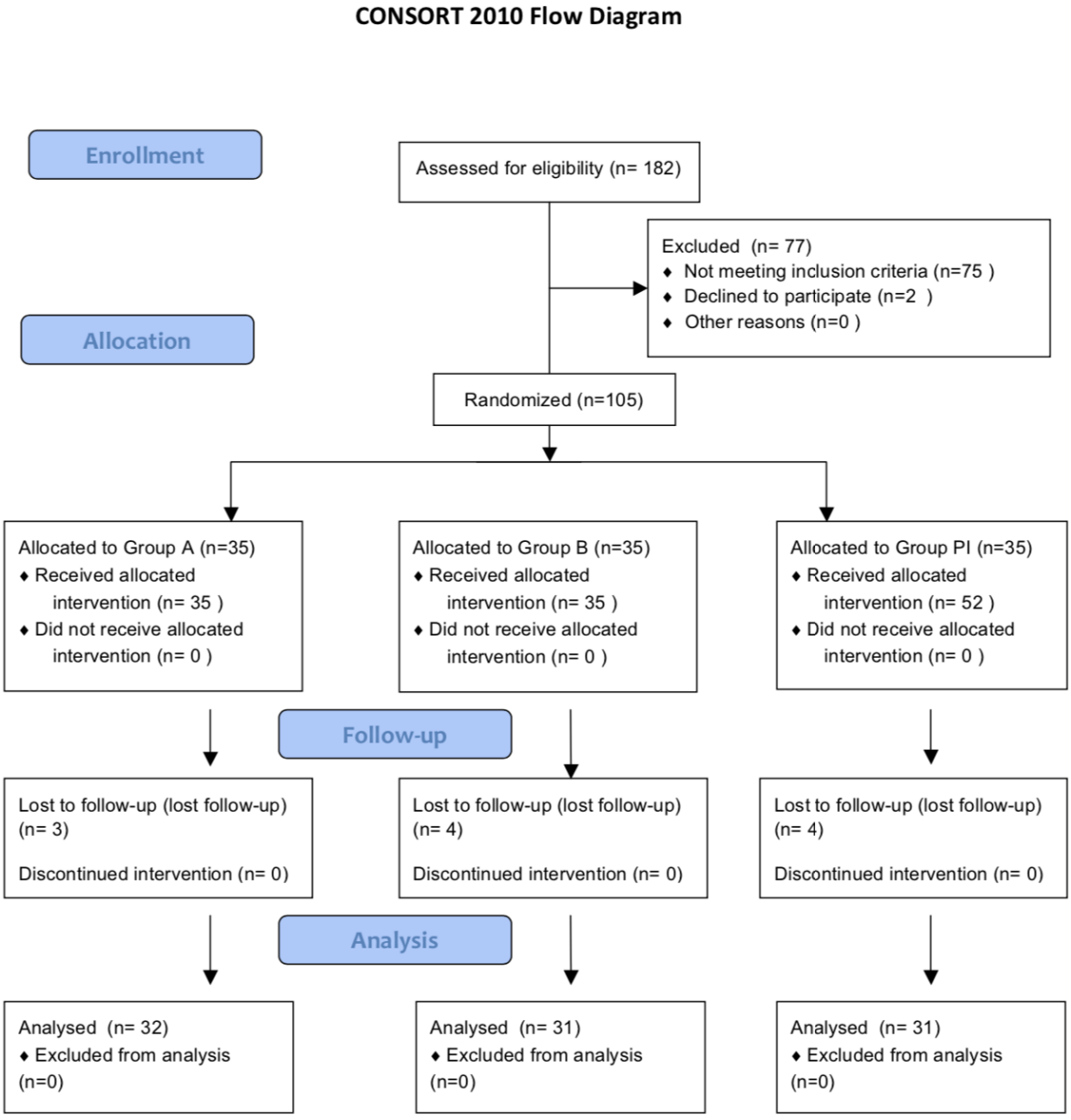

Figure 1 Flow diagram

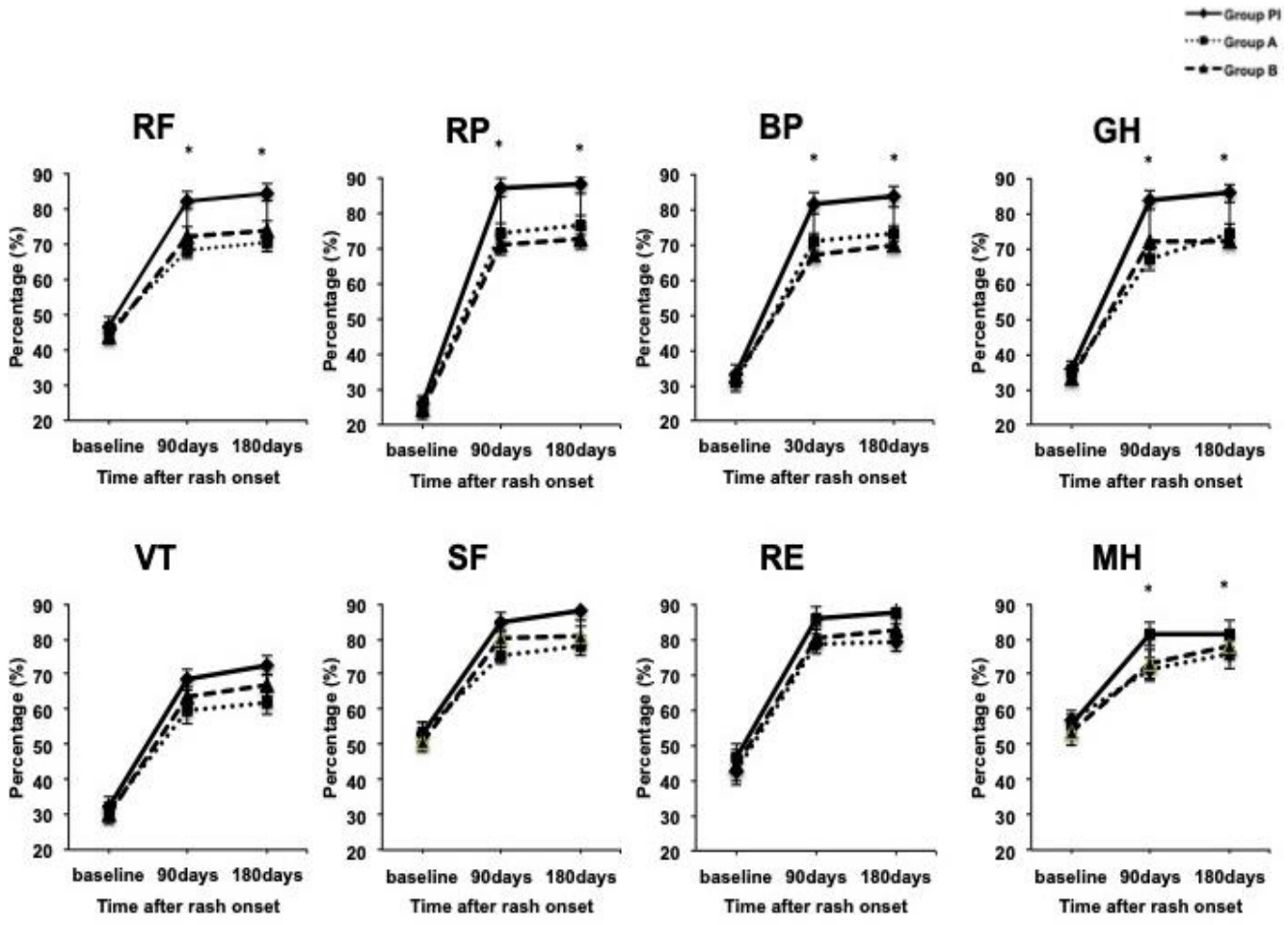

Fig. Quality of life (SF-36) before and after intervention among two arms. PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role emotional; MH = mental health. In all panels, higher scores indicate improvement. Error bar is represented by standard error. *P<0.05

Figure 2. SF-36 before and after intervention among three groups. PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role emotional; MH = mental health. In all panels, higher scores indicate improvement.

