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

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Study protocol

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Abstract

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

Herpes zoster (HZ) is a skin disease caused by the varicella-zoster virus that is latent in the neurons, and the onset is rapid, often accompanied by severe pain. 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. It is estimated that about one-third of people will have HZ in their lifetime. Delay in treatment results in nerve pain, and the incidence of postoperative neuralgia can be as high as 50% to 85% [1]. The incidence of HZ and the incidence of complications increase with age [2,3]. Acute pain associated with acute HZ (AHZ) and chronic pain with postherpetic neuralgia have multiple adverse effects on health-related quality of life. The incidence of postoperative neuralgia is especially high in elderly patients, and there is currently no effective treatment and prevention method, which has become a problem that plagues doctors and patients. These pain conditions can cause significant disruption to physical, emotional, and social functions [4, 5] and lead to increased health care costs [6].

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 the curative effect is not very satisfactory.

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 [7-11]. In addition, acupuncture is considered a safe treatment without side effects [12]. Fire needle and cupping therapy belong to traditional acupuncture therapy. Fire needle plus cupping have two advantages in promoting local skin lesion repair and rapid analgesia in the treatment of AHZ [13,14,15]. 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 adverse drug treatments.

Methods

Objective

The main purpose of this trial is to investigate whether a 1-week fire needle plus cupping treatment is non-inferior to famciclovir plus gabapentin or whether fire needles and cupping need to be combined with famciclovir plus analgesics to 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, single-blind, stratified, randomized, controlled trial consisting of the following: (a) fire needles and cupping arm, (b) famciclovir plus gabapentin arm, and (c) fire needles plus cupping plus famciclovir arm plus standardized analgesia regimen for the treatment of AHZ (Figure 2). After randomization, arms a and c receive 1 to 7 treatment sessions of fire needles plus

cupping therapy within 1 week. All patients in arms b and c receive oral medication according to a standardized scheme. The administration of gabapentin depends on the needs of the patient. In addition, patients can receive analgesic escape medication, so that a sufficient pain therapy is guaranteed. Visual analogue scale (VAS) scores, symptoms, and physical scores are obtained before treatment, on the fourth day after treatment, 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 the analgesic needs and side effects of the patients are recorded daily. The total follow-up time per patient is 6 months.

Participants and recruitment

This study will recruit 96 patients through the public poster, the website of the Sixth Affiliated Hospital of Kunming Medical University. The formal trial recruitment began in November 2018. The assistant researcher will assess and record the baseline status of the participants. After obtaining written informed consent, random assignments will be made.

Randomisation and allocation concealment

(1) Stratification: 96 subjects will be divided into two groups, F and M, according to gender. Each group has 48 subjects, who are then divided into four layers according to age: A1 layers, 18-29 years old; A2 layers, 30-39 years old; A3 layers, 40-49 years old; A4 layers, 50-59 years old. Each layer will consist of 12 subjects.

(2) Obtain random numbers: Starting with any number in the random number table, 12 numbers will be designated as A1 layers. In the F group, each number is divided by 3, and the remainder of 0 is arm a, the remainder of 1 is arm b, and the remainder of 2 is arm C. The same method is used to complete random stratification of the other layers. Operated twice like this to obtain random numbers of all subjects.

(3)2N envelopes numbered 1-N are loaded into groups of 1-N subjects and sealed. To ensure proper management of the randomization program, the serial number will be printed on the outside of the opaque envelope, and the group assignment will be sealed internally. All envelopes will be numbered in sequence. The above work was completed by LsH, an otolaryngologist at the Sixth Affiliated Hospital of Kunming Medical University. LsH 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 and acupuncturists will obtain the patient’s random number and arm assignment by telephone.

Blinding

To prevent the participants from being given other treatments or drugs, the dermatologist and the acupuncturist will be informed about the arming of the patients, but the patient will be unaware of the arming from the beginning to the end of the study. Scale information collectors and data analysts do not know about grouping and treatment of patients.

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

- Confirmed diagnosis of AHZ(recruitment at the Departments of Dermatology and Acupuncture and Moxibustion of the Sixth Affiliated Hospital of Kunming Medical University);
- 18 to 60 years old;
- 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;
- Those who do not follow the treatment plan;
- Pregnancy or lactation;
- Surgery within the past 3 months;
- Diseases affecting quality of life;
- 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.

Intervention

FC arm

- 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; for pain 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.

FG arm

The famciclovir hydrochloride dosage is 0.25g 3 times a day; the individual dose of gabapentin is 900-3600 mg/d. According to the manufacturer's 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

The use of fire needle plus cupping therapy and famciclovir of this arm is the same as in the above two groups.

