Vestibular prognosis in idiopathic sudden sensorineural hearing loss with vestibular dysfunction treated with oral or intratympanic glucocorticoids: a protocol for randomized controlled trial

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Study protocol

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Abstract

Background

Idiopathic sudden sensorineural hearing loss (ISSNHL) is a rapid-onset sensorineural hearing impairment with unclear etiology and unsatisfying treatment effects. Vestibular dysfunction has been considered as a poor indicator in the clinical manifestations and prognosis of ISSNHL, which occurred in approximately 28%-57% cases. Glucocorticoids, administered through oral or intratympanic way, is currently a regular and standard treatment for ISSNHL based on hearing outcome. However, little investigations have been conducted on the recovery process and treatment effects of glucocorticoids on vestibular dysfunctions of ISSNHL. This study aims to compare the efficacy of oral or intratympanic glucocorticoids in ISSNHL with vestibular dysfunction in terms of the pattern and trajectory of possible process of vestibular function recovery.

Methods/Design

A randomized, outcome-assessor- and analyst-blinded, controlled, clinical trial (RCT) will be carried out. A group of seventy-two patients with ISSNHL complaining of vestibular dysfunction appearing as vertigo, dizziness or imbalance will be recruited and randomized into two arms of either oral or intratympanic glucocorticoids therapy with a 1:1 allocation ratio. The primary outcomes will be vestibular function outcomes assessed by sensory organization test, caloric test, video head impulse test, and vestibular evoked myogenic potentials; the secondary outcomes include self-reported vestibular dysfunction symptoms; dizziness-related handicap, visual analogue scale for vertigo and tinnitus; and pure tone audiometry. Assessment will be performed at baseline and at 1, 2, 4, and 8 weeks post-randomization. To our knowledge, this will be the first randomized controlled trial focusing on the prognosis of vestibular dysfunction in ISSNHL and the efficacy of glucocorticoids therapy for the vestibular dysfunction in this disease.

Discussion

This trial will be the first RCT study focusing on the progress and prognosis of vestibular dysfunction in ISSNHL. Efficacy of two commonly used therapies of glucocorticoids will be compared in both auditory and vestibular function fields, rather than in the hearing outcome alone.

Trial registration

ClinicalTrials.gov, NCT03974867. Registered on July 23, 2019.

Administrative Information

Title{1}	Vestibular prognosis in idiopathic sudden sensorineural hearing loss with vestibular dysfunction treated with oral or intratympanic glucocorticoids: a protocol for randomized controlled trial
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Roles and responsibilities{5a}	Weiming Hao, MD1,2; Liping Zhao, MD1,2; Huiqian Yu, MD, PhD1,2; Huawei Li, MD, PhD1,2,3,4 1 ENT institute and Otorhinolaryngology Department of Eye & ENT Hospital, State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Fudan University, Shanghai, 200031, PR China 2 NHC Key Laboratory of Hearing Medicine (Fudan University), Shanghai, 200031, PR China 3 Institutes of Biomedical Sciences, Fudan University, Shanghai, 200032, PR China 4 The Institutes of Brain Science and the Collaborative Innovation Center for Brain Science, Fudan University, Shanghai, 200032, China
Name and contact information for the trial sponsor{5b}	Science and Technology Commission of Shanghai Municipality, contact at +86-021-23111111 Eye & ENT Hospital of Fudan University, contact at +86-021-64377134
Role of study sponsor{5c}	Select investigators and ensure the investigators are compliant with the protocol and the Institutional Review Board (IRB)
Composition, roles, and responsibilities of the coordinating centre, steering committee{5d}	Coordinate, evaluate and monitor the progress and tasks of the project; organizing regular meetings of investigators; ensure the accuracy and update of the record; Act quickly to the adverse event reports or other sudden events; submit report regularly to sponsors and ethical committees;

1. Background{6a,7,8}

Sudden sensorineural hearing loss (SSNHL) is a rapid-onset inner ear disease. It is defined as a sensorineural hearing loss of at least 30 dB over at least three test frequencies occurring within 72 hours. (1, 2) The reported incidence rate of SSNHL is about 5–20/100,000 people per year,(1) which has been widely-considered underestimated because of the unregistered cases with out-hospital spontaneous recoveries. The etiology in about 71% to 90% of SSNHL cases remains uncertain, which is named as idiopathic SSNHL (ISSNHL).(1),(3) Various postulated etiological theories have been proposed including microvascular impairment, viral infections, inner ear electrolytic disorders, trauma, autoimmune diseases and central nervous system (CNS) diseases.(3–7) Based on the close anatomic relationship between

cochlea and vestibule, approximately 28%–57% of ISSNHL patients have been reported of co-occurring symptoms of vertigo.(8)