Error bar is represented by standard error. *P<0.05

4. Discussion

Our results displayed that Jiaji point injection of SM twice a week and 6 times in all in the earlier course of HZ (within one week of rash onset), could effectively reduce the pain severity and shorten duration of pain. Furthermore, a significantly lower incidence of PHN was encountered after 90 and 180 days, and an apparent reduction in the dose of Gabapentin and Tramadol taken throughout the study period, as well as a significant improvement in the life quality according to SF-36 index scores. No adverse events were reported among the study participants, indicating that injection of SM at Jiaji point is a relatively safe treatment for HZ patients.

HZ associated pain or PHN is a kind of neuropathic pain, which characterized by spontaneous pain, hyperalgesia and allodynia, it is a devastating neurological disease that seriously affects patients' quality of life. Reducing the incidence of PHN is one of the primary goals in treatment of HZ [12]. A recent Meta-analysis [13] showed significant increases in the risk of PHN with clinical features of acute zoster including prodromal pain, severe acute pain, severe rash, and ophthalmic involvement, besides older age that was significantly associated with PHN. Thus, early intervention for the HZ, including reducing pain and treating rash, is crucial to reducing the incidence of PHN [6-14]. But so far, there is no particularly effec-

tive method in this regard [15]. Although early intervention for acute HZ is recommended [12-16], how to prevent its development into PHN remains controversial.

Oral administration of a certain dose of gabapentin has certain efficacy in the treatment of acute HZ and the prevention of PHN [17], though low-dose gabapentin in HZ seems not effective in the prevention of PHN, according to a prospective controlled study [18]. On the other hand, patients given gabapentin were significantly more likely to experience dizziness, somnolence, peripheral edema, ataxia or gait disturbance and diarrhea, and the side effects of gabapentin are more likely to occur with the increase of the dose, and many patients cannot continue treatment because they cannot tolerate the side effects during the clinical treatment [19, 20], especially the elderly female patients [21].

In Traditional Chinese Medicine, perpendicular puncture at Huatuo JIaji point has been demonstrated to have therapeutic effect on alleviating pain in acute stage of HZ [22]. The underlying mechanism is probably releasing endogen opioid peptides, inhibitions of inflammatory factors secretion and increasing barrier function [23]. When we used Jiaji point injection with *SM*, our results showed that, after 90 days, the incidence of PHN is respectively 6.45%, 19.35%, 18.75% in patients treated with *SM*, placebo injection and acupuncture ($p<0.05$). It became 3.23%, 16.13%, 15.63% respectively at 180 days ($p<0.05$). Our results indicated that the stimulation at Jiaji point (whether acupuncture or point injection) could relive the pain of HZ, but the combination of *SM* and Jiaji point had a better effect compared with the other two groups.

SM, a widely used Chinese herb, has been prescribed to treat angina pectoris, hyperlipidemia, acute ischemia stroke due to its pharmacological effects of dilating coronary arteries, increasing blood flow and scavenging free radicals in ischemia diseases [24-26]. The initial recorded of *SM* was in the "Shen Nong's herbal classic", for the efficacy of removing blood stasis and relieving pain and has traditionally used for centuries in Asian countries as antioxidant, anticancer, and anti-inflammatory agent. Tanshinone IIA (TIIA), the major compounds of *SM*, has been shown to suppress vasoconstrictor endothelin-1 production and reduce the expression of vascular adhesion molecules in vitro [27]. It has reported that TIIA has long-lasting pain-relieving effects and neuroprotective properties in neuropathic pain [28]. In particular, studies had shown that TIIA had significant anti-nociceptive effect in somatic and visceral pain. In a previous study, the authors found that *SM* combined with valacyclovir effectively relieved neuralgia and shorten the recovery time [29].

In addition, it was found that [30], TSN IIA can reduce the injury of sciatic nerve transection model in rats and promote nerve regeneration, which provides strong evidence for Tan IIA as an effective treatment of peripheral nerve injury. More recently, in a randomized, double blind, controlled animal trial [31], Hao et al found Tanshinone IIA could suppress the expression levels of inflammatory factors (IL-1β, TNF-α and IL-6) and attenuate cancer-induced ongoing pain and breakthrough pain in a dose-dependent manner. Cao et al [32] evaluated the antinociceptive and antihyperalgesic effects of TIIA on neuropathic pain by using spinal nerve ligation (SNL) pain model, and found TIIA inhibited SNL-induced neuropathic pain through depressing microglial activation and immune response by the inhibition of mitogen-activated protein kinases (MAPKs) pathways and suggest that TIIA might be a promising agent in the treatment of neuropathic pain. Ma et al [33] also indicated that tanshinone IIA inhibited SNL-induced neuropathic pain via multiple effects. Because the elevated cytokine levels in acute herpes zoster are assumed to induce PHN, it may be explained why early suppression of these cytokines by *SM* would prevent the development of PHN. Our findings were consistent with these results. We injected *SM* into Jiaji point, and results showed that pain score and analgesics consumption were significantly decreased in treatment group, compared to control group. It also reduced taken dosage of Gabapentin, thus decreasing the related side effects.