Rescue medication

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); step 2: moderate-strength opioids (tramadol tablets, maximum dose 600 mg/d); step 3: moderate-strength opioids (tramadol injection, 0.1g, once a day); step 4: recommend the use of stronger opioids (dezocine injection, 5mg, once a day). Patients are forbad to use other analgesic drugs or therapies.

Outcome

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-Ep in peripheral venous blood were 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 analgesic demands and side effects. 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

Sample size estimation

To prove the non-inferiority of fire needle plus cupping therapy, we will compare the efficacy of the fire needle plus cupping arm with the famciclovir plus gabapentin arm and fire needle plus cupping plus famciclovir arm. 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:

Due to technical limitations, Equation 1 has been placed in the supplementary files section.

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

To confirm whether experimental therapy E (fire needle plus cupping) is not inferior to reference therapy R (famciclovir plus gabapentin), the original statistical hypothesis is as follows [16]:

$H01: \mu R \leq \mu P$

$H02: \mu E - \mu R \leq -\Delta$

First, using the appropriate alpha level test for H01, H02 is further tested only if H01 is rejected, and if H02 is rejected, experimental therapy E is considered to be non-inferior to reference therapy R. The non-inferiority boundary value is calculated according to the preliminary test: $\Delta = 50\% \times (\mu R - \mu P) = 5$ mm.

The data will be entered into the ResMan public management platform of the China Clinical Trial Registry. Data analysis will be performed using SPSS 18.0. All data entry will be performed twice.

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 its non-inferiority by evaluating the efficacy of fire needle plus cupping compared with standard antiviral drug plus gabapentin. 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[13, 14, 15, 17]. 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 and cupping as the standard treatment for AHZ. In addition to observing the clinical efficacy of fire needle and cupping, we will also study the mechanism of action. This is the first protocol about fire needle plus cupping. It is hoped that this study can provide a reference for the clinical use of fire needle plus cupping. Second, pain and rash are the main symptoms of HZ, so the expected results not only confirm that fire needle plus 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[13, 14, 17] and the previous results of this study [15], we did not use a placebo-controlled method but rather compared fire needle plus cupping therapy with famciclovir plus gabapentin and fire needle plus 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 analgesic drugs 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 [13, 14, 17] and the previous clinical study of fire needle plus cupping for HZ, we set up the fire needle plus cupping therapy group directly but did not set up a placebo control group. The reasons are as follows: First, the use of placebo 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 plus cupping therapy with a placebo. Fourth, therapists are familiar with the difference between fire needle plus cupping in skin lesions and fire needle plus 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 plus 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 plus cupping therapy with antiviral Western medicine (gabapentin) and fire needle plus cupping plus antiviral Western medicine in three randomized controlled clinical studies. The design of this study is pragmatic, and it is expected to provide valuable new information on the clinical effects of fire needle plus cupping in the treatment of AHZ, so as to ensure that if fire needle plus cupping is found to be an effective treatment strategy for AHZ, its findings can be applied to clinical practice.

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 + cupping + famciclovir :FCF.

Declarations

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Authors' contributions

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 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.

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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°C	≤39°C	≥39°C
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							