There are two administration patterns of glucocorticoids therapy in ISSNHL: systemic (oral or intravenous) use and intratympanic use. Compared with the traditional oral administration, intratympanic therapy is thought to be superior for its: 1) bypassing the blood-labyrinth barrier and achieving higher drug concentrates in inner ear; 2) avoiding most of the systemic side-effects of glucocorticoids. A well-designed randomized trial was conducted in 2011 by Rauch and his colleagues, which supported the non-inferiority in hearing outcomes of intratympanic therapy compared with oral prednisone in ISSNHL.(9) However, the study was failed to reject the inferiority based on the 10 dB noninferiority standards in the subgroup analysis of ISSNHL with dizziness.(9)

Considering that few investigations have been carried out on progress and prognosis of ISSNHL-related vestibular dysfunctions after basic treatment, we designed this randomized, assessor- and analyst-blinded, controlled trial with two interventional arms, one is oral glucocorticoids therapy group and the other is intratympanic glucocorticoids therapy group.

2. Methods/design

This protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines (SPIRIT).(10)

2.1 Design, setting and participants{9}

This study is designed as an 8-week, single-center, randomized, assessor- and analyst-blinded, controlled trial with two parallel interventional groups in a 1:1 allocation.

Patients will be recruited from outpatient clinics of the Eye and ENT Hospital of Fudan University in Shanghai, qualified with well-trained doctors, staff and required facilities for this clinical trial.

The study protocol has been reviewed and approved by the institutional review board of Eye and ENT Hospital of Fudan University (Reference Number: 2017047).

2.2 Eligibility criteria{10}

Patients who meet all of the following inclusion criteria will be considered eligible:

1. Adults aged between 18 to 70 years old;
2. Diagnosed with unilateral ISSNHL according to the National Institute for Deafness and Communication Disorders (NICDC) criteria;(2)
3. Complained of vertigo/dizziness/lateropulsion together with abnormal results in at least one of the vestibular function tests, including sensory organization test(SOT), caloric test, video head impulse

test(vHIT), cervical vestibular evoked myogenic potentials(cVEMP) and ocular vestibular evoked myogenic potentials(oVEMP);
4. Onset of audio-vestibular symptoms occurred within 7 days;
5. Be willing to sign the informed consent of the study.

Patients with any of the following conditions will be excluded:

1. Definite etiologies are found or highly suspected after clinical evaluations, such as vestibular schwannoma, stroke, trauma or demyelinating disease;
2. Diagnosed with a present or previous hearing or balance disorders, such as Meniere's disease, benign paroxysmal positional vertigo, vestibular neuronitis, vestibular migraine, otosclerosis, luetic, congenital or genetic hearing loss, etc.;
3. Pure tone audiometry(PTA) Threshold of the unaffected ear is higher than 25dB;
4. Present with conditions contraindicated systemic glucocorticoids use, such as tuberculosis, hepatitis B or C infection, active herpes zoster infection, pancreatitis, insulin-dependent diabetes mellitus, severe osteoporosis or gastrointestinal ulcer;
5. A history of more than 3 days sufficient systemic glucocorticoids uses (≥1 mg/kg/d) within 3 months;
6. Not appropriate for receiving vestibular function tests;
7. Multiple organ dysfunction or unstable vital signs;
8. Pregnancy or lactation;
9. Unsuitable for the trial because of any other reasons identified by investigators.

2.3 Recruitments and randomization{16a,16b,16c,26a}

Patients who visit doctors from the outpatients in Eye and ENT Hospital of Fudan University, and suspected of ISSNHL with vestibular dysfunction will be screened for eligibility. Eligible patients who consent to participate will receive either oral prednisone or intratympanic methylprednisolone randomly in a 1:1 allocation. The randomization sequence will be generated through @RANDOM.ORG, an internet website (https://www.random.org) producing true random sequence according to atmosphere noise. The concealed randomization sequence file will be constructed and kept in sequentially numbered, sealed, opaque envelopes by a staff member (Zhao L.) in the Eye and ENT Hospital of Fudan University outside the study team. When a patient is officially enrolled and numbered, the staff member will be contacted by telephone and open the corresponding envelope to find the randomized treatment for this patient. Assessors in examination rooms and statistician analysts are not allowed to receive any information of the group allocation.

Following randomization, baseline information of the participants in demographic and clinical characteristics will be collected, including the objective vestibular function evaluated by SOT, videonystagmography (VNG), vHIT, cVEMP and oVEMP; the subjective vestibular dysfunction feelings

reflexed by DHI(dizziness handicap inventory) and VAS-V(visual analogue scale for vertigo); the hearing outcome and tinnitus condition assessed through PTA and VAS in tinnitus (VAS-T, visual analogue scale for tinnitus). Caloric test is routinely included in VNG. Acoustic impedance and magnetic resonance imaging of internal auditory canal (MRI-IAC) will be performed only once at the baseline examination to exclude the potential misdiagnosed SSNHL.

