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

**Ying Zhang**
The six affiliated hospital of kunming medical university
**Zuohui Liang**
The six afflilitated hospital of kunming medical university
**Shihua Li**
The six affiliated hospital of kunming medical university
**Ling Yang**
The six affiliated hospital of Kunming medical university
**Taipin Guo** ( gtphncs@126.com )
Yunnan University of Traditional Chinese Medicine https://orcid.org/0000-0002-5298-8132
**Xu Yan**
The third hospital of Yunnan province
**Juanjuan Yang**
The six affiliated hospital of kunming medical university
**Qiannan Xu**
The sis affiliated hospital of kunming medical university
**Qing Zhang**
The six affiliated hospital of kunming medical university
**Jian Zhao**
The six affiliated hospital of kunming medical university
**Cailian Li**
The six affiliated hospital of kunming medicial university
**Xiuhong Liu**
The six affiliated hospital of kunming medical university

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# Abstract

Background Herpes zoster (HZ) is a common skin disease caused by invasion of the varicella-zoster virus into the ganglia and skin. Severe pain caused by HZ seriously affects the normal life of patients; thus, pain often becomes the patient's first complaint. Fire needle plus cupping may be effective for acute herpes zoster (AHZ), but the evidence is insufficient.

Methods This is a three-arm randomized controlled trial with an observation time of 1 week. A total of 96 patients with AHZ pain are divided into three groups by stratified randomization, with 32 in each group: (a) fire needle + cupping (FC); (b) famciclovir + gabapentin (FG), famciclovir hydrochloride, 3 × 0.25 g/d orally (p.o.), with an individualized dose of gabapentin 900-3600 mg/d p.o.; and (c) fire needle + cupping + famciclovir (FCF). The above intervention lasts for 1 week, and all patients receive analgesia (nonopioid analgesics [analgin or paracetamol] and opioid analgesics [tramadol or morphine]). Groups a and c undergo 1 to 7 sessions of fire needles and cupping treatments per patient, with gabapentin and analgesic medication administered depending on the patient's needs. The primary outcome measure is the assessment of changes in pain intensity before and after treatment (visual analogue scale ranging from 0-100 mm). Secondary outcome measures are changes in substance P and beta-endorphin concentrations in peripheral plasma before and after treatment. Quantitative scoring methods are used to evaluate the symptoms and physical signs before and after treatment, including pain classification, local itching, burning sensation, fever, local lymphadenopathy, skin lesion area, blisters, herpes clusters, vesicular traits, ulcers, and pimples. In addition, analgesic needs and side effects are evaluated.

Discussion: The results of this study will be obtained by randomised controlled trial(RCT), and the outcomes will be analyzed and evaluated to prove FC may be effective for AHZ.

Trial registration :The registration number is ChiCTR1800015372. Registered on 28 March 2018.


# Background

HZ is a skin infection caused by reactivation of varicella zoster virus (VZV), which is latent in the sensory ganglia. Its typical feature is that it causes herpes along the sensory nerve in the corresponding segment, accompanied by severe neuralgia, which has a serious impact on the quality of life of patients [1]. Some patients often have pain only at the beginning, without herpes, so they are often misdiagnosed. When it occurs in the neck and shoulders, the patient often mistakes HZ for cervical spondylosis and lumbar disc herniation. It is especially misdiagnosed in the left chest as a heart-related disease.

HZ can occur at any age, but older people are more commonly affected. Epidemiological studies on HZ show that the incidence, complications, hospitalization rate and average cost of HZ in China increased with the age. The cumulative incidence of HZ is 22.6/1000among people aged ≥ 50 years old, the cumulative incidence of HZ among people aged≥ 80 years old was 3.34 times of that among 50-years old[2].

