Fire needle plus cupping for acute herpes zoster: Study protocol for a randomised controlled trial

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Abstract
Acute herpetic zoster (AHZ) is a common skin disease caused by invasion of the varicella-zoster virus into the ganglia and skin, and the severe pain is the most complaint, which seriously disturbs the normal life of patients. Fire needle plus cupping is a special acupuncture treatment, which is widely used to treat AHZ for its better analgesic effect in China although it has not been verified by rigorous the randomized controlled trial (RCT).

Methods To test the effect, a three-arm randomized parallel controlled trial protocol has been design. 105 AHZ patients suffering pain will be randomly divided into three groups in an equal proportion. The interventions are fire needle plus cupping (FC) in group A, famciclovir plus gabapentin (FG) in group B and fire needle plus cupping plus famciclovir (FCF) in Group C. All the group will be treated with one week, and the FC is to carry out 1 to 7 treatment sessions within 1 week, and the drug of famciclovir or gabapentin will take orally three times a day with seven times. Temporary analgesics medication will be administered if the intolerable pain constantly appeared. The primary outcome is pain intensity relief using visual analogue scale, and the secondary outcomes are changes in substance P and beta-endorphin concentrations in peripheral plasma, as well as analgesic needs, side effects, symptoms and physical signs including pain classification, local itching, burning sensation, fever, local lymphadenopathy, skin lesion area, blisters, herpes clusters, vesicular traits, ulcers, and pimples also will be evaluated. After 6 months, the participants will be followed up for postherpetic neuralgia.

Discussion: The results of this trial will give the evidence of FC comparing with FG and FCF, and may be provide another a credible treatment way to solve acute pain problem in AHZ.

Background
Herpes zoster (HZ), is a skin infection disease caused by reactivation of varicella zoster virus which is latent in the sensory ganglia, with typical feature is that it causes herpes along the sensory nerve in the corresponding segment, accompanied by severe neuralgia, and a serious impact on the quality of life of patients \(^{[1]}\). Pain symptom is the most common in early stage of disease and many of them without herpes, which is easy to be misdiagnosed as other diseases. Especially, misdiagnoses of cervical spondylosis or lumbar disc herniation when it occurs on the neck and shoulders, as well as
heart-related disease on left chest, are **not rare of ordinary occurrences** \([1]\). HZ can occur at any age, but older people are more commonly affected. Epidemiological study shows that the incidence, complications, hospitalization rate and average cost of HZ in China are climbing rapidly with the age increasing \([2]\). The cumulative incidence of HZ is 22.6/1000 among people aged over 50 years old, while it is 3.34 times than over 50-years old among over 80 years age people \([2]\).

The **conventional** drug therapies for HZ in acute phase are mainly antiviral, nutritional nerve, and analgesic \([3]\). The antiviral drugs are mainly oral famciclovir and valacyclovir. The nutritional nerve drug is mainly mecobalamin, and the pain relief drugs are mainly paracetamol tramadol, dezocine, morphine and gabapentin. According to the condition, glucocorticoid drugs can be administered orally or intravenously. The sequela phase is mainly analgesic and antianxiety, and the oral drugs include tricyclic antidepressants, strong opioids, gabapentin, tramadol, pregabalin, etc. In addition, the drugs such as methylprednisolone and triamcinolone acetonide can be used as nerve-blocking therapy. The above-mentioned treatment scheme has potential side effects, especially for patients with renal insufficiency or immune system diseases, and the above-mentioned scheme is difficult to implement \([3]\). Meanwhile, the cumulative medical cost is high for this disease, and many patients are not satisfied with the curative effect, and the complementary and alternative medicine like acupuncture is applied to treat it \([3-4]\).