2.4 Interventions{6b,11a}

Once a participant is randomized, the treatment procedure starts immediately. (**Table 1**)

2.4.1 Group1: Oral Prednisone Group

The participants in Group 1 will receive oral prednisone 1mg/kg/d (maximum daily dosage is no more than 60mg) for 7 days, followed by a 7-days taper. The patients are advised to take the medicine in 30 minutes before every breakfast, and not to divide the doses.

2.4.2 Group2: Intratympanic Methylprednisolone Group

The participants in Group 2 will receive 7 intratympanic 40mg/ml methylprednisolone injections in 14 days, one injection every other day.

The otolaryngologists in charge of the injection work are asked to inject at the posterior superior quadrant and fulfill the tympanic cavity using operating microscopes, after lidocaine spray anesthesia. Patients will be asked to keep supine position with the affected ear slightly up to 30 degrees and avoid swallow during injection and in 30 minutes after the injection. The drug for injection is Methylprednisolone Sodium Succinate for Injection by Pfizer Manufacturing Belgium NV.

The length of treatment would be extended for another week if the change in hearing threshold (average dB in PTA) is less than 10 dB, or average of PTA is worse than 55dB in patient's affected ear, under the participant's agreement. The salvage treatment regimen is 3 injections of 40mg/ml methylprednisolone every other day. For those with severe vertigo attacks, drugs for symptom control like mannitol or diazepam can be used temporarily.

2.5 Adverse events{11d,22}

Any untoward medical occurrences with unfavorable symptoms in the participants are defined as adverse events (AEs). AE is not necessarily to have a causal relationship with the treatment. If the AEs are life-threatening, result in death, persistent and significant disability or incapacity, or make the participants hospitalization, we define them as serious adverse events (SAEs). The investigators will routinely ask the patients if there have been any unexpected symptoms. Study-related and none-study-related AEs will be recorded in the patient's clinical history by doctors in clinics and then reported to a trial investigator (Yu H.). Participants experiencing AEs will be followed up until the end of the events or the end of the trial. Any SAEs in during this trial will be reported to the Chair of the study and Adverse Drug Reaction

Administration (ADRA) of the Eye & ENT Hospital of Fudan University within 48 hours at learning of the event.

We list some possible study-related AEs here:

1. Short-term systemic use of glucocorticoids related SAEs: fracture, sepsis, venous thromboembolism; (11)
2. Short-term systemic use of glucocorticoids related AEs: blood glucose problem, appetite change, sleep change, weight change;
3. Intratympanic injection related AEs: ear pain, ear infection, tympanic membrane perforation, worse vertigo after injection;

2.6 Participants withdrawal{11b,11c,18b}

The participants will be informed of the right to withdraw from the study at any time after consent. The enrolled participants who are found ineligible later, lost to follow-up, or withdraw consent for any reason, will be regarded as withdrawal. As for those who decided not to receive the protocol intervention, we will ask them if they would like to continue with the follow-up visits and if they agreed, their results will be regarded as variation other than withdrawals based on intention-to-treat (ITT) analysis.

We provide an online wechat and telephone contacts to all the participants for timely communication and health education, which will promote the participants retention and adherence to the intervention protocols. Furthermore, we optimized follow-up process by setting specialty clinic for SSNHL, minimizing the waiting time, and waiving extra examination and treatment fees.

2.7 Blinding{17a,17b}

We decide not to set blindness of the interventions to patients and doctors, because that setting blindness to patients and doctors will need placebo injections to some of the participants, which may bring unnecessary pain and tympanic membrane perforation risk to the patients. The specialists in test rooms and statistical analysts will be kept blinded during the trial until the statistical analyses are done.

2.8 Outcome Measurements and Follow-ups{12,18a}

In **Table 2**, criteria are listed in detail to distinguish the CVS compensation and PVS restoration according to following evidence:

1. SOT is a measurement for dynamic and static posturography, which may figure out the different roles of somatosensory, visual and vestibular system. The vestibular scores in SOT will help us to distinguish peripheral function self-restoration from CVS compensation.
2. Caloric test has been used to evaluate the lateral semicircular canal function with a good sensitivity. (12) In caloric test, unilateral weakness (UW), directional preponderance (DP) and spontaneous nystagmus (SpN) are three parameters to judge the different phases of central vestibular

compensation. UW presents at all three phases of acute injury, static compensation and dynamic compensation phase; DP presents at acute injury phase and static compensation phase; while SpN only present at acute injury phase.(13) While the caloric test results of completely function restoration in PVS should be the same as those in the normal individuals: absence of UW, DP or SpN;