At present, Western medicine has a clear understanding of the pathogenesis and pathological evolution of HZ, and it is confirmed that the pathogenesis of this disease is related to the body's immune function. Various factors that can cause the body's immunity to weaken can become the triggering conditions for the disease. According to the treatment plan of Western medicine, the acute phase is mainly antiviral, nutritional nerve, and analgesic. The antiviral drugs are mainly oral famciclovir and valacyclovir. The nutritional nerve is mainly mecobalamin, and the pain relief is mainly paracetamol and tramadol, dezocine, morphine, gabapentin. According to the condition, glucocorticoid drugs can be administered orally or intravenously. The sequelae phase is mainly analgesic and antianxiety. Oral drugs include tricyclic antidepressants, strong opioids, gabapentin, tramadol, pregabalin, and so forth. In addition, drugs such as methylprednisolone and triamcinolone acetonide can be used as nerve-blocking therapy. On one hand, the above-mentioned treatment scheme has a large side effect, especially for patients with renal insufficiency or immune system diseases, and the above-mentioned scheme is difficult to implement; on the other hand, the medical cost is high, and patients are not satisfied with the curative effect[3]. In addition, there are vaccines for the prevention of HZ. At present, the two HZ vaccines on the market are only for people over 50 years old. The vaccine can only reduce the incidence of HZ to a certain extent. The immune protection effect will decline after 3-4 years, and the efficacy will disappear completely in about 10 years, and the cost is expensive [4].

Although not a lifelong disease, HZ is quite painful and requires fast, economical, and effective treatments to relieve pain and shorten the course of the disease. Acupuncture may be an alternative therapy to HZ. Acupuncture has a good therapeutic effect on pathological neuralgia, and research on this aspect has made a lot of progress [5-9]. Fire needle and cupping which are integral part of the acupuncture therapy. The fire needle stimulates the meridians, dredges the meridians and collaterals, and accelerates the flow of Qi and blood. In addition, increases the nutrition around the lesion and promotes tissue regeneration, resulting in natural wound healing. From the perspective of modern medicine, the heat provided by fire needles promotes microcirculation in the lesion area through the regulation of cutaneous nerves, which is beneficial for the absorption of inflammation and metabolites [10]. Furthermore, the high temperature of fire needles directly kills the microorganisms and achieves anti-inflammatory effects [11]. Fire needle cupping has two advantages in promoting local skin lesion repair and rapid analgesia in the treatment of AHZ [12, 13, 15]. The method for treating AHZ has no side effects and is especially suitable for patients suffering from severe stomach diseases and/or liver and kidney dysfunction, which cannot be combined with drug treatment, and patients with obvious medical side effects.

# Methods

### Objective

The main purpose of this trial is to investigate whether a 1-week fire needle plus cupping treatment is different from that of famciclovir plus gabapentin or whether fire needles cupping need to be combined

with famciclovir better effect. The secondary objective is to analyse the correlation between the concentration of substance P and β-endorphin (b-Ep) in peripheral plasma and changes in pain intensity.

## Study design

As show in Figure 1, this study is a three-arm open randomized controlled trial consisting of the following: (a) fire needles plus cupping arm, (b) famciclovir plus gabapentin arm, and (c) fire needles plus cupping plus famciclovir arm (Figure 2). After randomization, arms a and 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 arm b. In addition, all patients can receive **temporary analgesics**, so that a sufficient pain therapy is guaranteed. Visual analogue scale (VAS) scores, symptoms, and physical scores are obtained before and after treatment. The concentrations of SP and β-Ep in peripheral plasma before and after treatment are detected by enzyme-linked immunosorbent assay, 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.

## Participants and recruitment

This study will recruit 96 patients by postering public posters in dermatology and acupuncture clinics and the website of the Sixth Affiliated Hospital of Kunming Medical University. When a potential participant sees the poster who can contact the dermatologists Zuohui Liang and Xiuhong Liu through the contact phone on the poster. Both dermatologists will enroll the participant in the study if all inclusion criteria and no exclusion criteria are met. After signing a consent form, they will contact Dr. Shihua Li by phone to unpack the envelopes and randomize the participants. The formal trial recruitment began in November 2018. The assistant researcher will assess and record the baseline status of the participants.

In order to achieve adequate participants enrollment to reach target sample size, we have developed two strategies to attract patients and published them on the recruitment poster: all participants are free of charge for using the treatment methods mentioned in the study plan; for participants with postherpetic neuralgia six months later, the Acupuncture Department provides 10 free acupuncture treatments.

## Randomisation and allocation concealment

1) Block setting: 96 participants will be numbered 1-96 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 96 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 96 envelopes and sealed, and all envelopes are numbered in order. 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.