Although HZ is not a lifelong disease, because of the excruciating pain, it requires more fast, economical, and effective treatments to relieve pain and more shorten treatment course. Acupuncture has a good therapeutic effect on pathological neuralgia, and a number of analgesic mechanisms have also been identified \([5-9]\). Fire needle and cupping are the traditional characteristic method in acupuncture treatment ways, and its history can be rooted in many ancient Chinese ancient literatures. The fire needle treatment is to use the alcohol lamp to burn the point of the special needle, and then the needle will be pierced into and pull out the meridian or acupoint quickly, which both have ordinary acupuncture and warming effects. When the needle operation is completed, the cupping therapy is implemented immediately. This combining therapy is widely used in the
treatment of acute pain symptoms of HZ in most Chinese hospitals although the efficacy of this treatment has not been confirmed by rigorous RCTs\cite{10-12}.

According to the theory of traditional Chinese medicine the treatment of fire needle plus cupping (FC) has a strong effect to promote qi and activate blood, which could increase the nutrition around the lesion and promotes tissue regeneration, and resulting in natural wound healing. It is found that the heat provided by fire needles can promote microcirculation in the lesion area through the regulation of cutaneous nerves, and is beneficial to the absorption of inflammation and metabolites \cite{13}. Furthermore, the high temperature of fire needles directly kills the microorganisms and achieves anti-inflammatory effects \cite{14}. So, the aim of this trial is further to validate the analgesic effect on acute herpes zoster (AHZ) treated by FC.

Methods

Objective

The main purpose of this trial is to investigate whether the treatment of FC could relieve the acute pain in AHZ with every other day with tree times in one week. The secondary objective is to analyse the correlation between the concentration of substance P and \(\beta\)-endorphin (b-Ep) in peripheral plasma and changes in pain intensity by FC intervention.

Study design

As show in Figure 1, this study is a three-arm open randomized controlled trial consisting of three groups. The interventions are fire needle plus cupping (FC) in group A, famciclovir plus gabapentin (FG) in group B and fire needle plus cupping plus famciclovir (FCF) in Group C. After randomization, Group A and Group C receive 1 to 7 treatment sessions of fire needles cupping therapy within 1 week. The administration of gabapentin depends on the needs of the patient of Group B. In addition, if the acute pain cannot be endured, patients will give the temporary analgesics medicine. The visual analogue scale (VAS) scores, symptoms, and physical scores will be obtained before and after treatment. The concentrations of SP and \(\beta\)-Ep in peripheral plasma also will be detected, and demand for temporary analgesics and side effects of the patients are recorded daily. After 6 months, the participants will be followed up for postherpetic neuralgia. (see Figure 2)
**Participants and recruitment**

This study will recruit 105 patients by posterizing public posters in dermatology and acupuncture clinics and the website of the Sixth Affiliated Hospital of Kunming Medical University. When potential participants have read the poster they can contact the dermatologists Zuohui Liang and Xiuhong Liu through the contact phone number recorded on the poster. Patients will be enrolled and the consent form will be signed if they meet the inclusion criteria by the assessment of dermatologists. Then, the randomize group number information will be get from Shihua Li by phone to unpack the envelopes.

The formal trial recruitment began in November 2018. The assistant researcher will assess and record the baseline status of the participants (Table 3).

In order to achieve adequate participants enrollment, we have developed two strategies to attract patients and published them on the recruitment poster. First, all participants are free of charge for using the treatment methods. Second, if participants with postherpetic neuralgia six months later, they could obtain another 10 times free comprehensive acupuncture treatments providing by the acupuncture department.

**Randomisation and allocation concealment**

1) Block setting: 105 participants will be numbered 1-105 according to the time of participation, the block length is 6, and 16 blocks are set.

2) Obtaining random numbers: Start with any two-digit number in the random number table, and take 105 numbers to the right.

3) Grouping: 6 random numbers of each block are sorted from small to large, sorts 1 and 2 are group A, sorts 3 and 4 are group B, and sorts 5 and 6 are group C.