Figures

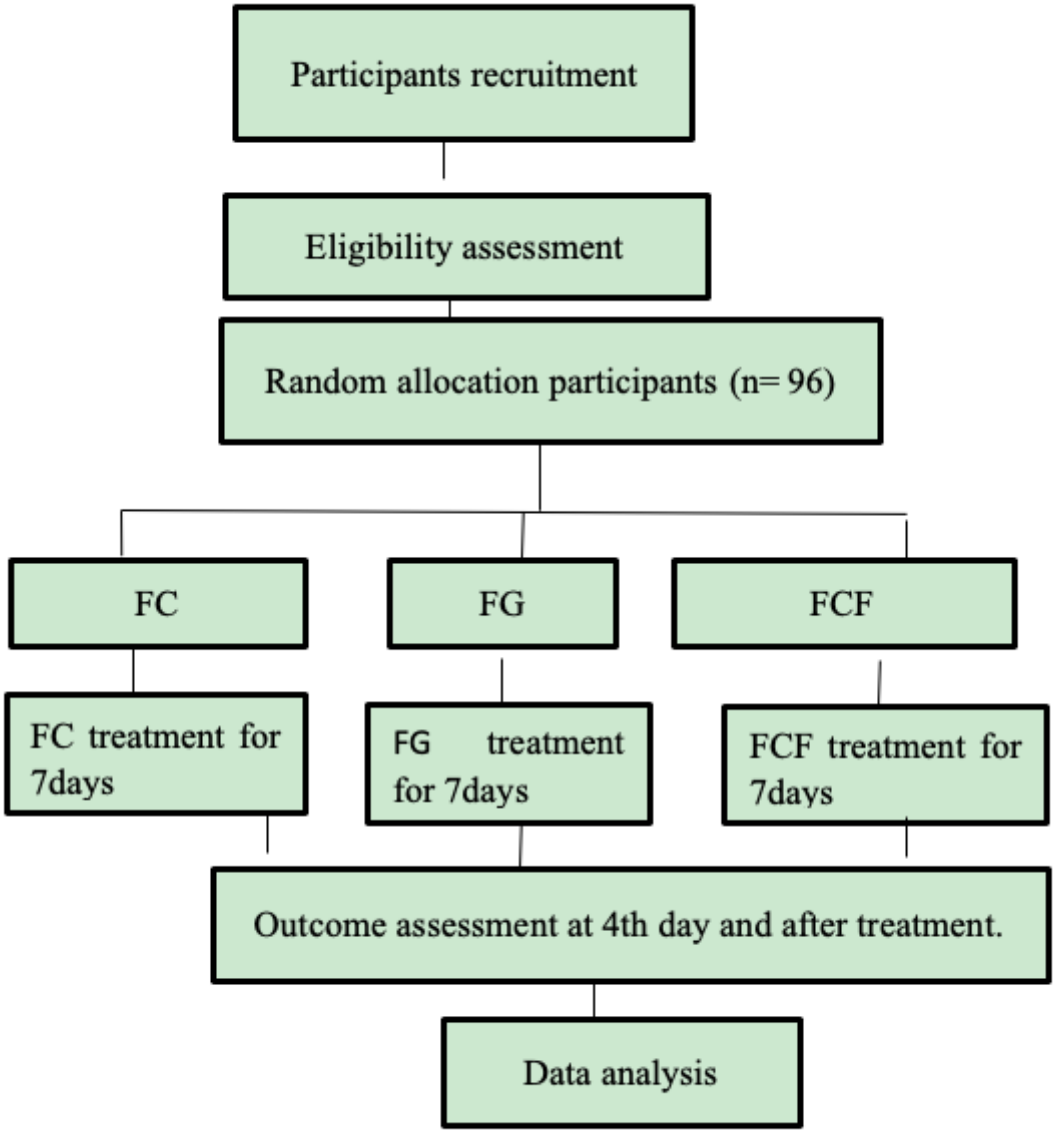

Figure 1

The flow chart of the trial.

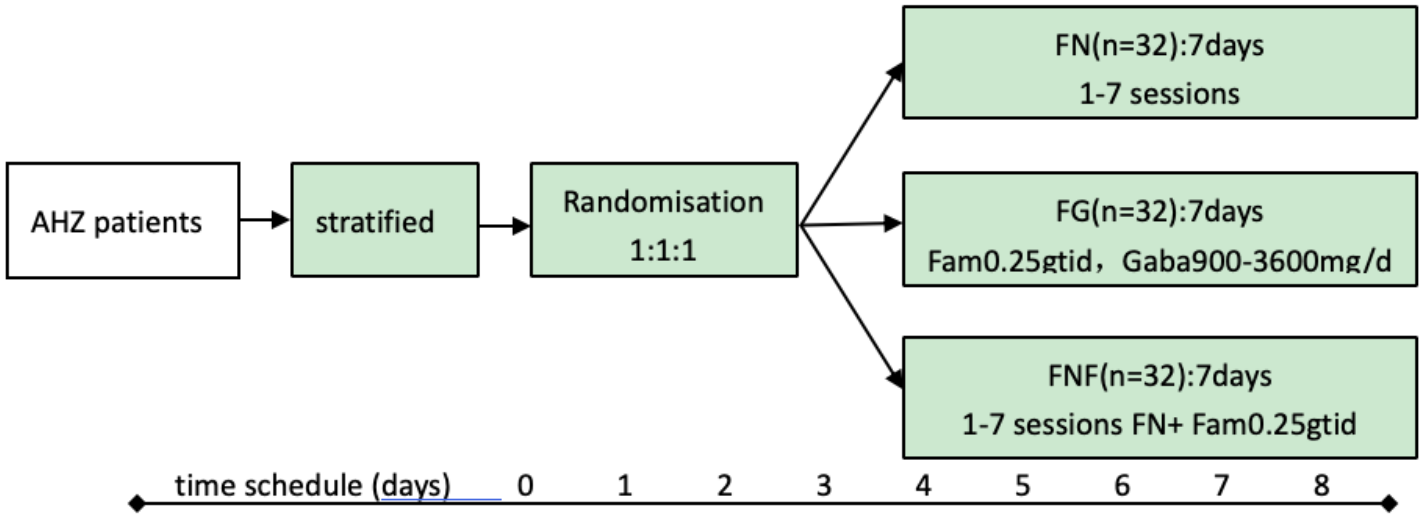

Figure 2

The time schedule of this trial.

Supplementary Files

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- supplement1.png
- supplement2.doc