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Efficacy of triple semicircular canal plugging versus intratympanic gentamicin for intractable Meniere's disease: study protocol for a multicenter, prospective, randomized controlled trial

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Study protocol

Keywords: Meniere's Disease, Semicircular Canal Plugging, Intratympanic Gentamicin, Vertigo, Randomized Controlled Trial, Study Protocol

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Additional Declarations: No competing interests reported.

Title {1a}

Efficacy of triple semicircular canal plugging versus intratympanic gentamicin for intractable Meniere's disease: study protocol for a multicenter, prospective, randomized controlled trial

Names of protocol contributors {3a}

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Abstract

Background: Intractable Meniere's disease is characterized by disabling vertigo attacks and progressive hearing loss that do not respond to conservative medical management. Intratympanic gentamicin is commonly used to control vertigo through chemical ablation, but it carries a risk of hearing deterioration. Triple semicircular canal plugging is an emerging surgical technique designed to eliminate vertigo while aiming to preserve residual hearing. This study aims to prospectively compare the clinical efficacy and safety of these two interventions.

Methods: This is a multicenter, prospective, open-label, randomized controlled trial. A total of 256 eligible adult patients diagnosed with intractable Meniere's disease will be recruited from 15 tertiary

referral centers in China. Participants will be randomly allocated in a one-to-one ratio to receive either triple semicircular canal plugging or intratympanic gentamicin. For the gentamicin group, a second dose will be administered one week after the first injection if criteria for withholding treatment are not met. The primary outcome is the proportion of patients achieving complete or substantial vertigo control at 24 months post-intervention. Secondary outcomes include balance recovery time, changes in hearing function, alterations of vestibular function, patient-reported quality of life, and the incidence of adverse events.

Discussion: Selecting the optimal intervention for intractable Meniere's disease remains challenging due to the trade-off between effective vertigo control and hearing preservation. By directly comparing triple semicircular canal plugging with intratympanic gentamicin in a rigorously designed multicenter trial, this study is expected to provide robust, high-quality evidence to guide clinical decision-making. The results may establish a new standard of care if the surgical intervention is proven to be superior in providing effective vertigo control while better preserving inner ear function.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2500108599. Registered on 2 September 2025.

Keywords

Meniere's Disease, Semicircular Canal Plugging, Intratympanic Gentamicin, Vertigo, Randomized Controlled Trial, Study Protocol.

Structured summary {1b}

Item	**Description**
Primary Registry and Trial Identifying Number {4}	Chinese Clinical Trial Registry, ChiCTR2500108599
Secondary Identifying Numbers	Not applicable
Source(s) of Monetary or Material Support	National Natural Science Foundation of China (No. 82471175) and Natural Science Foundation of Shandong (No. ZR2024MH027)
Primary Sponsor and contact information {3b}	Shandong Provincial ENT Hospital, Shandong University. Address: No. 4 Duanxing West Road, Huaiyin District, Jinan, Shandong, China.

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Role of sponsor and funder {3c}	The funders and the sponsoring hospital have no role in the study design; in the collection, management, analysis, and interpretation of the data; in the writing of the manuscript; or in the decision to submit the report for publication.
Contact for Public Queries	Daogong Zhang, zhangdaogong1978@163.com
Contact for Scientific Queries	Haibo Wang, whboto11@163.com
Public Title	A multicenter trial comparing triple semicircular canal plugging and intratympanic gentamicin for intractable Meniere's disease
Scientific title	Efficacy of triple semicircular canal plugging versus intratympanic gentamicin for intractable Meniere's disease: study protocol for a multicenter, prospective, randomized controlled trial
Countries of Recruitment	China
Health Condition(s) or Problem(s) Studied	Intractable Meniere's disease
Intervention(s)	Experimental group: Triple Semicircular Canal Plugging (TSCP) under general anesthesia. Comparator group: Intratympanic Gentamicin (ITG) injection under local anesthesia.
Key Inclusion and Exclusion Criteria	Inclusion criteria: Aged 18 to 70 years; Diagnosis of "definite" unilateral Meniere's disease; Disease duration ≥24 months; Intractable vertigo (failure of ≥6 months conservative management); Moderate-to-severe or profound sensorineural hearing loss (PTA ≥60 dB HL). Exclusion criteria: Bilateral Meniere's disease; Intracranial space-occupying lesion; Concurrent vestibular disorder; Known allergy to gentamicin; Contraindication to general anesthesia; Pregnancy or lactation.
Study Type	Multicenter, prospective, open-label, randomized, two-arm parallel-group (1:1 allocation ratio), superiority control trial.

