An healthy lifestyle consultant based on Traditional Chinese medicine versus routine patient education in the treatment of idiopathic sudden sensorineural hearing loss after failure of systemic therapy: Study protocol for a clinical randomized trial with a paired design

Yingping Fei (feiyingping@stu.scu.edu.cn)  
Sichuan University West China Hospital  
https://orcid.org/0000-0002-8844-3708

Yun Zheng  
Sichuan University West China Hospital

Dan Lai  
The Affiliated Hospital of Southwest Medical University

Ping Zhong  
Sichuan University West China Hospital

Jing-zhe Lu  
Sichuan University West China Hospital

Gang Li  
Sichuan University West China Hospital

Peng Liu  
Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital

Method Article

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Abstract

**Background:** Idiopathic sudden sensorineural hearing loss (ISSNHL) is an important cause of deafness. Despite advances of systemic therapy, some ISSNHL patients remains ineffective since the exact etiology for SSNHL is still unclear. Traditional Chinese medicine (TCM) has been used for treating disease for thousands of years. It is popular and widely practiced in Asia. TCM contains guidance on people's healthy lifestyle. In recent decades, the relationship between lifestyle and disease has been emphasized and unhealthy lifestyle may lead to illness. Thus, this study aims to compare the efficacy of the lifestyle modification based on TCM to the usual consultation of the ISSNHL after failure of two weeks systemic therapy, to provide a scientific basis for clinical decisions.

**Methods:** This is a clinical randomized trial with a paired design which will include 58 patients diagnosed with ISSNHL, according to the American Academy of Otolaryngology-Head and Neck Surgery sudden hearing loss clinical guideline published in 2012, but incomplete recovery from ISSNHL after of initial management. Participants will be randomized to either healthy lifestyle modification group based on TCM or control group. All patients will be followed for 3 months. The primary outcome measure is the effective rate of hearing improvement (defined as the proportion of patients with at least 15-dB improvement in the average thresholds by the hearing loss frequency). Secondary outcome measures are the improvements in pure-tone average (PTA) of the impaired frequencies, Word Recognition Score (WRS), Tinnitus Handicap Inventory (THI) and ear blockage. The assessments of the participants will be made at baseline, after lifestyle modification in 1 month and 3 months.

**Discussion:** This trial will determine the efficacy of healthy lifestyle modification based on TCM program for ISSNHL patients with incomplete recovery from after failure of initial systemic therapy. The results, if it is yielding positive results, will provide clinical evidence and TCM based healthy lifestyle could be recommended as salvage therapy for patients with ISSNHL.

**Trial Registration:** ClinicalTrials.gov, ChiCTR-INR-17011459. Registered on May 22 2017.

**Keywords:** ISSNHL, TCM, healthy lifestyle, Study protocol, randomized controlled trial

Background

Idiopathic sudden sensorineural hearing loss (ISSNHL) is a common otologic emergency presenting mostly as an acute hearing loss with an abrupt occurrence and is defined as a hearing loss of more than 30dB that occurs in at least 3 consecutive frequencies occurring within 72 hours [1]. Apart from hearing impairment, SSHNL can be associated with dizziness, tinnitus and/or ear fullness/blockage. The incidence of SSHNL is approximately 5-30/100,000/year in developed countries such as the United States, Sweden, and Japan by national surveys[1-4]. Only about 10% of patients with ISSNHL show a specific cause by detailed investigation [5]. Although the precise cause of ISSNHL has not been identified, a number of pathophysiological mechanisms have been proposed, including microcirculation, autoimmune pathology, viral infection, intra-cochlear membrane rupture, or hematologic problems [6].
Various studies have suggested that ISSNHL may not be due to a single pathological change, but rather a spectrum of pathologies that affect the cochlea [7].

The most common treatment options for ISSNHL is corticosteroids within the first two weeks [4]. 49%-89% of patients with ISSNHL showed recovery within systemic steroid therapy whereas the others no effects [8]. It is noteworthy that spontaneous recovery occurs in 32%-65% of the cases, usually within the first 14 days [9,10]. While after 2 weeks patients in whom there is no change would be unlikely to show much recovery [11]. Intratympanic steroid perfusion has been recommended as salvage therapy described in USA guidelines [1]. However, the clinical evidence is also controversial, and there is no consensus regarding the efficacy of intratympanic steroid therapy for ISSNHL [1,12,13]. Therefore, the problems of ISSNHL patients who failed with treatment within two weeks need further research and the development of therapies. Due to a significant spontaneous recovery rate and existing standard therapy for ISSNHL (systemic glucocorticoids), patients will only be enrolled into the study if no or insufficient recovery of hearing threshold could be observed after initial 14 days systemic therapy and reluctant to continue to receive medicine salvage therapy.