3. vHIT can be employed for evaluating horizontal and vertical semicircular canals, and has been taken as a specific indicator of peripheral vestibular function.(14, 15) The decreased gains and corrective saccades are signs of the corresponding semicircular canal dysfunction.
4. cVEMP is a widely used measurement for assessing the saccular and inferior vestibular pathway functions, while oVEMP for evaluating the utricular and superior vestibular pathway functions.(16) Based on the integrity of neural pathways, we may reasonably assume that if the dysfunction of otolith organ and its afferent pathway has not recovered in our participants, the compensation effects of CVS will not bring a normal VEMP result.(15, 17)

Here come two possible patterns in vestibular dysfunction recovery of ISSNHL. The first pattern (Pattern A) is that the patients undergo well central vestibular compensations with no recovery of PVS function. In this pattern, patients may show a quite normal ability of balance evaluated by subjective complaints, DHI or VAS-V; however, since the peripheral vestibular organs remain dysfunctional, vestibular test battery (i.e. SOT, caloric tests, vHIT and VEMPs) will come out with abnormal results. The second possible pattern (Pattern B) is that the PVS injuries are completely or partially restored in the patients. In this condition, not only the subjective complaints will disappear, but also the objective vestibular tests results will get back to normal, or at least less abnormal.

2.8.1 Measurements

The methodology details of following tests have been reported before.(18)

2.8.1.1 SOT

The SOT in our study is performed with the Synapsys Posturography System (SPS, SYNAPSYS, Inc. Marseille, France). Six sensory test modes are performed with changing supports and visual conditions. The results are analyzed comprehensively to give a score for each sensory system (somatosensory, visual and vestibular systems) and a composite score. Results are considered abnormal when the score is lower than the age-specific normative data.

2.8.1.2. Caloric Test

We deliver the caloric test using the air caloric irrigator system of ICS AirCal (GN Otometrics, Taastrup, Denmark) and record eye movements using videonystagmography (VNG) of SYNAPSYS VNG Ulmer (SYNAPSYS, Inc. Marseille, France). Patients are placed in a supine position in a darkroom, with the head flexed at 30°. The temperature of the warm and cool air is 50°C and 22°C. The unilateral weakness (UW) and directional preponderance (DP) are used to quantify the difference between the caloric responses of

the two ears. The abnormal caloric result is defined as an absolute value of UW% greater than 22% and/or an absolute value of DP greater than 27%.

2.8.1.3 vHIT

ICS Impulse system (GN Otometrics, Taastrup, Denmark) will be used for vHIT in this study. The examiner performs head impulses (150 to 200°/s peak head velocity) randomly in unpredictable timing and direction in the plane of each canal (the horizontal, anterior and posterior semicircular canal) and at least 15 impulses for each side are acquired. The software analysis algorithm calculates the vestibular-ocular gain. Normal gain is defined as >0.8 for the lateral canals and >0.7 for the vertical canals. The pathological saccade is defined as refixation saccades categorized as either covert saccades (occurring during a head movement) or overt saccades (occurring after a head movement).(19) The result of a semicircular canal will be considered abnormal when there are pathological saccades and the gain is out of normal range.

2.8.1.4 VEMP

The recording device of both cVEMP and oVEMP is the Bio-logic Navigator PRO (Natus Medical Inc., San Carlos, USA).

2.8.1.4.1 cVEMP

Patients are asked to lie in supine position on a bed, with head raised to 30° to 45° away from the bed during recording to ensure good muscle tone. Electrodes are placed as operation manual. Air-conducted sound with 500 Hz short tone bursts (2 ms rise/fall time and 2 ms plateau time) are presented through insert headphones as stimuli. The starting stimulus intensity is 95 dB nHL, and decreases by 5 dB nHL each time until the meaningful wave is undetectable. The lowest intensity with a characteristic waveform is defined as threshold. The result will be considered abnormal if one of the following conditions is met: 1) the amplitude asymmetry ratio (AR) is more than 37%; 2) the cVEMP meaningful waveform (where the waveforms with positive-negative-positive peak, P1-N1-P2, could be recognized and well repeatable) is absent at 95 dB nHL stimulus or the threshold is out of range compared with age-specific normative data; 3) delayed response: the cVEMP threshold shift is out of the range: P1 range 15.66±7.22; N1 range 23.42±5.18(the mean of normal range±2*SD). (20-23)

2.8.1.4.2 oVEMP

The recording device, software and stimuli are the same as those in cVEMP. The patients remain lying supine and are asked to look upward (approximately 30° above the horizontal plane) during recording. Electrodes are placed as reported in previous studies.(18) The recording procedure is the same as that in cVEMP and the lowest intensity with a characteristic waveform is defined as threshold. We define the abnormal result of oVEMP as 1) absence of meaningful waveform (where the waveforms with negative-positive peak, N1-P1, could be recognized and well repeatable); 2) the threshold out of range compared with age-specific normative data; 3) amplitude asymmetry ratio (AR) ≥40%.(20, 21)

All examinations will be performed by trained physicians skilled at neuro-otological tests.