Date of First Enrollment (planned)	1 November 2025
Sample Size	256 participants (128 per group)
Primary outcome(s)	Vertigo Control: The proportion of patients with complete (Class A) or substantial (Class B) control of definitive vertigo spells at 24 months post-intervention.
Key Secondary outcome(s)	Balance Recovery Time; Hearing Loss Rate (PTA and SDS); Vestibular Function (vHIT, Caloric testing, VEMPs); Patient-Reported Outcomes (FLS, DHI, VADL, THI, AFS); Incidence of Adverse Events.
Ethics Review	Approved by the Central Ethics Committee at Shandong Provincial ENT Hospital's Ethics Committee (Reference Number: 2025-058-01).
Individual Trial Participant Data sharing statement	Yes. De-identified individual clinical trial participant-level data (IPD) and statistical code will be shared upon reasonable request to the corresponding author after the publication of the trial results, for the purpose of scientific research and meta-analyses.

Protocol version {2}

version: 1.2, December 10, 2025

Introduction

Background and rationale {9a}

Meniere's disease (MD) is a chronic disorder of the inner ear characterized by a classic tetrad of symptoms: spontaneous episodic vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural fullness[1]. The unpredictable and debilitating nature of the vertigo attacks can severely impair patients' quality of life, affecting their ability to work, socialize, and perform daily activities, thereby posing a significant socioeconomic burden[2]. While pathophysiology is strongly associated with endolymphatic hydrops, the precise etiology of MD remains elusive, making curative treatment unavailable[3]. Consequently, current therapeutic strategies are primarily aimed at symptom management, with a focus on reducing the frequency and severity of vertigo episodes.

The management of MD typically follows a stepwise approach, beginning with conservative measures such as dietary salt restriction, diuretics, and betahistine[4]. However, a substantial proportion of patients, estimated to be between 15% and 20%, become refractory to these conservative measures and continue to suffer from disabling vertigo[5]. For this population with intractable MD, more invasive interventions are required, presenting a significant therapeutic dilemma for both clinicians and patients. The choice of therapy often involves a trade-off between vertigo control and the preservation of residual auditory function.

Intratympanic gentamicin (ITG) has become a widely accepted treatment for intractable MD. Administered directly into the middle ear, this aminoglycoside antibiotic induces a chemical labyrinthectomy by destroying vestibular hair cells. Numerous studies have reported that its vertigo control rate ranges from 56% to 97%[6]. Currently, ITG is recommended in many international guidelines. However, its therapeutic effect is achieved through functional ablation, which carries significant drawbacks. The primary concern is ototoxicity, with a notable risk of iatrogenic hearing loss, which can be profound and irreversible in genetically susceptible individuals[7]. Furthermore, the complete destruction of peripheral vestibular function can lead to poor central compensation, resulting in chronic imbalance, oscillopsia, and a persistent risk of falls, particularly in older patients[8]. The dose-response to gentamicin is also highly variable, and a globally standardized treatment protocol has yet to be established.

In recent years, triple semicircular canal plugging (TSCP) has emerged as a novel, function-preserving surgical alternative for intractable MD[9,10]. The procedure involves mechanically obstructing all three semicircular canals to control vertigo attacks, without destroying the sensory neuroepithelium. Retrospective and single-center prospective studies have reported excellent vertigo control rates, comparable to those of ablative procedures like labyrinthectomy, with some series reporting success in up to 97.8% of patients[9,11-13]. The principal advantage of TSCP is its preservative philosophy. By design, it aims to silence the semicircular canals while crucially preserving the function of the otolithic organs (utricle and saccule), which are vital for postural stability and gaze control[12,14]. Moreover, by leaving the vestibular sensory structures intact, TSCP may allow for better postoperative compensation and preserves the possibility of future restorative therapies, such as stem cell treatments[15].