Traditional Chinese medicines (TCM) originated in ancient China and have been used in therapeutic approaches in East Asia for more than 2,500 years. TCM includes not only well-known herbal medicine acupuncture, massage (tui na) but also lifestyle modification such as dietary therapy, exercise (taiji, qigong). It origins from Huang Di Nei Jing, a famous work of ancient TCM literature, which introduced keep the Yin-Yang imbalance of internal organs by a healthy lifestyle. From the perspective of TCM, all disease originates from the broken the balance. In China, Chinese patients prefer to use TCM methods as an optional choice of complementary and alternative medicines for the treatment of disease. The lifestyle change guided by TCM theory is also acceptable in Chinese people with disease.

Lifestyle has been suggested to use for some otology disease that is unable to be well controlled by medicine. Dietary habits such as low sodium can alter inner ear fluid homeostasis and auditory function. Endolymph compartment is maintaining a low-sodium concentration while keeping ionic balance with the surrounding perilymph and serum [14]. Evidence shows that more than 85% of the patients with Meniere's disease are helped by changes in lifestyle along with either medical treatment, or surgical procedures. These lifestyle changes include to reducing the consumption of salt, caffeine products, chocolate, alcohol, salt products as much as possible[15]. A cross-section study indicates a significant relationship between BPPV and inadequate carbohydrate and fiber intake, the subjects rich in polyunsaturated fatty acids. Food readjustment is suggested in patients with BPPV [16]. Furthermore, a descriptive longitudinal cohort study about 159 adult patients suffering from chronic primary tinnitus and sleep problems has shown that TCM based lifestyle counseling may relieve chronic primary tinnitus. After 6-26 months long-term follow-up, sleep quality were improved, and tinnitus loudness, the impact of tinnitus on sleep, concentration, and emotional state were also relieved [17].

Therefore, this randomized controlled clinical trial was designed to evaluate the efficacy of TCM based lifestyle modification as a salvage therapy for patients who have not recovered 14 days after the onset by
systemic steroid therapy of ISSNHL.

Methods

Objective

This RCT trial will evaluate the effectiveness of healthy lifestyle treatment instructed by TCM therapy for ISSNHL patients who have no or insufficient recovery of hearing threshold after initial systemic therapy for 14 days and reluctant to continue receive medicine salvage therapy.

Study design

The trial will recruit 56 patients. The participants who meet the inclusion criteria and written informed consent will be enrolled in the trial, which last 3 months period. A flow chart of the trial procedure is shown in Fig.1.

This trial is registered in China Clinical Trials Registry (Registration number: ChiCTR-INR-1701145) and has been approved by the Biomedical Branch of Ethics Committee of West China Hospital of Sichuan University (identifier 2016-180). We will perform the study according to the Declaration of Helsinki guidelines for clinical trials. The protocol was written in line with the SPIRIT checklist (see Additional file 1) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure (Fig. 2).

Recruitment

Participants who diagnosed with ISSNHL but failed with initial systemic treatment at least 14 days will be recruited by posters in the West China Hospital of Sichuan University.

Participants

Inclusion criteria

1. Signed informed consent form. Participants must be willing and able to consent to participate in the study.
2. Diagnosis of unilateral ISSNHL, defined as onset within 72 hours affecting three consecutive frequencies of unknown etiology [1].
3. Hearing loss occurred at least 14 days ago but less than or equal to a year.
4. Insufficient recovery of the ISSNHL at least 14 days after onset the patient received Chinese ISSNHL guideline recommended standard therapy.
5. Reluctant to receive drug including steroid therapy.
6. Age is greater than 18 years old and less than 60 years old.
7. Hearing in the contralateral ear is at least 20 dB.
8. Stop medication for more than 3 days.
Exclusion criteria

1. Previous disease or surgery in the affected ear
2. Hearing loss from an identified etiology, including head trauma, conductive hearing loss, Meniere's disease, tumor.
3. Patients unable to complete the relevant assessment such as cognitive impairment, mental disorder.
4. Serious comorbid conditions (like progressive central disorder or life-threatening condition)
5. Any reason, in the investigator's opinion, that prohibits inclusion into the study.

