

Original Article

Early application of salvia miltiorrhiza at huatuojiaji points reduces incidence of post-herpetic neuralgia

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Received April 1, 2018; Accepted May 6, 2018; Epub July 15, 2018; Published July 30, 2018

Abstract: Objective: This study aimed to investigate whether injection of salvia miltiorrhiza at huatuojiaji points in treating acute herpes zoster would reduce the intensity and duration of pain and incidence of post-herpetic neuralgia (PHN). Methods: A total of 104 patients, over 50 years old, were randomized to receive either saline (Arm 1) or salvia miltiorrhiza (Arm 2) injections at huatuojiaji points in addition to standard treatment. Visual analogue scale and total amount of analgesics (gabapentin and tramadol) were recorded during the initial visit, 1st, 3rd and 6th week after injection and 3rd and 6th month after rash onset, respectively. In the 3rd and 6th months after onset, PHN was assessed using Douleur Neuropathique 4 Questions. Patient satisfaction was evaluated using Medical Outcomes Study Questionnaire Short-Form 36. Results: Compared with Arm 1, Arm 2 had much lower scores of visual analogue scale at all follow up time points ($P<0.001$) and less incidence of PHN, after 3 and 6 months (both $P<0.05$). Additionally, there was a significant reduction in doses of gabapentin and tramadol in Arm 2 beginning the third week ($P<0.001$). Improvement experienced in Arm 2 was greater than in Arm 1, after 3 and 6 months ($P<0.05$). No serious adverse effects were reported during the study. Conclusion: Injection of salvia miltiorrhiza at huatuojiaji points can reduce incidence of PHN, decrease the intensity of pain, and shorten pain duration.

Keywords: Huatuojiaji points, salvia miltiorrhiza, herpes zoster, post-herpetic neuralgia, prevention

Introduction

Acute herpes zoster (AHZ) is a disease characterized by a painful skin rash with blisters in a dermatomal distribution, usually occurring when the latent varicella zoster virus within the dorsal root or cranial nerve ganglia is reactivated. The most common complication of AHZ is post-herpetic neuralgia (PHN), defined as pain persisting for over 3 months after rash onset [1, 2]. Incidence rate of PHN is about 20%-35% in individuals over 50 years old. PHN can severely affect quality of life (QoL). Unceasing pain can bring about serious physical, occupational, psychosocial, and social disabilities. Because of long-term suffering and limited efficacy of current medications, patients can develop drug dependency, sleep disturbance, hopelessness, depression, and even commit suicide [3, 4]. Families and the society are also affected by the financial burden due to medical costs and lost productivity.

Although PHN is a condition that has been known for decades, prevention of its development remains a challenge. Some studies have indicated that early intervention is crucial to reduce incidence of PHN [5, 6]. However, there have been no disease-modifying therapies available in this area. According to traditional Chinese medicine (TCM), causes of PHN include incomplete clearing of heat and dampness in the liver and spleen meridians, stagnation of qi and toxic pathogens, accumulation of yin, internal heat, and obstruction of meridians [7]. Acupuncture works by regulating qi and blood movement to dispel wind, clear heat, and dry dampness [8, 9]. A number of acupuncture points, including huatuojiaji points, have been used in the treatment of PHN [7, 10]. Salvia miltiorrhiza is a Chinese medicinal herb with various pharmacological properties for improving circulation and relieving stasis [11]. Lin et al. reported that short-term supplementation of salvia miltiorrhiza (250 mg per day for 7 days,

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by oral administration) can relieve delayed onset muscle pain induced by acute downhill running exercise [12]. The authors believed that salvia miltiorrhiza supplementation could reduce systemic inflammation induced by eccentric exercise, thus, resulting in fast recovery from muscle injury. Persistent inflammation of peripheral nerves is associated with development of PHN [13]. However, there have been no studies on whether early application of salvia miltiorrhiza at huatuoji points can prevent PHN. Therefore, in this study, a randomized, double-blinded, and controlled trial was designed to evaluate the efficacy of early injection of salvia miltiorrhiza at huatuoji points in reducing acute pain and incidence of PHN.