To date, clinicians are faced with a choice between a well-established ablative therapy (ITG) and a promising preservative surgery (TSCP) for managing intractable MD. However, there is a paucity of

high-level evidence directly comparing these two fundamentally different approaches. Most of the evidence supporting TSCP comes from retrospective case series or limited single-center randomized controlled trials (RCTs), which are susceptible to selection bias[13,16,17]. A rigorous RCT is urgently needed for comparison to guide clinical decision-making. Therefore, we have designed this multicenter RCT to evaluate the efficacy and safety of TSCP compared to ITG for the treatment of intractable MD. Our primary hypothesis is that TSCP is superior to ITG for long-term vertigo control. We further hypothesize that TSCP will result in better preservation of hearing, superior postoperative balance recovery, and an improved quality of life compared to ITG.

Explanation for the choice of comparator {9b}

Intratympanic Gentamicin (ITG) was selected as the active comparator for this trial because it represents a current global standard of care for intractable Meniere's disease. ITG is widely recommended in international clinical practice guidelines for patients who have failed conservative medical management[4,19-21], making it the most clinically relevant and meaningful comparator against which to evaluate the novel surgical intervention, TSCP. The primary objective of this trial is not to prove the efficacy of TSCP against a placebo but to determine its relative effectiveness and safety compared to a well-established, commonly used ablative therapy. A direct head-to-head comparison with ITG will provide clinicians and patients with the high-quality evidence needed to make informed decisions between a function-preserving surgical strategy and a function-ablating chemical treatment. A sham surgery or placebo control group was considered ethically inappropriate for this patient population. Exposing patients with debilitating vertigo to the risks of general anesthesia and a mastoidectomy without the potential for therapeutic benefit is untenable, especially when an effective active treatment like ITG is available[22]. Therefore, comparing TSCP to ITG provides the most ethically sound and clinically impactful trial design.

Objectives {10}

The **primary objective** is to compare the efficacy of TSCP versus ITG in controlling definitive vertigo spells at 24 months post-intervention in patients with intractable MD.

The **secondary objectives** are:

1) To compare the time to balance recovery between the two groups.
2) To compare the long-term effects of each intervention on hearing function in the treated ear.
3) To compare the effects on vestibular function.
4) To evaluate and compare changes in patient-reported dizziness-related handicap, functional level, and quality of life.

5) To assess and compare the safety and incidence of adverse events for both interventions.

The **exploratory objective** is to compare changes in endolymphatic hydrops as visualized by gadolinium-enhanced inner ear Magnetic Resonance Imaging (MRI) before and after each intervention.

Methods: Patient and public involvement, and trial design

Patient and public involvement {11}

Patients and the public were not involved in the design, conduct, reporting of the trial.

Trial design {12}

This is a multicenter, prospective, open-label, randomized, two-arm parallel-group, superiority control trial. The study will be conducted across 15 tertiary academic hospitals in China. Eligible patients with intractable MD will be randomly allocated in a 1:1 ratio to one of two treatment groups: the experimental group receiving Triple Semicircular Canal Plugging (TSCP) or the active comparator group receiving Intratympanic Gentamicin (ITG). Randomization will be stratified by participating center to ensure balance across sites. The trial is designed to assess the superiority of TSCP over ITG in vertigo control at 24 months post-intervention. All participants will undergo baseline assessments prior to randomization and will be followed up at 1, 3, 6, 12, and 24 months after the intervention. A detailed flow diagram of the trial is presented in Fig. 1. The study protocol has been developed and reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[18](Supplemental Table 1).

Methods: Participants, interventions and outcomes

Trial setting {13}

This is a multicenter study that will be conducted across 15 tertiary academic hospitals in China. The lead institution and coordinating center for the trial is Shandong Second Provincial General Hospital. To ensure procedural consistency and high-quality intervention delivery across all sites, all procedures will be performed by board-certified otolaryngologists with extensive experience in otologic surgery. All participating surgeons must meet the following eligibility criteria:1) A minimum of 10 years of post-residency clinical experience in otology; 2) Documented proficiency in performing at least 10 TSCP procedures for surgeons in the experimental arm, or extensive experience with intratympanic injection techniques for clinicians in the comparator arm; 3)All participating surgeons will be required to complete a standardized training workshop on the protocol-specified surgical and interventional techniques prior to enrolling their first patient.