4) Random group concealment: The grouping conditions of participants are packed into 105 envelopes, and all the envelopes are numbered in order and sealed. To ensure the randomization process, the serial number will be printed on the outside of the opaque envelope and the assignment of the group will be sealed on the inside of the envelope.

The above work will complete by Shihua Li, an otolaryngologist at the Sixth Affiliated Hospital of Kunming Medical University. Shihua Li will not involve in the treatment and the data collection of this
study.

The envelope will be opened according to the patient’s serial number, and the dermatologists will obtain the patient’s random number and assignment group by telephone.

**Blinding**

Since the acupuncturists and subjects could not be blinded to the FC treatment operation, we will conceal the randomized grouping method and the results of the grouping of subjects, and provide sensory tests (outcome evaluators), data inspectors and statistical analysts who are not aware of the grouping and treatment of subjects.

**Participating physicians**

Participating physicians in the trial are doctors in the departments of dermatology and acupuncture and moxibustion at the Sixth Affiliated Hospital of Kunming Medical University. Acupuncturists are responsible for the treatment of FC. All acupuncturists have received a master’s degree in acupuncture and moxibustion and have undergone training in unified Standardized operation plan.

**Patient and public involvement**

Patients and/or public were not involved in the design of this study.

**Participants**

**Inclusion criteria**

18 to 60 years old, and no gender limited;
Skin rash and clustered blister in asymmetrical skin area;
Precursor symptoms such as general discomfort and fatigue before rash;
Nervous pain in the affected area, skin hypersensitivity, etc.;
The rash is distributed along the innervated area;
Unilateral, not exceeding the midline of the body;
Pain intensity as assessed by VAS (0-100 mm) of 50 mm £ pain intensity £80 mm

**Exclusion criteria**

Insulin-dependent diabetes mellitus or other diseases that affect peripheral sensitivity (eg, polyneuropathy, chronic pain syndrome);
Bleeding tendency (eg, taking anticoagulants, coagulation dysfunction, thrombocytopenia, etc.);
Pregnancy or lactation;
Surgery within the past 3 months;
Diseases affecting quality of life (eg, cancer, paralysis);
Mental illness (eg, depression, schizophrenia, dementia) or severe heart/lung/kidney disease;
Exposure to fire needle, cupping, painkillers, or other complementary and alternative treatments for
this disease prior to treatment;
Contraindications for famciclovir, gabapentin, mecobalamin, paracetamol, tramadol, dextrozine, fire needles, and cupping.

**Dropout**

**Case dropout**

(1) Subjects experienced other comorbidities, complications, or special physiological changes during the trial. They were not suitable to continue the trial.

(2) During the trial, serious adverse events and important adverse events occur in the subjects, so that they are not suitable to continue the trial, and investigators decide to withdraw.

(3) Subjects have poor compliance. Medication compliance is calculated using the tablet counting method. Medication compliance = dose taken / prescription dose × 100%, medication compliance <80% or missed fire needle plus cupping treatment ≥ 1 time is defined as poor compliance.

(4) Violation of the test plan. Subjects change or add drugs other than the study protocol, and received other treatments other than the study protocol during the trial period.

(5) The subject withdraws by himself.

(6) Lost follow-up.

**Management of dropout cases**

For dropout cases, researchers should actively take measures to complete the last laboratory test as far as possible in order to analyse its efficacy and safety. For all dropout cases, the test conclusion form and reason for dropout shall be filled in the case report form.

**Intervention**

**Group A**

This group will be treated with only FC.

**Acupoints:** The main points are Ashi points (lesion area), corresponding nerve segment Jiaji points, and branch ditch points (SJ6); matching points are selected according to syndrome differentiation, pattern of dampness-heat in the liver meridian with Yang Ling Quan (GB34), pattern of dampness-heat in the spleen meridian with Yin Ling Quan (SP9), and pattern of obstruction of collaterals by blood stasis with blood sea (SP10).