2.8.1.5 DHI and VAS

The Dizziness Handicap Inventory (DHI) is a self-assessment questionnaire with 25 items, and the reliability of Chinese version has been verified.(24-27) The 25 items can be divided into 3 subscales: physical, emotional and functional aspects, and the total scores range from 0 to 100. The higher the score, the more severe the dizziness is in the patients.

Visual Analogue Scale is a universal psychometric scale evaluating subjective attitudes.(28, 29) When applied in vertigo or tinnitus (VAS-V or VAS-T), respondents specify their level of vertigoes or tinnitus by indicating a position along a continuous line between two end-points without marked scale. A score from 0 to 10 will be made based on the length of the line. The higher the score, the more severe the symptom is.

2.8.2 Primary outcomes

To evaluate the recovery of vestibular function, we set the recovery rates of the whole battery of vestibular function tests (SOT/caloric test/vHIT/VEMPs) as the primary outcome, which is the proportion of patients whose abnormal results of vestibular function tests at baseline recover to normal at 4- / 8- weeks follow-up:

$$recovery\ rate\ = \frac{number\ of\ patients\ recover\ from\ abnormal\ result\ at\ baseline\ to\ normal\ at\ 4-/8-\ weeks\ follow-up}{number\ of\ all\ enrolment\ participants} \times 100\%;$$

2.8.3 Secondary outcomes

Secondary outcomes include the change of subjective evaluations in vestibular, tinnitus and hearing assessments:

1. Change of DHI and VAS-V, VAS-T scores: change of DHI and VAS-V scores from baseline at 1-, 2-, 4-, 8-weeks follow-up.
2. Change of PTA: change of average of PTA from baseline at 1-, 2-, 4- and 8- weeks follow-up; in this study, we define a 10-dB PTA criterion as clinical significant difference based on a previous RCT.(9)

2.9 Time-points{13}

The study included 5 follow-up visits in total: a baseline visit to sign the consent and to record the baseline information; 2 visits during treatment interval to record subjective vestibular questionnaires (DHI, VAS-V and VAS-T) and hearing outcomes (PTA), and to monitor treatment safety outcomes; 2 follow-up visits at 4 weeks and 8 weeks to assess hearing and vestibular functions, and monitor safety outcomes. To optimize examination resources and reduce burden of examiners, among all five vestibular function

tests (SOT, caloric test, vHIT, cVEMP and oVEMP), only those with previous abnormal results will be repeated at follow-up visits.

Demographic and clinical information including gender, age, nationality, occupation, date of onset, predisposition, lesion side, description and duration of vertigo/dizziness/lateropulsion, chronological order of vertigo and hearing loss, coexisting systemic diseases and physical examination records will be collected.

The SPIRIT figure of enrolment, interventions, and assessments are presented in **Table 3**.

2.10 Sample size{14}

Due to lack of previous reported data on changes of vestibular function test results, this study sample size was calculated based on data from preliminary clinical practice in our hospital. Among patients who was diagnosed as ISSNHL and treated with oral prednisone, recovery proportion of the vestibular function tests (including SOT, caloric test and VEMPs) was 0.25; while the recovery proportion among those treated with intratympanic glucocorticoids was approximate 0.64. Using the program of G*Power 3.1 for Fisher's exact test, we calculated a sample size of 30 per arm with 80% power at two-tailed 5% level of significance.(30) To allow for 20% dropout, 36 participants per arm will be needed.

2.11 Data collection and management{21a,27}

A Data Monitoring Committee (DMC) has been established to store, monitor and check the authenticity, security and integrity of the database. All members in DMC are independent of the study sponsors and declared no competing interests. The DMC will periodically review the accumulated data and communicate the problems of its deliberations to the study team if necessary. The frequency of the interim analyses will be judged by the Chair of the DMC, based on the consultation with the investigating team. We anticipate that there might be 2-3 interim analyses before the final analysis. The Chair of DMC is Dr. Wu P.

Templates of Case Report Form (CRF) and AE form can be found as appendices (Appendix 1 and 2). The CRF will be filled and checked by two investigators (Ms. Wei T. and Dr. Hao W.). Questionnaires in CRF can be self-recorded by the participants in paper version or Wechat version online, and the scores will be collected by an investigator (Ms. Wei T.). AE form will be filled by clinic doctors and monitored by an investigator (Dr. Yu H.), and SAEs will be reported to the Chair of the study (Prof. Li H.) within 48 hours.