Characteristics of the people who are needed for the trial

Characteristic	The people we would expect to see included
Age	Participants will be adults aged 18 to 70 years, strictly defined by our inclusion criteria. Based on the typical epidemiological peak onset of Meniere's disease, we expect the median age of the enrolled cohort to be approximately 50 years.
Sex	We expect to include both Biological Male and Female participants
Gender	We expect to include men and women. Participants will be asked to self-report their gender identity during the baseline demographic assessment.
Race, ethnicity and ancestry	As the trial is conducted entirely within mainland China, we expect the vast majority of participants to be of Chinese ancestry (predominantly Han Chinese, along with ethnic minority groups depending on the diverse regional locations of the 15 participating centers)
Socioeconomic status	We expect to include participants from a wide range of socioeconomic backgrounds. Specific data regarding household income or socioeconomic status will not be systematically collected in this trial, as it is not an eligibility criterion and is not expected to influence the primary physiological outcomes of the surgical or injection interventions. All participants will be recruited from public tertiary hospitals under the coverage of the Chinese national basic medical insurance system.
Geographic location	All participants will be recruited in China. The study coordination site is in Jinan (Shandong Province), with 14 other participating tertiary referral centers

	located in major urban centers across various provinces (e.g., Beijing, Shanghai, Sichuan, Jiangsu, Xinjiang). Both urban residents and rural patients referred to these tertiary centers will be included.
Other characteristics relevant to the trial	Patients diagnosed with "definite" unilateral intractable Meniere's disease, with a disease duration of at least 24 months, failing conservative management for at least 6 months, and presenting with moderate-to-severe or profound sensorineural hearing loss (PTA ≥60 dB HL).

Eligibility criteria for participants {14a}

To be eligible for randomization into this trial, participants must meet all of the following inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

1) Aged 18 to 70 years, inclusive, and tolerable to general anesthesia.
2) Diagnosis of "definite" unilateral MD according to the 2015 diagnostic criteria of the Bárány Society[1].
3) Disease duration of at least 24 months.
4) History of intractable vertigo, defined as failure to respond to at least 6 months of conservative medical management (including lifestyle modification, diuretics, and betahistine), and having experienced at least one definitive vertigo spell per month on average over the 6 months preceding enrollment.
5) Moderate-to-severe or profound sensorineural hearing loss in the affected ear, defined as a pure-tone average (PTA) at 0.5, 1, and 2 kHz of ≥60 dB HL.
6) Willing and able to provide written informed consent and comply with all trial procedures and follow-up schedules.

Exclusion criteria:

1) Evidence or clinical suspicion of bilateral Meniere's disease.
2) Presence of a cerebellopontine angle tumor or other intracranial space-occupying lesion.

3) A concurrent diagnosis of another vestibular disorder that could explain the symptoms, such as vestibular migraine, benign paroxysmal positional vertigo, or persistent postural-perceptual dizziness.

4) A family history of unexplained deafness.

5) A documented history of conservative medical management for Meniere's disease lasting less than 6 months.

6) Known allergy or hypersensitivity to gentamicin.

7) Presence of a comorbidity that may interfere with the intervention or its assessment, such as active middle ear disease.

8) Age outside the range of 18 to 70 years, inclusive.

9) Medical contraindication to general anesthesia.

10) Current pregnancy or lactation, or planning pregnancy during the trial period.

11) Positive for Human Immunodeficiency Virus (HIV), in the replicative phase of Hepatitis B Virus (HBV) infection, or presenting with a fever of unknown origin.

12) A diagnosed psychiatric disorder likely to affect trial compliance.

13) Any other condition that does not meet the inclusion criteria, such as an unclarified etiology of vertigo or refusal to participate in the study.

14) Any other condition which, in the opinion of the investigator, would make the participant unsuitable for the trial.

Eligibility criteria for sites and those delivering interventions {14b}

To ensure the safety of participants and the consistency and high quality of the interventions across the multicenter setting, stringent eligibility criteria have been established for both the participating sites and the personnel delivering the treatments.