**Appliances:** Medium-sized fire needle (diameter 0.4mm), large-sized fire needle (diameter 0.65mm), glass fire cup No.1-5, medical cotton ball, alcohol lamp, lighter, iodophor, etc.

**Operational methods:** Routine disinfection of skin with iodophor with the order of the head, middle, and tail of herpes will be carrying out firstly. Holding 95% alcohol lamp by the left hand close to the needle,
and to burn the needle in the right hand to whitening by the external flame of the fire, acupuncturist will prick the head of the herpes cluster. Then the needles will be pricked into the blisters or rashes quickly from the surface of the skin to the base of the herpes. Pricking early-onset herpes at first, for larger pustules or blood blisters (diameter $\geq 5$cm) with a large-scale fire, acupuncturist will extrude blister fluid with disinfection cotton ball after puncture, and then cup with a suitable size of glass fire cup for 5-10 minutes. If the area of the herpes cluster is too large, more than one cup can be used. The remaining acupuncture points are treated with fire needle pricking, and each acupuncture point should be pricked three times. Finally, the skin should be sterilized with iodophor more than one times. The treatment should be performed once a day for a total of 7 days.

Skin care: After treatment, the iodophor is used to clean and disinfect the skin, and to keep the patient’s skin dry and clean during the treatment.

**Course of treatment:** The course of treatment is one week and from one to seven times. If there is no pain any more after one time of FC treatment, the course is just one time. Meanwhile, if the patient is still suffering pain, the FC will continue once a day unless the pain disappears. All the treatments will not be more than seven times no matter the pain or not.

**Mechanism of fire needle cupping**

The mechanism of FC for AHZ is not entirely clear up to now. Based on the theory of traditional Chinese medicine, the main causes of herpes zoster are dampness and heat, which could block the meridians and collaterals, and then led to the stagnation of blood and Qi, and finally the pain is generated. FC has a strong effect to eliminate the dampness and heat, and make the Qi and blood smooth running, and then the pain will be alleviated. Previous studies hint that FC can accelerate crusting and shedding of herpes, and also adjust the concentration of substance P in serum $^{[11-12]}$.

**Group B**

Patients in Group B are intervened with famciclovir plus gabapentin (FG). The famciclovir hydrochloride dosage is 0.25g/time, 3 times a day according to the manufacturer’s (Livzon Pharmaceutical Factory) recommendation. The individual dose of gabapentin is 900-3600 mg per day. According to the manufacturer’s (Jiangsu Hengrui Pharmaceutical Co., Ltd.) recommendation (Table 1), the initial dose of 300 mg per day is gradually increased to 900 mg per day and then increased according to the patient’s needs, and the maximum dose is 3600 mg per day.

Table 1 demonstrates the gabapentin intake scheme used to reach the wanted therapeutic dosage.

**Group C**

In group C, patients will receive the treatment of FC plus famciclovir (FCF). The FC is performed as same as group A, and the usage and dosage of famciclovir hydrochloride is in line with group B.
Temporary analgesics

If the patients in the three groups who still cannot endure the pain during the treatment or after one week treatment, we will provide the temporarily **analgesics medicine** to them. According to the recommendations of the World Health Organisation, all three groups are likely to receive standardized analgesic treatment as step 1: non-opioid analgesics (paracetamol 4 ´ 1.0g), 60mm£ VAS£ 50mm; step 2: moderate-strength opioids (tramadol tablets, maximum dose 600mg/d), 80mm£ VAS£ 70mm; step 3: moderate-strength opioids (tramadol injection, 0.1g, once a day), VAS=90mm; step 4: recommend the use of stronger opioids (dezocine injection, 5mg, once a day), VAS=100mm. Patients are forbaid to use other analgesic drugs or therapies. Temporary analgesics demand will be recorded (table 2).