Randomization

To ensure each treatment condition has an equal proportion, a randomized paired design, a special case of a randomized block design, will be adopted. Participants will be matched and paired based on similar baseline assessment such as gender, age, the degree of hearing loss, duration of ISSNH at the time of study entry. Number each pair, such as 1-1, 1-2, 2-1, 2-2, ..., 28-1, 28-2. Within each pair, subjects are randomly assigned using a computer-generated random number to either intervention group or control group. The random Numbers prepared in advance and enclosed in a sealed envelope. It is also specified in advance that, in odd numbers, patients numbered 1 in the pair will be in the control group and patients numbered 2 in the pair will be in the experimental group, even numbers, just the opposite. The distribution ratio of the two groups will be 1:1. An independent researcher not involved in the study will be responsible for the randomization procedures.

Intervention

Participants in the control group will receive routine care, while those in the intervention group will receive additional lifestyle counseling based on TCM.

The routine care includes the following two aspects.

- Educate participants about ISSNHL natural history of the condition, the limitation of existing evidence regarding efficacy. Answer their questions about ISSNHL.
- Counsel participants the benefits of amplification, hearing assistive technology and other supportive measures, especially for those the hearing loss lasted more than three months.

The lifestyle counseling will consist of four sessions. The first step is to complete the lifestyle survey of each participant, and then one-to-one targeted counseling based on the survey results.

- Dietary According to the theory of traditional Chinese medicine, Yang qi is an important reason for maintaining normal human function and a food's energy can have a huge effect on your health. Therefore, the diet should be dominated by staple food, while paying attention to avoid eating “cold” energy food. In simple terms, the central components of the dietary strategy are the Chinese main food (“neutral” energy) such as rice and wheat meanwhile avoids “cold” energy food such as most
fruits from the TCM perspective. The dietary adopted a principle encouraged participants to consume Chinese Main foods and stir-fry vegetables by “hot” energy pepper with a ratio of 7:3. Meanwhile, try to be avoided eating food with animal products. Because it contains too much fat.

- **Sleep** Go to bed at night and avoid to stay up late, get up at dawn, just as nature does. It is recommended to fall asleep by 10-11 pm and rising 5-7 am, ensuring an in bed sleeping window between 10 pm and 5 am. So it was necessary to reduce water intake before sleep to avoid getting up in the night to urinate. Participants had better not sleep at daytime. A less than 30 min short nap before 2 pm will be advised for those nonadaptation patients.

- **Mood** The physician communication with participants to answer their doubts and discuss the relationship between mood and SSNHL and the importance of good mood to health. Reduce participants fear, despair and anxiety as much as possible.

- **Physical activity** All participants were encouraged to be moderately physically active such as do Taiji (a kind of traditional Chinese sport), housework, walk and leisure activities. Patients should not recommend engaging in deliberate strenuous physical exercise, especially before going to bed or on a full stomach and avoid being too tired.

We will also take the following measures to improve patient compliance and reduce the drop-out rate.

All participants are entitled to free all assessment including audiology tests, one-to-one consultation, and lifestyle assessment. In addition, without registration fee for first-level expert outpatient service of west China hospital. At the end of the experiment, a free online consultation service will be provided for one year.

Especially with the lifestyle modification group, we will provide the weekly one-to-one consultant with regular consultants, as well as periodic check-ins over the phone, in order to reinforce the importance and significance of the lifestyle change and answer their question about it. Encourage participants to keep a symptom log, includes ear associated symptoms and systemic symptoms. Symptoms will be recorded by means of recovery, partial recovery, no change, and aggravation. Meanwhile, providing daily email contacts about the journal of their lifestyle: Sleep and wake times, daily diet (see Additional file 2). Participants will be required to fill in the form daily within one month of treatment.

**Outcome measures**

The outcomes will be evaluated at baseline, 1 month and 3 months after intervention.

