Healthy lifestyle consultation 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 randomised trial

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Study protocol

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Abstract

Background: Idiopathic sudden sensorineural hearing loss (ISSNHL) is an important cause of deafness. Despite the advances in systemic therapy, some cases of ISSNHL are untreated, because the exact ISSNHL aetiology is unclear . Traditional Chinese medicine (TCM) has been used for treating diseases for thousands of years and is popular and widely practic ed in Asia. TCM includes guidance on healthy lifestyle. In recent decades, the relationship between lifestyle and disease has been emphasised. Moreover, an unhealthy lifestyle may lead to illnesses . Thus, this study aims to compare the efficacy of lifestyle modification based on TCM with the usual consultation of ISSNHL after failure of a 2 weeks systemic therapy to provide a scientific basis for clinical decisions. Methods: This study is a clinical randomised trial that involves 56 patients diagnosed with ISSNHL but with incomplete recovery after initial management (at least 2 weeks routine Western medical treatment). The study is performed in accordance with the sudden hearing loss clinical guideline of the American Academy of Otolaryngology – Head and Neck Surgery , which is published in 2012 . Participants are randomly distributed into two groups, namely, the healthy lifestyle modification group based on TCM and the control group (1:1 ratio). Patient follow-up lasted for 3 months. The primary outcome measure is the effective rate of hearing improvement, which is defined as the proportion of patients with at least 15 dB improvement in the average thresholds by the hearing loss frequency . The secondary outcome measures are the improvements in word recognition score, tinnitus handicap inventory for tinnitus and visual analogue scale for ear blockage and dizziness. Assessments are made at baseline after lifestyle modification for 1 and 3 months. Discussion: The efficacy of healthy lifestyle modification based on a TCM programme for patients with ISSNHL with incomplete recovery after failure of initial systemic therapy is determined in this trial. Positive results provide clinica l evidence on the effects of TCM - based healthy lifestyle, which could be recommended as salvage therapy for patients with ISSNHL.

Background

Idiopathic sudden sensorineural hearing loss (ISSNHL) is a common otologic emergency, which presents mostly as an acute hearing loss with an abrupt occurrence; ISSNHL is defined as a hearing loss of more than 30dB that occurs in at least three consecutive frequencies occurring within 72 h[1]. Apart from hearing impairment, ISSHNL can be associated with dizziness, tinnitus and/or ear fullness/blockage. National surveys indicate that the incidence of ISSHNL is approximately 5–30/100.000/year in developed countries, such as the United States, Sweden and Japan[1-4]. Only approximately 10% of patients with ISSNHL show a specific cause as suggested by detailed investigations[5]. Although the precise cause of ISSNHL has not been identified, several pathophysiological mechanisms, including microcirculation, autoimmune pathology, viral infection, intracochlear membrane rupture or haematologic problems, have been proposed[6]. Various studies have suggested that ISSNHL may not be due to a single pathological change but a spectrum of pathologies affecting the cochlea[7].

The most common treatment option for ISSNHL is corticosteroids within the first 2 weeks[4]. A total of 49% to 89% of patients with ISSNHL showed recovery via systemic steroid therapy, whereas therapy had no effects on other patients[8]. Spontaneous recovery occurs in 32% to 65% of the cases, usually within the first 14 days[9,10]. However, recovery amongst patients who did not show improvement after 2 weeks is low[11]. Intratympanic steroid perfusion described in the US guidelines has been recommended as salvage therapy[1]. However, its clinical evidence remains controversial, and no existing consensus suggests the efficacy of intratympanic steroid therapy for ISSNHL[1,12,13]. Therefore, the failure of a two-week treatment amongst ISSNHL patients should be further researched, and alternate therapies should be developed.

Traditional Chinese medicines (TCMs) originated in ancient China and have been used in therapeutic approaches in East Asia for more than 2,500 years. TCM includes well-known herbal medicine acupuncture, massage (tui na) and lifestyle modifications, such as dietary therapy and exercise (taiji and qigong). TCMs originated from Huang Di Nei Jing, a famous work of ancient TCM literature, which introduced the maintenance of the Yin–Yang balance of internal organs by following a healthy lifestyle. From the perspective of TCM, all diseases originate from a broken balance. In China, Chinese patients prefer to use TCM methods with complementary and alternative medicines for the treatment of diseases. Lifestyle change guided by TCM is also acceptable amongst Chinese people with diseases.