Adverse events

Adverse events like symptoms or diseases occurring during the trial will be recorded (table 2) and assessed at each session of intervention. There may be adverse events of abnormal gastrointestinal reactions, allergic reactions, dizziness, burns and other medical conditions. The relevance and severity of the adverse events will be assessed. Whether the participant could continue the treatment or not will be decided according to the assessments. To those who suffer harm as a result of the treatment will be compensated in accordance with relevant regulations.

Follow up

To evaluate the incidence of postherpetic neuralgia symptom, all participants will be followed up by telephone 6 months later from the end of one week of treatment, and the result will be recorded (table 2).

Outcomes

Primary outcome

The primary outcome is to assess the changes in pain intensity before and after treatment (VAS 0-100 mm, where 0 = painless and 100 = maximum imaginable pain).

Secondary outcomes

Before and after treatment, the plasma of the participants will be collected, centrifuged and stored in
a - 80°C refrigerator, and then the substance P and b-Epin in serum will be detected by an enzyme-linked immunosorbent assay. Quantitative scoring methods were used to evaluate the symptoms and physical signs before and after treatment, including pain intensity local itching burning sensation rash colour, numbers of blisters clusters ulcers fever local lymphadenopathy rash area(Table 2).

**Data management and monitoring**

The study will be conducted according to common guidelines for clinical trials (Helsinki Statement, 2008 Chinese Edition, http://www.chictr.org.cn/index.aspx) and will be jointly audited by the Audit Office, Science and Technology Department and Finance Department of Kunming Medical University. Trial auditing will be twice a year since that is the frequency of meeting with the Trial Steering Group of principal investigators. Data will be uploaded to the ResMan Public Management Platform of the China Clinical Trial Registry for adequate quality and safety control. The registration number is ChiCTR1800015372. Therefore, no Data Safety Monitoring Committee is needed. The principal investigator is responsible for project oversight, will make the final decision to terminate the trial, and will have access to the final trial dataset.

**Confidentiality and dissemination**

The personal information of all the participants stored on computers is kept on a secure server and will always be kept confidential. All the documentations of this study will be kept in a locked and secure environment (locked office and cabinets) at the Six Affiliated Hospital of Kunming Medical University. The review will be submitted to a peer-reviewed journal prospectively to spread our findings.

**Statistical methods**

**Samplesize estimation**

We will compare the difference in efficacy of the three groups. Sample size estimation is based on the method of the book of *health statistics*[^15], with type I error alpha = 0.05 and type II error beta = 0.1, using the bilateral test. According to the literature, the cure rates of famciclovir and for fire needle plus cupping for HZ were 37.8% and 76.4%, respectively. It was speculated that the cure rate of famciclovir plus fire needle plus cupping was 80.0%, which was substituted into the formula:
Where $P_{\text{max}} = 0.80$ and $P_{\text{min}} = 0.378$. The calculated result was a sample size of 32 subjects per group. Therefore, the number of samples required for the three groups was 96. This study required a total of 105 samples adding a 9%-10% dropout rate.

**Statistical analysis**

The purpose of this study is to confirm whether the therapeutic effect of experimental therapy (fire needle cupping) is different from that of reference therapy (famciclovir plus gabapentin and fire needle cupping plus famciclovir). Spss20.0 statistical software will be used for data analysis. When the main efficacy indicators of individual subjects are missing, the last observation carried forward will be conducted, and the non-main efficacy indicators will not be carried forward. The mean ± standard deviation is used for statistical description of measurement data, and the frequency (constituent ratio) is used for statistical description of counting data. The baseline characteristics will be recorded as in Table 3. The group t-test (Bonferroni method) will be used to compare the measurement data between groups. All reported $P$ values will be two-tailed with 95% confidence intervals. $P \leq 0.05$ will be considered statistically significant. PPS analysis and Fas analysis will be performed at the same time. SS analysis is used for safety evaluation.