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

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

### Blinding

Since the acupuncturists and subjects could not be blinded to the fire needle and cupping treatment, in order to reduce the bias, 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 fire needles and cupping. All acupuncturists have received a master's degree in acupuncture and moxibustion and have undergone training in unified fire needle and cupping treatment.

### 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;
- 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 occurr 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 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 analyze 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

### FC arm

This arm will be treated with Fire needle cupping, instead of famciclovir hydrochloride and gabapentin.

- 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- Medical cotton ball, alcohol lamp, lighter, iodophor, etc.
- Operational methods: Routine disinfection of skin with iodophor, lesions in accordance with the order of the head, middle, and tail of herpes, first prick the head, herpes cluster as a unit to prick in turn. The left handheld 95% alcohol lamp is close to the needle position (10-15cm). The needle in the right hand is burned to whitening by the external flame of the fire. Then prick into blisters or rashes. The needle goes straight out and penetrates into the skin of the herpes to reach its base (depending on the size of the blister). Prick early-onset herpes at first. For larger pustules or blood blisters (diameter ³5cm) with a large-scale fire, 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 is pricked three times. Then, sterilize skin with iodophor again. The treatment should be performed once a day for a total of 7 days. (Note: If there is no herpes and no pain, stop the fire needle and cupping treatment; forpain without herpes, continue the fire needle and cupping treatment until the pain disappears.)
- Skin care: After treatment, iodophor is used to clean and disinfect the skin. Ask patients to keep their skin dry and clean during treatment.

### Mechanism of fire needle cupping

Based on the theory of traditional Chinese medicine, herpes zoster is dampness and heat that blocks the meridians and collaterals, causing blood stasis and Qi stagnation, so it is painful.After being burned, the pinhole of the fire needle pricking the herpes wall is bigger, and it is not easy to close quickly. With the negative pressure absorption of the cupping, the damp heat and blood stasis in the herpes area will be completely discharged with the pinhole of the fire needle, making the Qi and blood unobstructed without pain. Previous studies have shown that fire needle cupping can accelerate crusting and shedding of herpes[14]; on the basis of conventional western medicine, the method of fire needle cupping can adjust the concentration of SP in serum, so as to accelerate the relief of local neuralgia in AHZ[15].

### FG arm

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/d.According to the manufacturer's (Jiangsu Hengrui Pharmaceutical Co., Ltd.) recommendation (Table 1), the initial dose of 300 mg/d is gradually increased to 900 mg per day and then increased according to the patient's needs (maximum dose: 3600 mg/d).

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

### FCF arm

This arm will be provided with therapy of fire needle cupping and famciclovir. The usage of fire needle cupping of this arm is the same as FC arms. Usage and dosage of famciclovir hydrochloride of this arm is the same as FG arm.

### Temporary analgesics

If the patient's pain can not be controlled below 50mm (VAS score) during the treatment, we will temporarily give additional analgesics. According to the recommendations of the World Health Organisation, all three groups are likely to receive standardized analgesic treatment: 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 forbad to use other analgesic drugs or therapies. Temporary analgesics demand will be recorded (table 2).

### Adverse events

Adverse events (symptoms or diseases occurring during the trial) will be recorded and assessed at each session of intervention. The adverse events mainly include 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.

### Fllow up

All participants will be followed up by telephone 6 months after the end of treatment to ask if there is postherpetic neuralgia.

### Outcomes

### Primary outcome

Changes in pain intensity before and after treatment (VAS 0-100 mm, where 0 = *painless* and 100 = *maximum imaginable pain*).

### Secondary outcomes

Substance P and b-Epin in peripheral venous blood will be detected by enzyme-linked immunosorbent assay before and after treatment.

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 No. of blisters blisters clusters ulcers fever local lymphadenopathy rash area. In addition, there are analgesics demands side effects and follow up results. For details, please see 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. 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.

### Statistical methods

### Samplesize estimation

We will compare the difference in efficacy of three therapies in arm a, b and c. Sample size estimation is based on the method of Health Statistics [16]. Type I error alpha = 0.05, 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:

[Please see the supplementary files section to access the formula.]

where$P_{max}$ =0.80 and $P_{min}$ =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. The rate of loss of follow-up should not exceed 10%.

### Statistical analysis

For details of baseline characteristics, please see Table 3.