Lifestyle change has been suggested amongst patients with otological diseases whose conditions are not controlled well by medicine. Dietary habits, such as low sodium diet, can alter inner ear fluid homeostasis and auditory function. The endolymph compartment maintains a low sodium concentration, whilst ionic balance is maintained in the surrounding perilymph and serum[14]. Evidence shows that more than 85% of patients with Meniere's disease are helped by lifestyle changes along with either medical treatment or surgical procedures. Lifestyle changes include reducing the consumption of salt, caffeinated products, chocolate, alcohol and salt products as much as possible[15]. A cross-section study indicates a relationship between benign paroxysmal positional vertigo and inadequate carbohydrate and fibre intake and a diet rich in polyunsaturated fatty acids. Food readjustment is suggested amongst patients with it[16]. Furthermore, a descriptive longitudinal cohort study amongst 159 adult patients with chronic primary tinnitus and sleep problems has shown that TCM-based lifestyle counselling may relieve chronic primary tinnitus. After 6–26 months of follow-up, sleep quality and tinnitus loudness were improved, and the effect of tinnitus on sleep, concentration and emotional state were also relieved[17].

Therefore, this randomised 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 of ISSNHL by systemic steroid therapy.

Methods/design

Objective

Given the significant spontaneous recovery rate and existing standard therapy for ISSNHL by using systemic glucocorticoids, patients will only be enrolled in the study if no or insufficient recovery of hearing threshold could be observed after the initial 14 days of systemic therapy and if they are reluctant to continue receiving salvage therapy. This randomised controlled trial will evaluate the effectiveness of healthy lifestyle treatment based on TCM therapy for ISSNHL patients who have no or insufficient recovery of hearing threshold after the initial systemic therapy for 14 days and are reluctant to continue receiving salvage therapy.

Study design

A total of 56 patients will be recruited for the trial. Participants who will meet the inclusion criteria and submit written informed consent will be enrolled in the trial, which will last for 3 months. A flowchart of the trial procedure is shown in Fig. 1.

This trial is registered in the 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 Standard Protocol Items: Recommendations for Interventional Trials checklist (Additional file 1), as shown in Fig. 2.

Recruitment

Participants diagnosed with ISSNHL but did not respond to initial systemic treatment for 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 participation in the study
2. Diagnosis of unilateral ISSNHL, defined as onset within 72 h affecting three consecutive frequencies of unknown aetiology[1]
3. Hearing loss occurring at least 14 days but less than or equal to 1 year
4. Insufficient recovery from ISSNHL for at least 14 days after onset and after receiving the Chinese ISSNHL guideline-recommended standard therapy
5. Reluctance to receiving drugs, including steroid therapy
6. More than 18 years old but less than 60 years old
7. Hearing in the contralateral ear of at least 20 dB HL
8. Stopped receiving medication for more than 3 days

Exclusion criteria

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

Criteria for trial termination and dropout are as follows: if a patient develops a severe disease unrelated to participation in the trial; if a patient chooses other treatments and drugs; if a patient requests termination or withdraws; and if a patient no longer receives the trial treatment regimen and examination.

Randomisation

Patients who will meet the requirements and whose eligibility is confirmed will participate in sociodemographic and clinical data collection and complete the informed consent form during the first visit. The patients will be paired by sex (male and male and female and female), age difference (within 10 years) and hearing loss level. A total of 28 pairs of subjects will be numbered, with each pair having two numbers: 1, 2; 3, 4;…;55, 56. A statistician who is not part of the clinical intervention will use Statistical Package for Social Sciences SPSS 21.0 (IBM, Chicago, IL, USA) to generate a randomisation code, which will be embedded into opaque and numbered envelopes. Patients will be allocated to the intervention or control group. If a patient with a single number matches another with a singular number, they will enter the experimental group; meanwhile, the double number in the same pair will enter the control group, and vice versa.

Intervention

Participants in the control group will receive routine care, whereas those in the intervention group will receive additional lifestyle counselling based on TCM. In this system, patient care will focus on health maintenance and prevention by encouraging patients to adhere to simple health and lifestyle practices[18].

Routine care includes the following two aspects:

- Educating participants about the natural history of ISSNHL and the limitations of existing evidence regarding efficacy; answering patients' questions about ISSNHL
- Counselling participants about the benefits of amplification, hearing-assistive technology and other supportive measures, especially for those whose hearing loss has lasted more than 3 months

Lifestyle counselling will consist of four sessions. The first step is the completion of the lifestyle survey of each participant and one-to-one targeted counselling based on the survey results.