The data entry will be performed by two investigators, and checked by another investigator within a week after the entry. All original clinical files of participants (patients' clinical files and examination reports) will be copied by the study team in photographs, and stored with other original research files (CRFs, questionnaires and AE forms) in a secure manner with a unique code for each person. Access to the research data will be restricted and recorded. Routine checks of data will be applied every month after the start of the trial. Data discrepancies will be corrected appropriately based on checks of the original files

and discussions among the data managers. Any changes to the data already written into the database will be evaluated carefully and recorded by the data manager.

2.12 Statistical methods{20a,20b,20c}

Categoric variables will be expressed as rates, while numerical variables as the mean ± SD. We will use chi-squared test to analyze the difference between the two groups for dichotomous outcomes (e.g. recovery rates). For change of SOT vestibular scores, UW of caloric test, PTA and scores in DHI, VAS-V and VAS-T, we will use mixed-model with repeated measures (MMRM) analyses of variance, with group and time as fixed effects and subject as a random effect. A value of $p < 0.05$ is considered statistically significant. We will calculate Relative Risk (RR) with corresponding 95% confidence intervals to compare dichotomous variables, and mean difference (MD) for continuous variables.

An ITT analysis and a per-protocol analysis will be both performed at each outcome. For the missing data in ITT analyses, if there is any, multiple imputation methods will be used. Up-to-date versions of SPSS (SPSS, Chicago, IL, USA) will be used to conduct analyses. A statistician from Medical College of Fudan University will perform the analyses. Not until the statistician complete the analysis, will he be unblinded to the group allocations and the study hypotheses. All data sent to the analyst will be anonymised and the study groups will be coded as Group A and B.

2.13 Ethics and disseminations{23,25,31a,31c}

This protocol and the template informed consent forms have been reviewed and approved by the sponsor, the Institutional Review Board (IRB) and the Ethical Committee of Eye & ENT Hospital of Fudan University. The Investigators and members of DMC will make safety and progress reports to the IRB at least annually and within three months of study completion.

Patients and the public were not involved in the design of this study. However, the study was initially discussed with ISSNHL patients' representative on how best to involve patients throughout the proposed project. Finally, the study results will be informed to the public via peer-reviewed journals or academic conferences.

3. Discussion

Vestibular dysfunction, commonly complained by patients as vertigo, dizziness or lateropulsion, has been considered as a risk factor of profound hearing loss and poor prognosis.(31–33) Recently researchers made their efforts to specify the lesion patterns of vestibular system in ISSNHL, and proposed that the utricle and superior vestibular pathway is the most vulnerable vestibular site in ISSNHL, followed by the lateral semicircular canal and superior vestibular pathway(34). Severe vertigo and static imbalance markedly improve over a couple of days or weeks in most of patients, while some may suffer from long-term residual dizziness. Recovery of peripheral vestibular function and central vestibular compensation might be involved in this process. Vestibular function tests, such as SOT, caloric test, vHIT and VEMP, are

effective and objective methods to distinguish restoration of peripheral vestibular function and compensation of central vestibular. It has been reported that in a few cases of SSNHL, function of otolith organs reflexed by VEMPs were absent at onset and recovered or improved after weeks to months.(17) These cases suggested the role of peripheral vestibular function restorations. When peripheral vestibular injury is failed to recover by itself, the central compensation will take place. However, due to few previous researches in this field, the roles and proportions of central compensation versus peripheral recovery remains uncertain.

We assume that appropriate treatments for ISSNHL may have favorable effects promoting the vestibular recovery process, as those in hearing outcomes. Glucocorticoids therapy is currently a regular and standard treatment for ISSNHL according to guidelines.(1, 35) The plausible mechanisms include anti-inflammatory, immune-suppressive and inner-ear-homeostasis-related gene regulative effects.(36) Regrettably，with numerous studies of different evidence levels delivered in past six decades, the effectiveness of glucocorticoids in treating ISSNHL remains uncertain. Most of the RCTs and meta-analyses on this topic claimed of disappointing results with little measurable improvements in glucocorticoids over placebo arms.(37–39) It is worth noting that many confounding factors like various regimens and administration of drugs, different time points of starting treatments and different probable causes existed in these studies. Few studies have focused on the effects of glucocorticoids in vestibular recovery of ISSNHL. Taking the previous researches in acute unilateral vestibulopathy for reference, improvements has been found evaluated by vestibular function tests, the symptom loads and DHI scores.(40, 41) Hereby, we may speculate that glucocorticoids could possibly accelerate vestibular function recovery via restoration of peripheral vestibular system.