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 (LOCF) 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 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 comparing fire needle plus cupping therapy with famciclovir plus gabapentin and fire needle plus cupping plus famciclovir. As far as we know, this is the first clinical trial to demonstrate fire needle cupping effect is different from that of reference therapy (famciclovir plus gabapentin and fire needle cupping plus famciclovir). Compared with previous studies on fire needle plus cupping therapy for HZ, this study has a more rigorous scientific design and will include more subjects.

There have been some previous Chinese literature reports on fire needle and cupping for HZ[12, 13, 14, 16]. However, on one hand, the Chinese literature makes it difficult for the therapy to gain international recognition; on the other hand, there is insufficient evidence to recommend fire needle cupping as the standard treatment for AHZ. In addition to observing the clinical efficacy of fire needle cupping, we will also study the mechanism of action.This is the first protocol about fire needle cupping. It is hoped that this study can provide a reference for the clinical use of fire needle cupping. Second, pain and rash are the main symptoms of HZ, so the expected results not only confirm that fire needle cupping is the basic treatment for HZ neuralgia but also can analogize other painful neuropathies and skin diseases. However, because of the patient age and gender distribution, which could result in different pain perceptions in this patient cohort, we cannot control each patient's symptoms individually. We believe that the balanced randomisation process explains the source of this bias.

Referring to the literature[12, 13, 16] and the previous results of this study [14], we did not use a placebo-controlled method but rather compared fire needle cupping therapy with famciclovir plus gabapentin and fire needle cupping plus famciclovir.The inclusion and exclusion criteria of this study are pragmatic, so as to facilitate screening and recruitment. Exclusion criteria exclude diseases that interfere with sensory perception. For all patients with AHZ, there is no single treatment program that shows complete effectiveness, and in actual clinical situations, it is usually necessary to combine antiviral Western medicine and analgesics to achieve local pain relief, so this study chose the fire needle and cupping therapy combination, famciclovir and gabapentin combination, and famciclovir fire needle and cupping combination.

Based on the Chinese literature of fire needle plus cupping for HZ and the previous clinical study of fire needle plus cupping for HZ [12, 13, 14, 16], we set up the fire needle cupping therapy group directly but did not set up a placebo control group (a sham fire needle cupping group). The reasons are as follows: First, the use of sham fire needle and cupping in clinical trials results in methodological problems. For example, a sham operation that is not in the lesion can activate the pain-suppressing system by stimulating the patient's mechano-sensitive Aβ-fibres[18,19], thus depriving the credibility of the cupping. In addition, all of these methods have a common problem affecting blind therapists. Second, Asian patients are familiar with cupping therapy, and it is not acceptable to operate fire needles and cupping on their non-lesional areas and claim to be effective. Third, HZ is accompanied by severe pain. It is contrary to ethical principlesto compare fire needle cupping therapy with a placebo. Fourth, acupuncturists are familiar with the difference between fire needle cupping in skin lesions and fire needle cupping therapy in non-lesional areas. Fifth, technical equipment and manual acupuncture skills cannot be directly compared, and they are also likely to result in variation in patients' beliefs in the treatment effects [20].

This is the first English article detailing the clinical study of fire needle cupping therapy. This study not only evaluates its clinical efficacy but also examines its analgesic mechanism. It is also the first comparison of fire needle cupping therapy with antiviral Western medicine plus gabapentin and fire needle cupping plus antiviral Western medicine in three-arm randomized parallel controlled trial. The design of this study is pragmatic, and it is expected to provide valuable new information on the clinical effects of fire needle cupping in the treatment of AHZ, so as to ensure that if fire needle cupping is found to be an effective treatment strategy for AHZ, its findings can be applied to clinical practice.

# Trial Status

This trialprotocol is version 2.1, dated 24 April 2019. This trialwill 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 + cupping + famciclovir :FCF.

# Declarations


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### Authors' contributions

* Correspondences are Xh L (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. Professor LgH and TpG participated in the design of the study. LsH performed the sample size estimation and was responsible for the blocked randomization of patients. YL is responsible for coordination of the study. LxH, LzH, and YjJ are responsible for subject recruitment. XqN, ZQ, QjW, and ZJ 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.