- Die According to the theory of Yellow Emperor's Inner Canon (Huangdi Neijing), a classical Chinese medicine book[19], yang qi is an important reason for maintaining normal human function and a food's energy can have a remarkable effect on health. Therefore, diet should be dominated by staple food, whereas 'cold' energy food should be avoided. In simple terms, the central components of the dietary strategy are the staple Chinese food ('neutral' energy), such as rice and wheat. 'Cold' energy food includes most fruits from the TCM perspective. The diet adopted in this study will encourage participants to consume staple Chinese food.
- Sleep. Patients will go to bed at night, avoid staying up late and wake up at dawn. Patients will be recommended to fall asleep by 10m. to 11 p.m. and rise by 5 a.m. to 7 a.m., ensuring a sleeping window between 10 p.m. and 5 a.m. Thus, reducing water intake prior to sleep is necessary to avoid waking up at night to urinate. Participants should not sleep at daytime. A less than 30 min short nap before 2 p.m. will be advised for nonadaptive patients.
- Mood. A physician will communicate with participants to answer their doubts and discuss the relationship between mood and ISSNHL and the importance of good mood to health. Participants' fear, despair and anxiety should be reduced as much as possible.
- Physical activity. All participants will be encouraged to be moderately physically active by doing taiji (a traditional Chinese sport) and housework and by walking and participating in leisure activities. Patients will be discouraged from engaging in deliberate strenuous physical exercise, especially before going to bed or on a full stomach and avoid being too tired.

The following measures will be taken to improve patient compliance and reduce drop-out rate. All participants are entitled to free assessments, including audiology tests, one-to-one consultation and lifestyle assessment. In addition, no registration fee will be required for first-level expert outpatient service from the West China Hospital. At the end of the experiment, a free online consultation service will be provided for 1 year.

We will provide weekly one-on-one consultations and periodic check-ups over the phone, especially with the lifestyle modification group to reinforce the importance of lifestyle change and answer related questions. Participants will be encouraged to keep a symptom log on ear-associated and systemic symptoms. The patients should provide daily email updates about their lifestyle journal, including information about their sleep and wake times and daily diet (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.

Primary outcome measure

The efficient rate is the percentage of patients with improvement in pure tone average (PTA) of impaired frequency that at least suggests effective recovery compared with the baseline. Effective recovery is

defined as an improvement of 15–30 dB HL improvement in PTA (dB HL). On the basis of the 2012 practice guideline on sudden hearing loss published in America, an improvement within 10 dB HL of initial HL or within 10 dB HL range of the unaffected ear's hearing threshold is defined as complete recovery; an improvement of more than 30 dB HL improvement in PTA (dB HL) from pretreatment hearing levels is defined as significant recovery; and an improvement of less than 15 dB HL in PTA is defined as no recovery[1,20]. Patients under the no recovery criterion will be excluded.

Secondary outcome measure

Based on the visual analogue scale (VAS), the secondary outcome will include improvement of adherence to TCM lifestyle, evaluation of changes in word recognition score (WRS)[21], tinnitus handicap inventory (THI)[22] for patients with tinnitus and change in common symptoms, such as dizziness and ear blockage. These outcomes will be measured at the first and during protocol visits.

Blinding

The audiologist, research assistants and statisticians involved in the study will be blind with the allocations. Given the nature of counselling, blinding amongst consultants and patients is impossible. Thus, consultants and other researchers will not communicate amongst one another about the patient group during the trial. Patients will also keep their treatment methods confidential. At the completion of the trial, patients in the control group will be offered access to the lifestyle modification intervention.

Sample size

To the best of our knowledge, no randomised pilot study has been conducted to assess the effectiveness of lifestyle changes on ISSNHL. Therefore, we could not calculate the sample size based on previous studies. On the basis of our retrospective analysis (unpublished) and clinical experience, the efficiency ratio of the intervention group is conservatively estimated to be 50%, and the natural recovery rate of over two weeks is 10%[9]. Using a formula[23] for calculating the sample size of optimal treatment in the clinical trial and considering α=0.05, β=0.1, by the table of normal distribution quantifiers $U_{\alpha(0.05)}$=1.65, $U_{\beta(0.1)}$ = 1.28, we require a patient sample size of 23 per group. We allow for a 20% loss to follow-up (approximately 10 cases), with a total sample size of 56 patients (28 per group) in the study.