In this present study, we also observed the changes of serum β-EP before and after treatment. On the 90^{th} and 180^{th} day after treatment, the level of plasma β-EP in three groups was significantly higher than that before treatment, and that in PI group was highest among these groups. β-EP is a strong opioid agonist, mainly distributed in the thalamus, pituitary, adrenal gland and other peripheral tissues. It is an inhibitory transmitter, which can inhibit the release of substance P of sensory conduction. The low activity of β-EP can increase the release of substance P, further aggravate the pain and form a positive pain feedback circuit. Studies [34] has shown Oxycontin in treating patients with cancer pain, can decrease the β-EP level, ameliorate the clinical symptoms, effectively relieve the pain. Previous studies have shown that electroacupuncture at some points improve the content of β-EP in plasma, interrupt the pain circuit, and thus achieve the analgesic effect, and the underlying mechanism may be

related to stimulation of the release of endogenous β-EP and inhibition of inflammatory mediators (5-HT and PGE2) [35]. Researchers [36] considered the pain score was negatively correlated with the level of β-EP in the plasma, through the analysis of the correlation between the β-EP in the plasma and the therapeutic effect of Jiaji point warm acupuncture on patients with lumbar disc herniation. After the treatment of Jiaji point, the pain score of these patients can be significantly reduced, and the level of plasma β-EP will be significantly increased. This suggests that the analgesic effect of warm acupuncture may be related to the increase of plasma β-EP and the blocking of pain circuit. The results showed that β-EP in PI group was significantly higher than that in the other two groups, indicating that injection of Salvia miltiorrhiza at Jiaji point could increase the level of β-EP in plasma, which might be one of the mechanisms of analgesia of injection of Salvia miltiorrhiza at Jiaji point.

Since acupuncture or Jiaji point injection has no serious side effects, it can be used repeatedly if necessary. Point injection can effectively relieve pain and improve quality of life in patients with Hz who are intolerant to side effects of oral drugs or refuse to receive invasive treatment such as spinal cord stimulation and pulsed radio frequency therapy.

The main limitation of this study was that, even though pharmacological compounds of *SM* were identified, it is unknown which compound of the herb supplementation was effective. Additionally, anti-inflammation of *SM* was assumed to reduce the incidence of PHN, however, we did not monitor the cytokines levels of the patients in the current study. In the current study, we have proved the clinical effect of early injection of *SM* injection at Jiaji point. However, we have not explored the possible mechanism of this effect. For example, we cannot compare the function of peripheral nerve fibers before and after point stimulation because most patients refuse to accept more invasive tests. We did not use fMRI to detect the changes of CNS brain area before and after treatment to explore the possible mechanism. In clinical observation, there was no stratified study on herpes in neck, chest and waist, nor stratified study according to the number of segments involved in the rash. The selected patients in this study are all acute patients within 7 days of herpes zoster rash, but we did not compare them with other time periods, such as 7-30 days of rash, and 30-60 days of rash. It is not clear whether the same clinical effect will be achieved if injection of SM at Jiaji point is given after 7 days.

5. Conclusion

There were no obvious adverse reactions during the treatment period, indicating that Jiaji point injection of SM injection is a relatively safe treatment for HZ patients. Early Huatuo Jiaji Point injection with SM can quickly relieve herpes zoster-related pain, shorten the course of disease, reduce the incidence of PHN and improve the quality of life of patients. The dosage of gabapentin or tramadol sustained-release tablets was significantly reduced, thus the drug adverse were reduced.

Author Contributions

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Conflicts of Interest

The authors declare no conflict of interests.

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