**Discussion**

This study is a randomized controlled clinical trial with the comparison of FC, FG and FCF. As far as we know, this is the first clinical trial to demonstrate the FC effect which may be different from the reference therapy. Some previous Chinese literature reports on fire needle and cupping for HZ$^{12, 13, 14, 16}$. Many of them are not the rigorous design trial and is insufficient evidence to recommend the treatment of FC is effect for AHZ.

The main aim of this study is to test the analgesic effect in acute phase of disease. Besides, then skin of rash is also the concern for patient, we also observe the scores of skin lesions. The substance P and b-Epin is often regards as the analgesic mechanism, and we also want to detect variation in serum. The occurrence of postherpetic neuralgia is also be observed because of it's a common and difficult solve problems in AHZ.
The symptom of acute pain is that the AHZ patient want to solve mostly and cannot approve to participate in an invalid treatment group. There is not separately set sham acupuncture as another control group. The FC treatment is a combination of two types of acupuncture, which is hard to implement the fake ways. Meanwhile, the ethical principle is demanded to protect the interests of patients, and the sham acupuncture cannot fit for the act pain patients. The recognized medicine is set as the control intervention is the forceful persuasion the effect of FC. The result is enough to give the evidence to clinician and the aim is to be achieved though the psychological effects cannot be ruled out for lack of sham acupuncture group [18,19]. The FCF is also set as the control, which to judge whether the combination of drug with FC is better than the individual. It is also could provide suggestion in clinical practice.

It's found in our clinical practice, some acute pain will be amplified with the development of the disease. So the temporary short-acting painkillers will be permitted to use in three groups. This has no obvious effect for the results of the evaluation.

The limitation of this trial is that the psychological factors can't be eliminated according to the present design, and the difference in immunity is relative to the recovery of HZ which may led to differences in prognosis. According to the actual clinical situation, the drug dose, as well as the number of FC intervention, has certain volatility and do not restrict sternly. The blind method is impossible for acupuncturists and subjects because of the operation of FC. This study is closer to the clinical real-world research but these confounding factors cannot be completely avoided. In all, this protocol will provide a reference of clinical methodology and may give a definite evidence the effect of FC intervention for AHZ when it completed.

**Trial Status**

This trial protocol is version 2.1, dated 24 April 2019. This trial will be recruited on 10 October 2019, and recruitment will be completed about on 10 October 2020.

**Abbreviations**

Herpes zoster: HZ; acute herpes zoster: AHZ; randomised controlled trial: RCT; β-endorphin: b-Ep;

Visual analogue scale: VAS; fire needle + cupping: FC; famciclovir + gabapentin: FG; fire needle +
cupsing + famciclovir: FCF.

Declarations

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Authors’ contributions

* Correspondences are XhL (734182946@qq.com) and TpG (gtphncs@126.com);+YZ and ZhL are the co-first authors of this paper. YZ and TpG conceived of the study and drafted the manuscript. YX and TpG participated in the design of the study. YX performed the sample size estimation and was responsible for the blocked randomization of patients. YL is responsible for coordination of the study. XhL, ZhL, and JiY are responsible for subject recruitment. QnX, QZ, CLL, and JZ are responsible for fire needle and cupping treatment. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol has been approved by the Medical Ethics Committee of Yuxi people's Hospital(No.: 20170730-01). Written informed consent will be obtained from each participant.

Consent for publication
Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**References**

1. BLACK S. Herpes Zoster Vaccine and the Medicare Population. Clin Infect Dis. 2017; 64(6): 794-795.

2. Li Y, An Z, Yin D, Liu Y, Huang Z, Xu J, Ma Y, Tu Q, Li Q, Wang H. Disease Burden Due to Herpes Zoster among Population Aged 50 Years Old in China: A Community Based Retrospective Survey. PLOS ONE. 2016; 11(4): e0152660.

3. Phuc L, Michael R. Herpes zoster infection. BMJ. 2019; 364: k5095.

4. Coyle ME, Liang H, Wang K, Zhang AL, Guo X, Lu C, Xue CC. Acupuncture plus moxibustion for herpes zoster: A systematic review and meta-analysis of randomized controlled trials. Dermatol Ther. 2017; 30(4): e12468.