The primary outcome measure

The effectiveness hearing improvement, measured by pure tone average in their hearing loss frequency band. The effects will be divided into four categorize, according to patients gains pure tone thresholds. Complete recovery defined as hearing loss within 20 dB HL or reached the level of the normal unaffected ear. Significant recovery defined as hearing gains more than 30 dB HL, effective recovery is gains of 15-30 dB H, and ineffective is gains of less than 15 dB HL [1,18].
Secondary outcome measure

Word recognition score (WRS)[19] for all participants. Participants with tinnitus will be measured by Tinnitus Handicap Inventory (THI) [20], and common company symptoms dizziness and ear blockage also be evaluated for those have it. Other outcomes that will be evaluated are impedance audiometry, distortion product otoacoustic emission, and lifestyle change based on the lifestyle questionnaire.

Blinding

The audiologist, research assistants and statisticians and participants involved in the study will blind with the allocations. As the nature of the counseling, it is impossible to blind in the consultant. During the process, consultant and other researchers will request not to communicate with each other about the patient group. Patients will also to keep their treatment methods secret. At the completion of the trial, patients in the control group will be offered access to be lifestyle modification intervention.

Sample size

To the best of our knowledge, no randomized pilot study has been conducted to assess the effectiveness of lifestyle changes on ISSNHL. We, therefore, could not calculate the sample size based on the previous studies. Basing on retrospective analysis, the efficiency ratio of the intervention group and the control group were conservatively estimated to be 50% and 10%. Using the following formula for calculated the sample size of optimal treatment in the clinical trial and considering $\alpha=0.05$, $\beta=0.1$, by the table of normal distribution quantifiers $U_{\alpha}=1.65,U_{\beta}=1.28$. A 23-patient sample size per group was required. We allow for a 20% loss to follow-up, giving a total sample size of 56 patients (28 per group) in the study.

\[
\begin{align*}
n &= (U_{\alpha}+U_{\beta})^2P(1-P)/(P_1P_0)^2 \quad [21] \\
P &= (P_1-P_0)/2 \times 100\%
\end{align*}
\]

$P_0$: Original efficacy, $P_1$: expected efficacy

Safety

Throughout the course of the trial, any adverse events and discomfort experiences will be recorded by patients and data collectors.

Participants may withdraw from the study for any reason at any time. The researchers will record the reason in case report forms.

Statistical analysis

The data will be analyzed using the Statistical Package for the Social Sciences V.21.0 statistical software package (SPSS, Chicago, IL, USA), with the significance level set at 0.05(two-tailed) by statisticians who are independent of the research team. When testing the baseline differences between the two groups,
continuous variables will be described using means and standard deviations and tested with t tests. Categorical variables will be presented using percentages and tested with chi-squared tests. The two-way ANOVA will be used to compare the effect of the treatments between the two study groups. Logistic regression will be used to describe data and to explain the relationship between effect and lifestyle. All analyses will utilize an intention-to-treat principle.

Data management

To ensure the accuracy of the data, two independent researchers blinded to the group allocation will input the data on the Excel spreadsheet, and the data will be checked twice. It will be confirmed with original case report forms when any different data entry is discovered. Paper files and electronic documents will be kept in a locked filing cabinet and protected computer separately. Only principal researcher will allow accessing. Researchers will be unable to modify data after it. The researcher shall keep the information of the impartments strictly confidential and shall not disclose it under any circumstances. Meanwhile, the researcher shall sign a confidentiality agreement.

Discussion

ISSNHL is an acute disorder that occurs throughout life and usually cannot find etiology. Although 49%-89% cases have been returned to the normal hearing by existing therapy with oral or intravenous steroids and 32-65% spontaneous recovery rate, patients who have incomplete recovery from ISSNHL after the failure of initial management remains a problem. Some patients reluctant to receive recommend glucocorticoids treatment due to fear of side effects, contraindications, and drug-to-drug interactions. The salvage therapy recommended by the 2012 ISSNHL guidelines is IT steroid perfusion, hearing improvement ranging from 53% to 90% in the treatment group [22,23]. The dose and concentration of steroids vary, as do the criteria used to define hearing improvement.

Previous studies indicate that patients who do not show any improvement within the first 14 days are unlikely to have much recovery afterward [9,10]. Thus the patient's usual loss hope to continue therapy. Therefore, an acceptable and simple therapy is required to improve the effects of refractory ISSNHL for these patients.

TCM has been used for thousands of years to treat diseases in China and Chinese people easily accept it. Lifestyle, as part of traditional Chinese medicine, has been integrated into Chinese culture. All the time, there is a tradition and sustained interest in the benefits of TCM recommend lifestyle, especially for patients cannot be effectively treated by western medicine. We designed this trial with the hope of verifying that lifestyle based on TCM can provide help of hearing loss and concomitant symptoms in patients with ISSNHL. If successful, this intervention will at least help refractory ISSNHL patients in China.