Eligibility criteria for participating sites:

1) Must be a certified tertiary academic hospital in China with a specialized Department of Otolaryngology-Head and Neck Surgery.
2) Must be equipped with comprehensive and standardized audiological and vestibular testing

facilities, including pure-tone audiometry, video Head Impulse Test (vHIT), bithermal caloric testing, and Vestibular Evoked Myogenic Potentials (VEMPs) equipment.

3) Must have fully equipped operating rooms with surgical microscopes, otologic drills, and general anesthesia capabilities, as well as an established protocol for postoperative care.
4) Must have obtained local Institutional Review Board (IRB) or Ethics Committee approval prior to the initiation of participant recruitment.

Eligibility criteria for individuals delivering the interventions:

All participating surgeons must meet the following eligibility criteria:

1) A minimum of 10 years of post-residency clinical experience in otology;
2) Documented proficiency in performing at least 10 TSCP procedures for surgeons in the experimental arm, or extensive experience with intratympanic injection techniques for clinicians in the comparator arm;
3) All participating surgeons will be required to complete a standardized training workshop on the protocol-specified surgical and interventional techniques prior to enrolling their first patient.

Who will take informed consent? {32a}

At each participating centre, potential participants will be identified by their treating otolaryngologist. A qualified and trained member of the research team will then provide a detailed explanation of the study, including its procedures, risks, and benefits. Participants will receive a written information sheet and be given sufficient time to ask questions and consider participation. Written informed consent will be obtained by the trained research staff from all participants prior to any trial-related procedures.

Additional consent provisions for collection and use of participant data and biological specimens {32b}

This study does not involve the collection of biological samples from participants.

Intervention and comparator

Intervention and comparator description {15a}

Experimental Arm: Triple Semicircular Canal Plugging (TSCP)

The procedure will be performed under general anesthesia. A postauricular approach will be utilized to perform a cortical mastoidectomy, thereby exposing the otic capsule. The three semicircular canals (superior, posterior, and lateral) will be meticulously identified and skeletonized. Using a small

diamond burr under low-speed drilling, a fenestration approximately 1.5 mm in diameter will be created at the midpoint of the bony labyrinth of each canal. Care will be taken to preserve the integrity of the endosteal membrane to minimize perilymph leakage. After three canals have been fenestrated, plugs will be prepared. Autologous temporalis fascia will be harvested and trimmed into small pieces (approximately 3 mm x 4 mm), which will then be used to wrap bone pâté collected during the drilling. These composite plugs will be used to sequentially occlude each fenestration. The plug material must completely fill the bony defect, leaving no gaps. The surface of the plug should be flush with or slightly proud of (<0.5 mm) the surrounding bone of the otic capsule. Over-packing will be avoided to prevent iatrogenic damage to the ampullary structures. Finally, the plugged sites will be reinforced with an overlay of bone pâté and sealed with bone wax. Meticulous hemostasis will be achieved before the wound is closed in layers. A compressive mastoid dressing will be applied to conclude the procedure.

Comparator Arm: Intratympanic Gentamicin (ITG)

A transtympanic injection of gentamicin will be performed on the affected ear under local anesthesia. The patient will be placed in a supine position with the head turned, ensuring the affected ear is facing upward to allow for optimal exposure of the tympanic membrane. The external auditory canal and the tympanic membrane will be sterilized with 75% alcohol. Topical anesthesia will be achieved by applying tetracaine solution to the surface of the tympanic membrane. The injection solution will be prepared by diluting 80 mg/2 mL of gentamicin sulfate with 1 mL of 5% sodium bicarbonate. Subsequently, a 1 mL volume of this solution (equivalent to 26.7 mg of gentamicin) will be drawn into a syringe. Using a fine needle, the solution will be injected into the middle ear cavity via a perforation made in the anteroinferior quadrant of the tympanic membrane. Following the injection, the patient will be closely monitored for any immediate adverse reactions and will be instructed to remain in the contralateral decubitus position for 30 minutes before returning to the ward. Each participant is scheduled to receive a total of two injections, administered one week apart. The second injection will be withheld if either of the following criteria is met: 1) A post-injection audiogram reveals a decrease in the bone-conduction threshold of >10 dB at any two contiguous frequencies compared to baseline (as independently assessed by an audiologist blinded to the study). 2)The participant develops symptoms indicative of vestibular hypofunction, such as new-onset dizziness, vertigo, or imbalance, accompanied by a documented decrease in the vestibulo-ocular reflex (VOR) gain on the video Head Impulse Test (vHIT).