$$n= (U_{\alpha}+U_{\beta})^2 P(1-P)/(P_1-P_0)^2$$

$$P=(P_1+P_0)/2\times 100\%$$

P_0: Original efficacy, P_1: expected efficacy

Safety

Any adverse events and discomfort throughout the course of the trial 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

Data will be analysed using SPSS V.21.0 (Chicago, IL, USA), with the significance level set at 0.05 (two-tailed) by statisticians who are independent of the research team. Patient baseline characteristics will be summarised by a treatment arm by using appropriate summary statistics to assess baseline comparability only. Data analysis will be conducted with the intention-to-treat (ITT) principle and the per-protocol analysis. We will calculate the effective rates at 1 and 3 months for the primary outcome and compare the intervention and control groups by using the χ^2 test. For secondary outcomes, continuous variables, including THI, VAS and WRS, will be compared between the two groups at all follow-up time points by using *t*-test or the Wilcoxon signed-rank test as appropriate. Categorical variables, including different degrees of hearing loss, will be compared using the Chi-square test or Fisher's exact test. For dropout analysis, we will use multiple imputations for ITT analysis. Sensitivity analysis will be performed to assess the effect of missing data assumptions.

Data management

Data accuracy will be ensured by completing paper copies of the case report form. Two independent researchers blinded to the group allocation will input data on an Excel spread sheet, and data will be checked twice. Data will be validated using original case report forms when any discrepancy is discovered. Paper files and electronic documents will be stored in a locked filing cabinet and protected computer separately. Only principal researchers will be allowed access to data. Researchers will be unable to modify data and keep information strictly confidential and shall not disclose it under any circumstances. Meanwhile, researchers will sign a confidentiality agreement.

Discussion

ISSNHL, whose aetiology remains unknown, is an acute disorder that occurs throughout life. Although 49% to 89% of patients achieved normal hearing through existing therapy with oral or intravenous steroids and with 32% to 65% spontaneous recovery rate, treatment amongst patients who have incomplete recovery from ISSNHL after failure of initial management remains a problem[8-10]. Some patients are reluctant to receive recommended glucocorticoid treatment due to fear of side effects, contraindications and drug-to-drug interactions. The salvage therapy recommended by the 2012 ISSNHL guidelines is steroid perfusion that results in hearing improvement ranging from 53% to 90% in the treatment group[24,25]. The dose and concentration of steroids vary as do the criteria used to define hearing improvement.

Previous studies have indicated that patients who do not show any improvement within the first 14 days are unlikely to show remarkable recovery afterwards[9,10]. Thus, patients usually lose hope in continuing 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 and is widely accepted in the treatment of diseases in China. Lifestyle, as part of TCM, has been integrated into the Chinese culture. Tradition and sustained interest in the benefits of TCM-recommended lifestyle have remained, especially for patients whose conditions have not been effectively treated by Western medicine. We designed this trial with the hope of verifying that TCM-based lifestyle can provide help concerning hearing loss and concomitant symptoms amongst patients with ISSNHL. If successful, this intervention may help refractory ISSNHL patients in China.

The study is designed to explore the efficacy of TCM-based lifestyle change for ISSNHL patients with no or insufficient recovery after initial systematic Western medicine treatment. Although IT steroid perfusion for this kind of ISSNHL has been used in Western treatment, the evidence of its efficacy remains unclear. In this study, the effective rate of hearing improvement will be used as the primary outcome measure and is the most common parameter for ISSNHL. Secondary outcome measures include WRS, THI and accompanying symptoms, including dizziness and ear fullness. In addition to hearing loss, many people with ISSNHL complain of poor hearing, tinnitus and dizziness. The exact mechanisms that explain the effects of TCM-based lifestyle change on ISSNHL require further detailed research and discussion in the future.

Study limitations

One of the major drawbacks of this study is that the currently widely adopted lifestyle questionnaire will not be used. Lifestyle includes sleep, diet, mood and exercise; thus, the factor that plays a key role in improving ISSNHL remains unknown. Therefore, well-designed and randomised controlled trials that compare different lifestyle factors with one another are necessary in the future.

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.

Abbreviations

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

Declarations

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

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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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Additional Files

Additional file 1: SPIRIT Checklist. The Recommended items to address in a clinical trial protocol and related documents.