Materials and methods

Participants

The study was approved by the Ethics Committee of Ruijin Hospital Luwan Branch, Shanghai Jiao Tong University School of Medicine. All cases were conducted in the same institute. A total of 104 adult patients, with pain associated with herpes zoster (HZ), were recruited from the Pain Clinic.

Inclusion criteria: (1) Patients had a herpetic eruption for less than one week; (2) Patients had a visual analog scale (VAS) score over 3; (3) Patients aged over 50 years; and (4) Patients had no other treatment except for appropriate antiviral therapy.

Exclusion criteria: (1) Rashes localized on face and head; (2) Eruption lasting for more than one week; (3) Infection at the site of injection; (4) Patients had a history of renal or hepatic disease, coagulopathy, diabetes, and malignancies; (5) Patients had immune dysfunction; and (6) Patients allergic to salvia miltiorrhiza.

Methods

During the first visit, medical histories were checked and clinical examinations conducted. Afterward, the study procedure (injections and follow up) was explained to patients and written informed consent was obtained.

Patients were assigned to different groups using computer-generated random numbers. Patients in Arm 1 received injection of saline as placebo at huatuoji points, while patients in

Arm 2 received injection of salvia miltiorrhiza (manufacturer: Zhengda Qingchunbao Pharmaceutical Co. Ltd, State Food and Drug Administration Approval No. Z33020177) at huatuoji points. Syringes containing solutions of salvia miltiorrhiza or saline were prepared by a pain physician that did not participate in the study or data collection.

Huatuoji points are located half an inch (1.3 cm) away from the lower spinous process of spine at the vertebral level. Appropriate points must be selected corresponding to the location of the involved dermatome of HZ (plus 1-2 dermatomes above and below the vertebral level of lesion) [7, 14]. A No. 7 puncture tip was used to pierce the skin, vertically, until the needle reached lamina. Salvia miltiorrhiza (4 mL) was diluted to 20 mL with normal saline solution. A volume of 1-3 mL was injected at each point, while the total amount was no more than 20 mL. Treatment started from their first visit and was performed once every 7 days for 3 weeks.

All patients received 1,000 mg valacyclovir, three times a day, for 7 days (initially within 72 hours of onset of symptoms) and 300 mg gabapentin three times a day, later gradually increased to a maximum of 1,800 mg/day. Tramadol was available as needed. If a patient reported mild pain (VAS \leq 3), the amount of gabapentin could be reduced every other day on the condition that pain scores remained less than 3 with each reduction.

Outcome measures

Main outcome measures were as follows: (1) VAS: VAS was used for evaluating severity of zoster associated pain. Scores were on a scale of 0-10: a score of 10 represented most severe pain, whereas 0 represented no pain; a score of 3 or less was defined as mild pain; a score of 4 to 6 was defined as moderate pain; and a score of 7 and higher was defined as severe pain. VAS evaluations were conducted at initial visit (basal), the 1st, 3rd and 6th week after injection, and 3rd and 6th month after rash onset (approximately at 8-10 AM each day); (2) Percentage of patients with neuropathic pain (incidence of PHN): Douleur Neuropathique in 4 Questions (DN4 questionnaire) served as a useful tool for diagnosing neuropathic pain [15-17]. The scale contained ten items. A "yes" response was scored as 1. The questionnaire was made up of

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Table 1. Subscales in medical outcomes Study Questionnaire Short-Form 36

Subscale	Description
Physical functioning	Ten items measuring limitations in performance of various physical activities, ranging from vigorous activities to simple self-care functions
Role physical	Four items which measure functionality in work and other daily activities as a result of physical health
Bodily pain	Two items which measure degree of pain and pain-related functional limitations
General health	Five items which measure an individual's appraisal of their overall health
Vitality	Four items which measure energy level
Social functioning	Two items which measure functionality in work and other daily activities as a result of emotional health
Role emotional	Three items measuring functionality in work and other daily activities as a result of emotional health
Mental health	Five items which measure the presence and degree of depression and anxiety