### Publisher's Note



### Authors' information

1.The Six Affiliated Hospital of Kunming Medical University, Yuxi 653100, China

2.School of Acupuncture-Moxibustion and Tuina and Rehabilitation, Yunnan University of Chinese Medicine, Kunming 650500, China

3.The Third People's Hospital of Yunnan Province, Kunming 650011, China

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# Tables

Table 1: Gabapentin Scheme

| Day Time | 8:00 a.m. | 14:00p.m. | 22:00 p.m. |
|---|---|---|---|
| 1 | - | - | 300 mg |
| 2 | 300 mg | - | 300 mg |
| 3 | 300 mg | 300 mg | 300 mg |
| Increase depending on patient’s needs | | | |
| 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℃ | ≤39℃ | ≥39℃ |
| Local lymphadenopathy | no | ≥0.5cm | 0.5-1 cm | ≥1cm |
| Rash area reduction percentage | 0 | ≥30% | ≥60% | 100% |
| **Analgesic demand(day)** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| Paracetamol(g) | | | | | | | |
| Tramadol (mg) | | | | | | | |
| Tramadol injection(g) | | | | | | | |
| Dezocineinjection(mg) | | | | | | | |
| **Side effects** | | | | | | | |

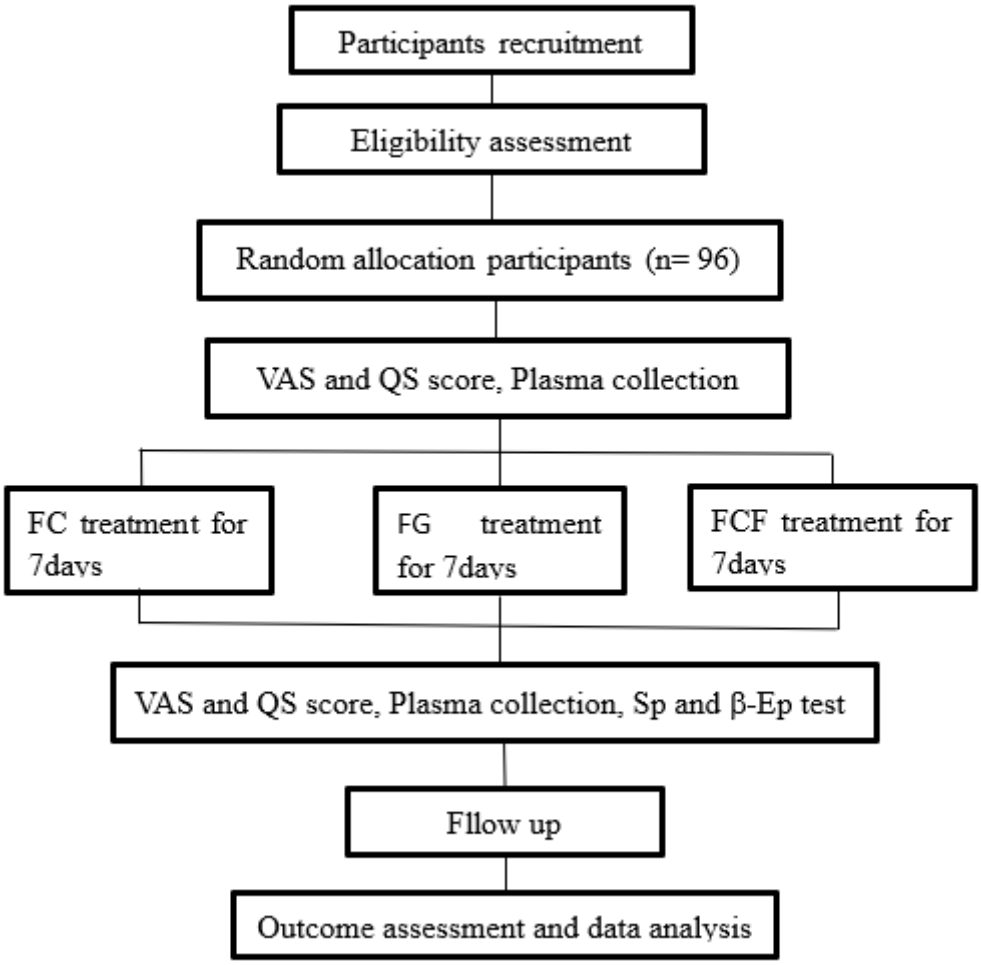
**Table 3. Baseline characteristics**

| 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

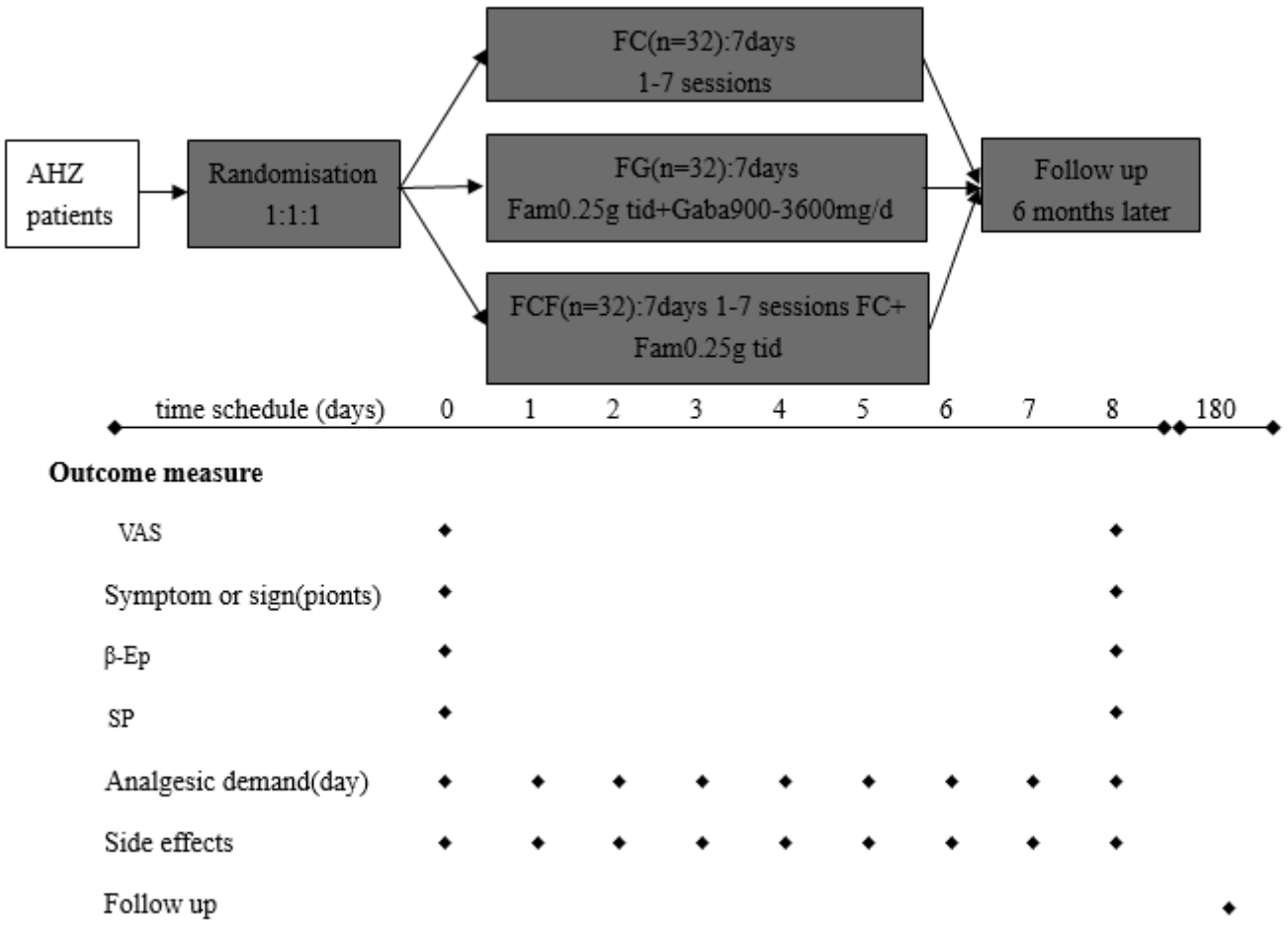



**Figure 2**

The time schedule of this trial

# Supplementary Files

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

- Additionalfile4Informedconsent.pdf
- Equation.docx
- SPIRITChecklistdownload8Jan13.doc