Additional file 2: Lifestyle Diary. Participant accomplish the table to record the journal of their sleep time and daily diet.

Figures

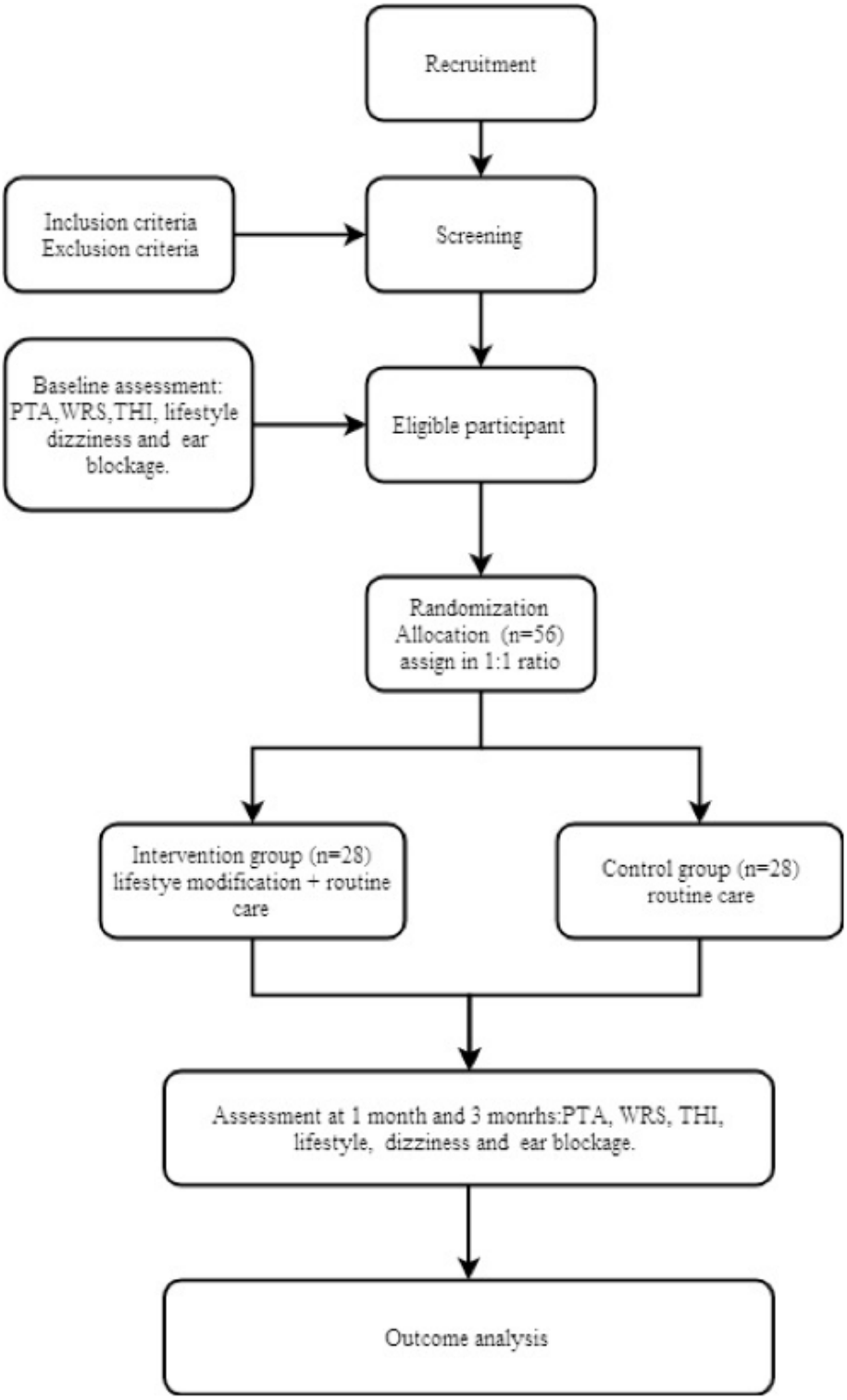

Figure 1

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-interventi on 0 months	1	3
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Hearing tests: PTA,WRS	X			
Lifestyle assessment	X			
Assessment of dizziness and ear blockage	X			
Allocation		X		
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			X	X
Secondary outcome variables: WRS, THI and Assessment of dizziness and ear blockage			X	X

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

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

- Additionalfile1SPIRITChecklist.doc
- Additionalfile2LifestyleDiary.docx