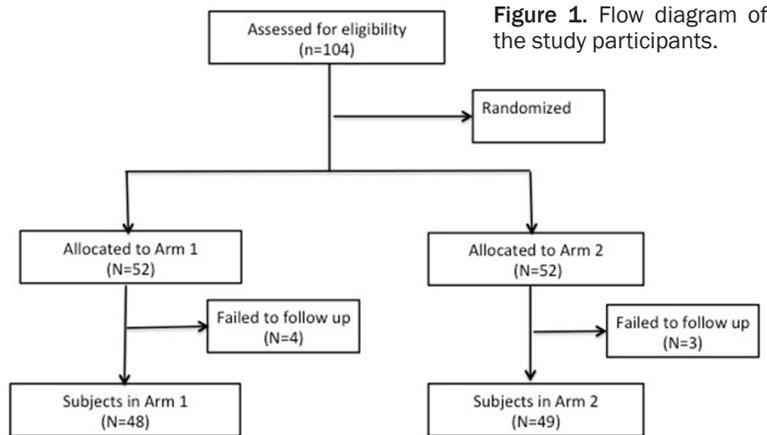


Figure 1. Flow diagram of the study participants.

(2) QoL: Medical Outcomes Study Questionnaire Short-Form 36 (SF-36), a 36-item self-report survey containing eight sections, was used to assess the QoL. The system included the following items: physical functioning (PF: 10 items), role physical (RP: 4 items), general health (GH: 5 items), mental health (MH, 5 items), vitality (VT, 4 items), role emotional (RE, 3 items), bodily pain (BP; 2 items) and social functioning (SF, 2 items). Scores for the 8 scales ranged from 0 (worst QoL) to 100 (best QoL) [19]. Remaining categories were associated with experience of change in general health in the past few years. SF-36 scores were assessed prior to the treatment and in the 3rd and 6th month after rash onset (**Table 1**); (3) Side effects: any reported adverse event would be recorded, including time of onset, type of event, duration, and severity.

Table 2. Clinical characteristics of patients

	Arm 1 (n=48)	Arm 2 (n=49)
Age (year, mean ± SE)	63±2.45	66±1.57
Sex (male/female)	22/26	24/25
Duration of pain after rash onset (day; mean ± SE)	3.3±0.25	3.5±0.23
VAS (min, mean ± SE)	7.3±0.11	7.6±0.14
Area		
Cervical region	5 (10%)	6 (12%)
Thoracic region	17 (35%)	15 (31%)
Lumbar region	26 (55%)	28 (57%)

Note: VAS, visual analog scale; Arm 1: injection of saline at huatuojiaji points; Arm 2: injection of salvia miltiorrhiza at huatuojiaji points.

descriptors (seven items) and signs related to sensory test (three items). A score over 4 suggested an existence of neuropathic pain [18]. Evaluations using DN4 questionnaire were performed during initial visit (basal) and 3rd and 6th month after rash onset.

Secondary outcome measures were as follows: (1) Total dosage of medication: at each assessment visit, the amount of analgesia on-request and amount of gabapentin used were recorded;

Statistical analysis

According to a study by Lapolla et al., sample size was determined based on the assumption that expected incidence of PHN in patients above 50 years old in the control group was 20% [20]. With an aim of lowering incidence to 5%, a sample size of 47 was calculated to detect an incidence reduction of 15% with 92% power and significance level of 0.05.

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Table 3. VAS before and after treatment in the two groups (mean \pm SE)

Time	VAS		t, P	Group effect F, P	Time effect F, P	Group * time interaction F, P
	Arm 1	Arm 2				
Basal	7.3 \pm 0.10	7.6 \pm 0.13	1.824, 0.071	10.22, 0.002**	2.96, 0.012***	2.05, 0.071
1 st week	4.5 \pm 0.17	3.1 \pm 0.10	7.134, <0.001*			
3 rd week	3.6 \pm 0.17	2.3 \pm 0.10	6.624, <0.001*			
6 th week	2.3 \pm 0.16	0.3 \pm 0.10	10.658, <0.001*			
3 rd month	1.3 \pm 0.13	0.15 \pm 0.07	6.994, <0.001*			
6 th month	1.1 \pm 0.10	0.08 \pm 0.01	10.254, <0.001*			

Note: VAS, visual analog scale; Arm 1: injection of saline at huatuojiaji points; Arm 2: injection of salvia miltiorrhiza at huatuojiaji points; *P<0.0083, **P<0.01, ***P<0.05.