5. Lauren N. Spezia Adachi, Rafael Vercelino, Carla de Oliveira, Vanessa L. Scarabelot, Andressa de Souza, Liciane F. Medeiros, Stefania G. Cioato, Wolnei Caumo, Iraci L.S. Torres. Isoflurane and the analgesic effect of acupuncture and electroacupuncture in an animal model of neuropathic pain. J Acupunct Meridian Stud. 2018; 11(3):97.
6. Irene Estores, Kevin Chen, Brian Jackson, Lixing Lao, Peter H. Gorman. Auricular acupuncture for spinal cord injury related neuropathic pain: a pilot controlled clinical trial. J Spinal Cord Med. 2017; (40)4: 432.

7. Xiao-mei Shao, Zui Shen, Jing Sun, Fang Fang, Jun-fan Fang, Yuan-yuan Wu, Jian-qiao Fang. Strong manual acupuncture stimulation of (Huantiao) (GB 30) reduces pain-induced anxiety and p-ERK in the anterior cingulate cortex in a rat model of neuropathic pain. Evid Based Complement and Alternat Med. 2019: 235491.

8. Du, X. H. Wen, D. S. Liu et al. Preliminary study on the therapeutic effect and effect mechanism of fire needling. Journal of Clinical Acupuncture and Moxibustion. 2018; 34(9): 1–4.

9. Yue Luo, Le Kuai, Ningjing Song, Xiaojie Ding, Xiaoying Sun, Ying Luo, Yi Ru, Seokgyeong Hong, Meng Xing, Mi Zhou, Bin Li, Xin Li. Efficacy and safety of fire needle therapy for nodular prurigo: A quantitative study. Evid Based Complement and Alternat Med. 2019:

10. HUANG Guofu, ZHANG Hongxing, XU Zusen, LI Jianwu. Comparison of Therapeutic effects of different types of acupuncture interventions on herpes zoster in acute stage. Acupuncture Research. 2012; 37:403.

11. Ying Zhang, Zuohui Liang, Xiuhong Liu, GuohuaLin, Qiannan Xu, Jianwen Qu. Journal of Yunnan University of traditional Chinese medicine. Observation on therapeutic effect of fire needle cupping on acute herpes zoster. 2016; 39(1): 50-53.

12. Ying Zhang, Shihua Li, LinYang, Qiannan Xu, Wenya Pei, Zuohui Liang, Xiuhong Liu, Juanjuan Yang, GuohuaLin. Shallow Fire-needle Acupuncture Stimulation Plus Cupping Relieves and Down-regulates Serum Substance P Level in Patients with Actue Herpes Zonster. Acupuncture Research.2018; 43:492-494.

13. Jae-Hwan Jang, Yu-Kang Kim, Won-Mo Jung, Hyung-Kyu Kim, Eun-Mo Song, Hee-Young
Kim, Ju-Young Oh, Ji-Yeun Park, Yeonhee Ryu, Mi-Yeon Song, Hi-Joon Park. Fire needle acupuncture regulates Wnt/ERK multiple pathways to promote neural stem cells to differentiate into neurons in rats with spinal cord injury. Front Neurosci. 2019; 13:995.

14. Hsiang-Chun Lai, Yi-Wen Lin, Ching-Liang Hsieh. Acupuncture-analgesia-mediated alleviation of central sensitization. Evid Based Complement and Alternat Med. 2019: 6173412.

15. Yang Shuqin. Health statistics. 3rd edition. Beijing: People's Medical Publishing House. 1992:148.

16. HUANG Shixi, WANG Yinghui, MAO Mei, et al. Parallel-controlled clinical study on assistance fili-fire needling and fili-fire needling combine with moxibustion for actue herpes zoster in the elderly. Journal of Traditional Chinese Medicine. 2012; 20:1742.