The study has designed to explore the efficacy of TCM instructed lifestyle change for ISSNHL patients with no or insufficient recovery of initial systematic Western medicine treatment. Even though there are
suggestion with IT steroid perfusion for this kind of ISSNHL in Western medicines, the evidence of their efficacy is still unclear. In this study, the effective rate of hearing improvement will be used as the primary outcome measure. It is the most common parameter for ISSNHL. The secondary outcome measures including WRS, THI and accompany system including dizziness and ear fullness. Because in addition to hearing loss, many people with ISSNHL complain of cannot hear clearly, tinnitus and dizziness. The exact mechanisms that explain lifestyle based on TCM effects on ISSNHL need further detailed research and discussion in the future.

Study limitations

One of the major drawbacks is the lifestyle questionnaire currently widely adopted are not used. The main reason is that we recommend the method is different from lifestyle which emphasis on the general trend rather than specific quantification, the existing tools are not suitable. Since lifestyle includes sleep, diet, mood and exercise, the factor that play a key role is still unknown. Therefore, well-designed randomized controlled trials that compare different factor of lifestyle with each other are necessary in the future.

Abbreviations

ISSNHL: Idiopathic sudden sensorineural hearing loss, TCM: Traditional Chinese medicine, PTA: pure tone average, WRS: word recognition score, THI: tinnitus handicap inventory.

Declarations

Trial status

The protocol was was registered on May 22, 2017 and the registration number is ChiCTR-INR-17011459. The participant recruitment began on August 9, 2017 and is ongoing at the time of manuscript submission. We expect this process to be completed in May 2019.

Ethics approval and consent to participate

This trial has been approved by the Biomedical Branch of Ethics Committee of West China Hospital of Sichuan University (identifier 2016-180). Study participation is voluntary and can be cancelled at any time without provision of reasons and without negative consequences for their future medical care. The informed consent will be obtained from all study participants before they enroll in the trail by us.

Consent for publication

All authors and investigators give their consent for publication.

Availability of data and material
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

There is no funding for this protocol. This trial will conducted with no external funding and will be instead from the education fund for graduate students and Professor zheng's individual research fund.

Authors' contributions

DL designed this trial. YPF drafted the manuscript. YZ and PL contributed to supervise this study and participated in revising the manuscript. PZ and JZL provided advice and support. GL was responsible for reasonable statistical analysis. All authors read and approved the final manuscript.

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Authors' information

1 Hearing Center/Hearing and Speech Science Laboratory, Department of Otolaryngology Head and Neck Surgery, West China Hospital of Sichuan University, No. 37, GuoXue Xiang, Chengdu, Sichuan 610041, People's Republic of China

2 Department of Otolaryngology Head and Neck Surgery, The Affiliated Hospital of Southwest Medical University, 25 Taiping street, Jiangyang District, Luzhou, Sichuan 646000, People's Republic of China

3 Department of Otolaryngology Head and Neck Surgery, The first affiliated Hospital of Guangzhou University of Chinese Medicine, No. 16Yard, airport road, Guangzhou 510405, People's Republic of China.

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Figures
Figure 1

Trial flow chart. PTA pure tone average, WRS word recognition score, THI tinnitus handicap inventory.
| STUDY PERIOD | Enrolment | Allocation | Post-allocation(months) |
|--------------|-----------|------------|-------------------------|
| Recruitment stage |           | Pre-intervention 0 months | 1 | 3 |

**ENROLMENT:**
- Eligibility screen
- Informed consent
- Hearing tests: PTA, WRS
- Lifestyle assessment
- Assessment of dizziness and ear blockage
- Allocation

**INTERVENTIONS:**
- Intervention group
  - (Lifestyle modification + routine care)
- Control group
  - (routine care)

**ASSESSMENTS for intervention group and control group**
- Primary outcome variables: The effective rate of hearing improvement
- Secondary outcome variables: WRS, THI and Assessment of dizziness and ear blockage

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**Figure 2**

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure: proposed schedule for enrolment, intervention and assessment. PTA pure tone average, WRS word recognition score, THI tinnitus handicap inventory.

**Supplementary Files**
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