To assess the vestibular functions, we intend to perform a battery of vestibular function tests including 1) the SOT for assessing static and dynamic posture control ability of somatosensory, visual and vestibular systems distinguishingly and comprehensively; 2) caloric test for evaluating horizontal semicircular canal functions and superior vestibular integrity; 3) vHIT for evaluating functions of horizontal and vertical semicircular canals; 4) cVEMP for investigating saccular function and the inferior vestibular pathway and oVEMP for assessing utricular function and the superior vestibular pathway.(12, 14, 16, 42, 43) Moreover, we plan to perform DHI and VAS-V, two qualified and widely-used subjective measurements, to assess the severity of symptoms and negative influence on patients' daily lives. (26, 44)

In conclusion, our study will be the first to assess and follow the vestibular function conditions of ISSNHL up using a whole battery of vestibular function tests. Based on our clinical practice experience, we hypothesize that the effects of intratympanic glucocorticoids will be superior to that of oral therapy in terms of the outcome measurements mentioned above. Moreover, we expect that participants in the intratympanic group will experience more significantly reduced DHI scores, lessened VAS-V scores; and better enhanced recovery of PTA.

4. Study Status

The planned date of first enrolment is 1st Sep 2019. The estimated time required for recruitment is 12 months. The total duration of this study is expected to be 18 months, including statistical analysis and article writing.

5. Abbreviations

ISSNHL	Idiopathic sudden sensorineural hearing loss
RCT	Randomised controlled trial
CNS	Central nervous system
PNS	Peripheral nervous system
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials guidelines
ENT	Ear, nose and throat
VEMP	Vestibular evoked myogenic potentials
cVEMP	Cervical vestibular evoked myogenic potentials
oVEMP	Ocular vestibular evoked myogenic potentials
SOT	Sensory organization test
vHIT	Video head impulse test
PTA	Pure tone audiometry
VNG	videonystagmography
DHI	Dizziness handicap inventory
VAS	Visual analogue scale
VAS-V	Visual analogue scale for vertigo
VAS-T	Visual analogue scale for tinnitus
MRI-IAC	Magnetic resonance imaging of internal auditory canal
AE	Adverse event
SAE	Severe adverse event
ITT	Intention to treat

UW	Unilateral weakness
DP	Directional preponderance
SpN	Spontaneous nystagmus
AR	Asymmetry ratio
DMC	Data monitoring committee
CRF	Case report form
RR	Relative risk
IRB	Institutional review board

6. Declarations

Authors' contributions {31b}

All authors have made an intellectual contribution to this protocol. Li H. is the principal investigator of the trial, with full responsibility for the project. Hao W. and Zhao L. conceived the design, developed the protocol, and wrote the first draft of this manuscript. Li H. and Yu H. revised and approved the final version of the study protocol and the final manuscript. All the authors read and approved the final manuscript. Li H. and Yu H. are corresponding authors of this paper.

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Availability of data and materials{29,31c}

Our trial was registered at ClinicalTrials.gov, NCT03974867. The datasets used in the current study are available from the corresponding author on reasonable request.

The results of this trial will be published in peer-reviewed journals and presented at national and/or international conferences.

Consent for publication{32}

Consent will be obtained from all participants of this trial before participating.

Competing interests{28}

None declared.

Ethics approval and consent to participate{24}

The study has been approved by the Ethical Committee of Eye & ENT Hospital of Fudan University (reference number.2017047-1) and informed consent will be obtained from all participants of this trial before participating.

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Tables

Table 1. Glucocorticoids therapy protocol in each group

	Drug	Protocol
Group 1	Pred.	Glucocorticoids therapy: d1-d7: Oral Pred. 1mg/kg/d (maximum daily dosage is no more than 60mg); d8-d9: Oral Pred. 10mg less than d7; d10-d11: Oral Pred. 10mg less than d9; d12: Oral Pred. 10mg less than d11; d13: Oral Pred. 10mg less than d12; d14: Oral Pred. 10mg less than d13;*
Group 2	Met.	Glucocorticoids therapy: One intratympanic injection of 40mg/ml Met. at d1, d3, d5, d7, d9, d11 and d13;**

*If the patient's weight is less than 50kg, the administration will be stopped after the day with < 10mg prednisone administered, for example, a patient weighs 45kg will stop receiving glucocorticoids at the 13th day;

**One day early or late of injection is allowed for practicality.

Pred., prednisone; Met., methylprednisolone; d=day;

Table 2. Difference in Vestibular Function Tests between Compensation of Central Vestibular System and Restoration of Peripheral Vestibular System

	Compensation of CVS	Restoration of PVS
Subjective Complaints	Normal	Normal
SOT	Abnormal	Normal
Caloric test	Static compensation: UW+ DP+ Dynamic compensation: UW+ DP-	UW- DP-
vHIT	Abnormal	Normal
cVEMP/oVEMP	Abnormal	Normal

CVS: central vestibular system; PVS: peripheral vestibular system; UW: unilateral weakness; DP: directional preponderance; SpN: spontaneous nystagmus

Table 3. Due to technical limitations, Table 3 is provided in the Supplementary Files section.