17. Le Bars D: The whole body receptive field of dorsal horn multireceptive neurones. Brain Res Brain Res Rev. 2002; 40:29-44.

18. Bini G, Cruccu G, Hagbarth KE, Schady W, Torebjork E. Analgesic effect of vibration and cooling on pain induced by intraneural electrical stimulation. Pain. 1984;18:239-248.

19. Kaptchuk TJ, Goldman P, Stone DA, Stason WB. Do medical devices have enhanced placebo effects? J ClinEpidemiol. 2000; 53(8):786-792.

Tables

Table 1: Gabapentin Scheme

| Day | Time          | 8:00 a.m. | 14:00 p.m. | 22:00 p.m. |
|-----|--------------|-----------|------------|------------|
| 1   |              |           |            | 300 mg     |
| 2   | 300 mg       |           | -          | 300 mg     |
| 3   | 300 mg       | 300 mg    | 300 mg     |
| 4   | 300 mg       | 300 mg    | 600 mg     |
| 5   | 600 mg       | 300 mg    | 600 mg     |
| 6   | 600 mg       | 600 mg    | 600 mg     |
| ... |              |           |            |            |
| 7   | Maximum dose | 1200 mg   | 1200 mg    | 1200 mg    |
Table 2: Secondary outcomes

| Symptom or sign(points) | 0   | 1   | 2   | 3   |
|-------------------------|-----|-----|-----|-----|
| Pain intensity          | no  | mild| medium, tolerable | severe, unbearable |
| local itching           | no  | mild| medium, tolerable | severe, unbearable |
| Burning sensation       | no  | mild| medium, tolerable | severe, unbearable |
| Rash colour             | no  | light red | red, no edema | red, edema |
| No. of blisters         | no  | 1-10 | 11-15 | 26 |
| Blisters clusters       | no  | 1-2 | 3-4 | 4-5 |
| Ulcer                   | no  | epidermis | superficial ulcer | deep ulcer |
| Fever                   | no  | ≤38°C | ≤39°C | 39°C |
| Local lymphadenopathy   | no  | 0.5cm | 0.5-1 cm | 1cm |
| Rash area reduction     | 0 | 30% | 60% | 100% |
 a reduction percentage |
| Analgesic demand(day)   | 1   | 2   | 3   | 4   | 5   | 6   | 7   |
| Paracetamol(g)          |     |     |     |     |     |     |     |
| Tramadol (mg)           |     |     |     |     |     |     |     |
| Tramadol injection(g)   |     |     |     |     |     |     |     |
| Dezocineinjection(mg)   |     |     |     |     |     |     |     |
| Side effects            |     |     |     |     |     |     |     |

Table 3. Baseline characteristics

| characteristics | value |
|-----------------|-------|
| Age, mean±SD, y |       |
| Gender, n (%)   | male  |
|                 | Female |
| Onset days, mean±SD, d | |
| VAS score, mean±SD | |
| Quantitative score, mean±SD | |

Onset days are the time from the patient's onset of pain or rash to inclusion.

Quantitative score is quantitative score of symptoms and signs

Figures
Figure 1

The flow chart of the trial
AHZ patients → Randomisation 1:1 → Group A (n=35): 7 days 1-7 sessions → Group B (n=35): 7 days Fam0.25g tid + Gaba 900-3600mg/d → Follow up 6 months later → Group C (n=35): 7 days 1-7 sessions FC+ Fam0.25g tid

Session of the three groups

Outcome measure

- VAS
- Symptom or sign(pients)
- β-Ep
- SP
- Analgesic demand(day)
- Side effects
- Follow up

Figure 2

The time schedule of this trial
### Figure 3

The schedule of enrollment, interventions, and assessments (according to the SPIRIT statement 2013)

#### Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Equation.docx
- SPIRITChecklistdownload8Jan13.doc