Table 4. Incidence of PHN at various time points

	3 months	6 months
Arm 1 (48)	10/48 (20.83%)	7/48 (14.58%)
Arm 2 (49)	3/49 (6.12%)*	1/49 (2.04%)*

Note: PHN, post-herpetic neuralgia; Arm 1: injection of saline at huatuojiaji points; Arm 2: injection of salvia miltiorrhiza at huatuojiaji points; *P<0.05 vs. Arm 1.

Allowing for 10% loss to follow up, 104 patients were included. Quantitative data are expressed as mean \pm standard error and categorical data as percentages. For demographic data, Student's t-test was used to compare quantitative variables, while Fisher's exact test and Chi-square test were used for categorical variables. Repeated measures analysis of variance (ANOVA) was conducted for analyzing intergroups (Arm 1 vs. Arm 2) effects, intra-groups (different time points) effects, and interaction (group * time) effects related to VAS score, dose of tramadol, dose of gabapentin on-request, and SF-36 score. Inter-group differences, at each time point, were examined by t-test with Bonferroni's correction (two-sided alpha level of 0.05/number of time point). A two-sided alpha level of 0.05 was considered statistically significant, except for Bonferroni's t-test. Statistical analysis was performed by SPSS version 16 (SPSS Inc., Chicago, IL) [14].

Results

A total of 104 adult patients, above 50 years old, were randomly assigned into two groups (with 52 in each). Four patients in Arm 1 and three patients in Arm 2 were excluded from the study because they were unavailable for follow up (Figure 1). Baseline demographic characteristics were similar between the two groups (Table 2).

Comparison of VAS scores between the two groups at basal, 1st, 3rd, 6th week, and 3rd and 6th month after treatment are shown in Table 3. There were no significant intergroup differences in VAS scores at basal. Results of repeated measures ANOVA showed that VAS scores decreased in both groups during the study period (time effect, P=0.012) and significant differences in VAS existed between the two groups (P=0.002). Besides, VAS scores at each time point after treatment in Arm 2 were much lower than those in Arm 1 (all P<0.001). No significant effects of group-time interaction were observed (P=0.071).

Incidence of PHN was lower in Arm 2 than in Arm 1, after 3 months (6.12% vs. 20.3%, P<0.05) and 6 months (2.04% vs. 14.58%, P<0.05). See Table 4.

By performing the same analytical procedure, it was found that use of gabapentin and tramadol decreased significantly in both groups (all P<0.001), while reduction in the doses of these two drugs in Arm 2 were even greater compared with those in Arm 1 after the third week (all P<0.001). See Tables 5 and 6.

It can be seen in Figure 2 that Arm 2 experienced more improvement than Arm 1 in terms of SF-36 index scores in the 3rd and 6th month after treatment (all P<0.017).

No serious adverse effects were reported during the study period. Drowsiness occurred in 5 patients in Arm 1 and 6 patients in Arm 2, in the first week. However, this symptom was much improved during the second week. No patients required any additional treatment.

Discussion

Results of the present study demonstrated that injection of salvia miltiorrhiza at huatuojiaji

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Table 5. Gabapentin dosage (mg/week) in the two groups (mean ± SE)

Time	Gabapentin dosage		t, P	Group effect	Time effect	Group * time interaction
	Arm 1	Arm 2		F, P	F, P	F, P
1 st week	5431±201	5249±217	0.612, 0.542	10.78, 0.001*	3.49, 0.008*	2.35, 0.054
3 rd week	3645±178	1960±41*	9.494, <0.001*			
6 th week	2310±93	907±76*	11.63, <0.001*			
3 rd month	1960±41	392±68*	19.60, <0.001*			
6 th month	945±55	56±21*	17.87, <0.001*			

Note: Arm 1: injection of saline at huatuojiaji points; Arm 2: injection of salvia miltiorrhiza at huatuojiaji points; *P<0.01.