Figures

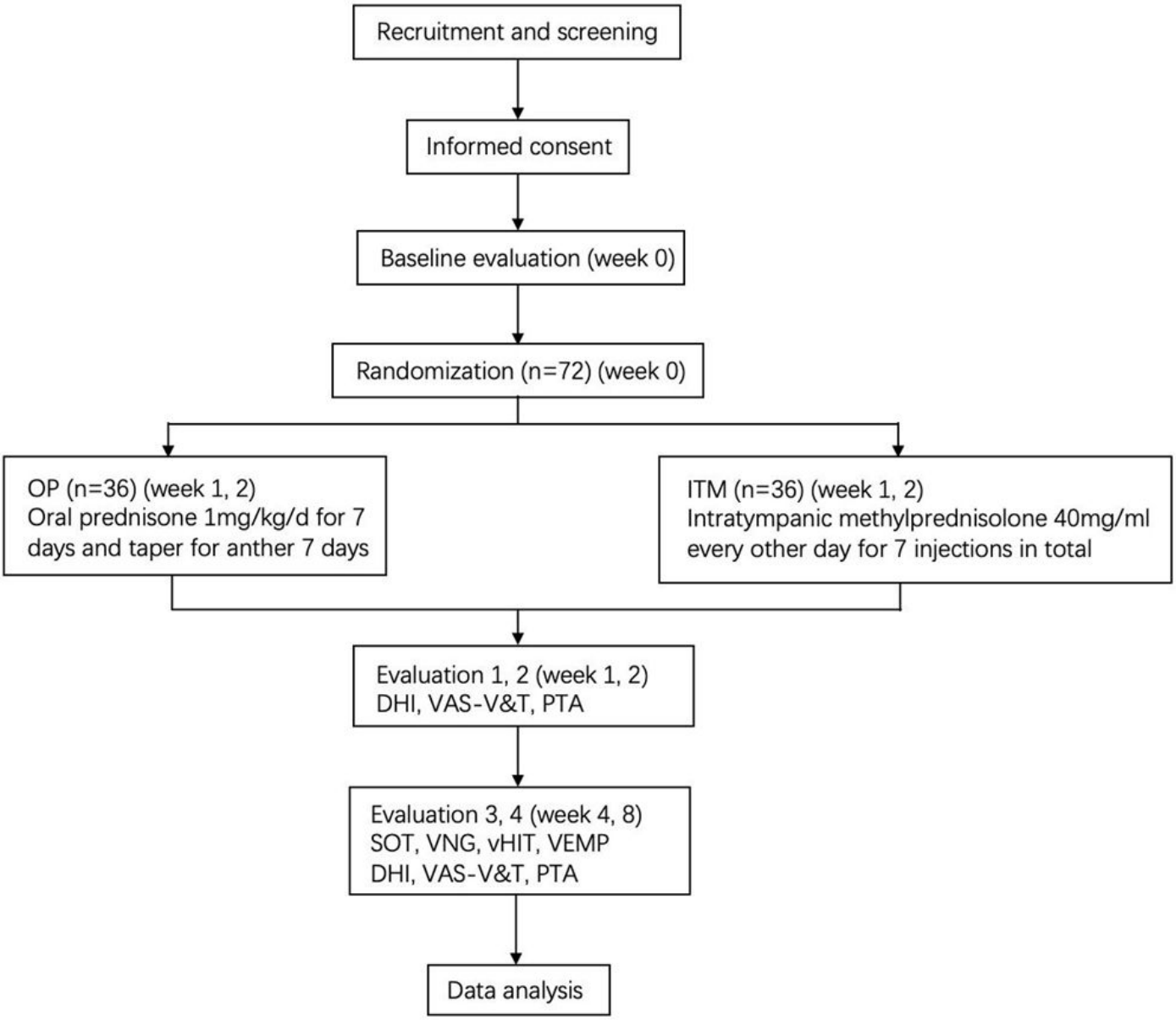

Figure 1

Study flow diagram (OP, oral prednisone; ITM, intratympanic methylprednisolone; DHI, dizziness handicap inventory; VAS-V&T, visual analogue scale for vertigo and tinnitus; PTA, pure tone audiometry; SOT, sensory organization test; VNG, videonystagmography; vHIT, video head impulse test; VEMP, vestibular evoked myogenic potentials)

Supplementary Files

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

- Appendix2.AdverseEvent.pdf
- table3.png
- Appendix1.CaseReportForms.pdf