Table 6. Tramadol dosage (mg/week) in the two groups (mean ± SE)

Time	Tramadol dosage		t, P	Group effect	Time effect	Group * time interaction
	Arm 1	Arm 2		F, P	F, P	F, P
1 st week	875±45	840±41	0.575, 0.567	11.13, 0.001*	3.71, 0.006*	2.37, 0.052
3 rd week	210±47	18±11	4.010, <0.001*			
6 th week	175±45	11±4	3.665, <0.001*			
3 rd month	52±12	5±2	3.907, <0.001*			
6 th month	35±7	1±1	4.856, <0.001*			

Note: Arm 1: injection of saline at huatuojiaji points; Arm 2: injection of salvia miltiorrhiza at huatuojiaji points; *P<0.01.

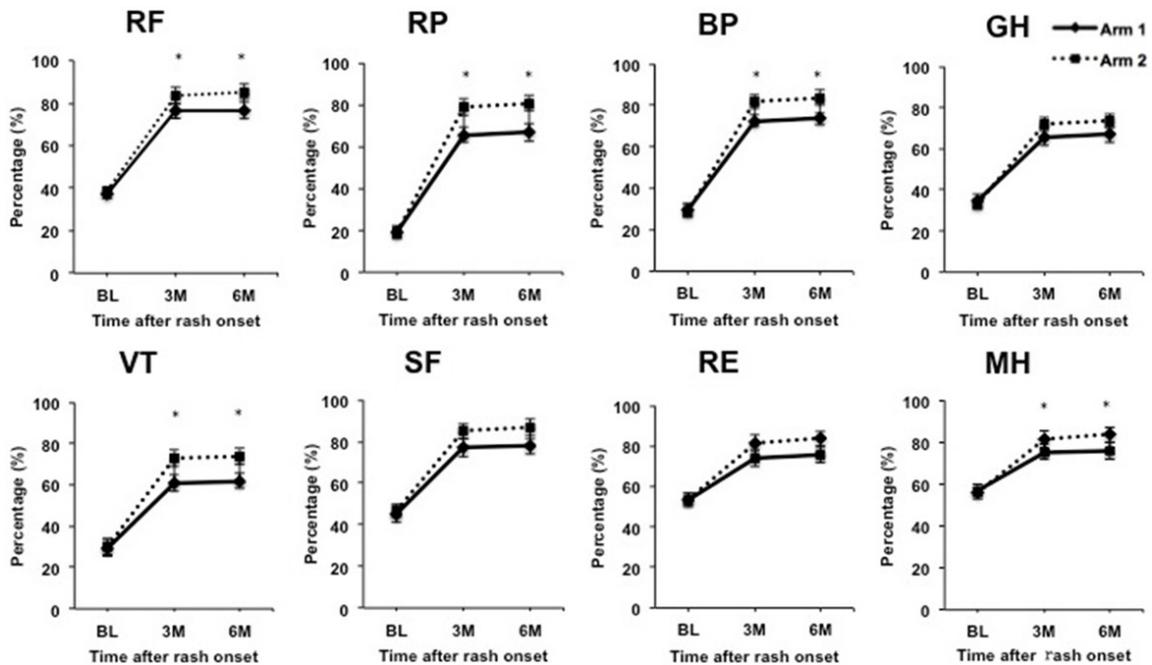


Figure 2. Quality of life (SF-36) before and after intervention between the two arms. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; in all panels, higher scores indicate improvement; error bar is represented by standard error; *P<0.05.

points, within first week of rash onset, could help reduce pain intensity and shorten pain duration. Furthermore, if patients received this injection every 7 days for 3 weeks, they experienced much lower incidence of PHN after 3 and 6 months, a marked reduction in doses of

gabapentin and tramadol, and a great improvement in QoL as measured by SF-36.

Neuronal injury and skin damage are believed to be the causes of acute pain in patients with HZ [21]. Pain can be exacerbated by movement

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or contact and level of pain is related to the location of the affected area. Antiviral agents and analgesics are, currently, part of the standard treatment modality for HZ [22, 23]. In the present study, all patients received valacyclovir (1,000 mg, three times a day for 7 days), gabapentin (up to 1,800 mg per day), and tramadol as needed. In TCM, perpendicular punctures at huatuojiaji points have been demonstrated to have therapeutic effects on relieving pain during the acute stage of HZ [24]. Possible mechanisms behind this are that the treatment can help release endogenous opioid peptides, inhibit secretion of inflammatory factors, and enhance barrier function [25].

Salvia miltiorrhiza, a Chinese medicinal herb, has been widely used in the treatment of ischemic diseases due to its pharmacological effects of dilating arteries, increasing blood flow, and scavenging free radicals. Other studies have found that salvia miltiorrhiza, combined with valacyclovir, could effectively relieve neuralgia and shorten the recovery from AHZ, consistent with our findings [26]. Results of the present study showed that pain scores and use of analgesics were much lower in the treatment group than in control group.

PHN is known to have severely negative effects on QoL [27, 28]. Reducing incidence of PHN is one of the primary goals in treating HZ [29]. Early intervention during AHZ is recommended [29, 30]. However, standard therapy, with oral administration of antiviral agents and gabapentin, can't reduce incidence of PHN and methods of preventing its development remain controversial.

Increase in local cytokines related to neuralgia might be the potential mechanism for inducing PHN. Zhu et al. found that incidence of PHN was correlated with levels of interleukin (IL)-1 β , IL-6, IL-8, tumor necrosis factor (TNF), and IL-10 [31]. Interventions with anti-inflammatory effects have been applied clinically for preventing development of PHN. In the single treatment mode, neither epidural nor paravertebral block can reduce incidence of PHN, whereas repetitive interventional treatments, including paravertebral block and low-level laser therapy, have the potential to prevent development of the disease. The present study adopted the repetitive mode, in which salvia miltiorrhiza was injected at huatuojiaji points every 7 days

for 3 weeks. Study results found that incidence rates of PHN in patients treated with salvia miltiorrhiza and placebo were 6.12% and 20.83% in the 3rd month ($P < 0.05$) and 2.04% and 14.58% in the 6th month, respectively ($P < 0.05$). This finding indicates that repetitive injections of salvia miltiorrhiza at huatuojiaji points could significantly reduce incidence of PHN. The effectiveness of this repetitive intervention might be due to persistent inhibition of inflammatory factors.

This present study was the first study to demonstrate that repetitive injections of salvia miltiorrhiza at huatuojiaji points can prevent development of PHN. As major components of salvia miltiorrhiza, tanshinone IIA and salvianolic acid B have been found to suppress the production of vasoconstrictor endothelin-1 and lower expression of vascular adhesion molecules *in vitro* [32]. Modern pharmacological studies have proven that salvia miltiorrhiza can prevent calcium overload, eliminate oxygen free radicals, combat inflammation, and improve microcirculation with significant antinociceptive effects on somatic and visceral pain [33]. More recently, in a randomized, double blind, and controlled animal trial, Hao et al. found that tanshinone IIA could suppress expression of inflammatory factors (IL-1 β , TNF- α and IL-6) and attenuate cancer-induced ongoing pain and breakthrough pain in a dose-dependent manner [34]. Since elevated cytokine levels in AHZ are assumed to induce PHN, it may explain why early suppression of these cytokines by salvia miltiorrhiza can prevent development of PHN.

There were some limitations to the present study. For example, it was unclear which component of salvia miltiorrhiza played the effective role during treatment, even though pharmacological compounds of the herb have all been identified. Additionally, cytokines levels were not monitored in patients, although the anti-inflammatory effects in salvia miltiorrhiza were assumed to reduce incidence of PHN.

In conclusion, injection of salvia miltiorrhiza at huatuojiaji points during early stage, in combination with antiviral agents, can be a safe and effective method for treatment of AHZ. It can decrease the intensity of acute pain, shorten pain duration, reduce incidence of PHN, and improve patient QoL.

Acknowledgements

This work was financially supported by the Traditional Chinese Medicine Scientific Research Fund of Shanghai Municipal Commission of Health and Family Planning (2016LP008), and the Funding Project of Health and Family Planning Commission of Huangpu District, Shanghai (HKW201602001).

Disclosure of conflict of interest

None.

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