Criteria for discontinuing or modifying allocated intervention/comparator {15b}

Patients may decide to withdraw from the trial at any time without providing any specific reason for

their decision, and the withdrawal date will be recorded on the case report form.

Strategies to improve adherence to intervention/comparator {15c}

To promote adherence, a detailed explanation of the study protocol will be provided to all participants during the informed consent process. A designated research coordinator at each center will maintain regular contact with participants to provide support and send appointment reminders. For the TSCP group, as it is a single-session surgical intervention, adherence to the primary intervention is ensured post-procedure. For the ITG group, coordinators will proactively schedule and send reminders for the second injection to ensure completion of the planned treatment course. Any reasons for not completing the second injection will be documented. Post-intervention, all participants in both groups will be encouraged to complete a standardized rehabilitation program.

Concomitant care permitted or prohibited during the trial {15d}

There are no relevant interventions or other types of care that are prohibited while participants are in the trial.

Ancillary and post-trial care {34}

For participants who may suffer harm as a result of participating in this trial, the institutions of each study site will ensure that all necessary support is provided for the participants' post-trial care.

Outcomes {16}

Primary Outcome

Vertigo Control: The proportion of patients with complete (Class A) or substantial (Class B) control of definitive vertigo spells. This will be calculated based on the average monthly number of spells during the last 6 months in the 24-month follow-up compared to the 6 months pre-intervention, according to the 1995 AAO-HNS guidelines[23]. Data will be collected from patient-completed daily vertigo diaries.

Secondary Outcome

Balance Recovery Time: Time (in days) from intervention to the ability to walk independently in a straight line and turn without assistance. This will be assessed via structured questioning and the Berg Balance Scale (BSS).

Hearing Loss Rate: The incidence of clinically significant hearing loss will be assessed at 24 months by comparing audiometric data to the poorest documented pre-treatment results, which will serve as the baseline. Hearing loss is defined as an increase of >10 dB in the Pure-Tone Average (PTA), calculated from bone-conduction thresholds at 0.5, 1, and 2 kHz, and/or a decrease of >15% in the Speech Discrimination Score (SDS). In cases of discordance between these criteria, the PTA change will take precedence for the final classification.

Vestibular Function: Change in vestibulo-ocular reflex (VOR) gain for all three canals as measured by the video Head Impulse Test (vHIT) and change in unilateral weakness (UW%) on bithermal caloric testing. Abnormal rate of cervical and ocular Vestibular Evoked Myogenic Potentials (cVEMP and oVEMP).

Patient-Reported Outcomes: Change from baseline to 24 months in total scores of the following validated questionnaires: Functional Level Scale (FLS), the Dizziness Handicap Inventory (DHI), the Vestibular Disorders Activities of Daily Living Scale (VADL), the Tinnitus Handicap Inventory (THI), and the Aural Fullness Scale (AFS).

Safety: All adverse events (AEs) and serious adverse events (SAEs) will be systematically collected throughout the study. For each reported AE, the type, incidence, and severity will be documented. The severity of AEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The causality of each AE in relation to the study interventions (TSCP or ITG) will be assessed by the site investigator based on a predefined attribution scale outlined in the study protocol. The primary safety analysis will focus on the incidence and nature of treatment-related SAEs.

Harms {17}

All adverse events (AEs) and serious adverse events (SAEs) will be systematically documented throughout the trial. An AE is defined as any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the treatment. An SAE is any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. The severity of all AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The site investigator or a designated research coordinator is responsible for documenting all AEs in the electronic Case Report Form (eCRF). This documentation will include a

description of the event, time of onset, duration, severity (CTCAE grade), action taken, outcome, and an assessment of its relationship to the study intervention (causality).

In the event of an SAE, the site investigator must take immediate and appropriate action to ensure the participant's safety. All SAEs, regardless of causality, must be reported to the central ethics committee at Shandong Provincial ENT Hospital and the local institutional review board within 24 hours of the investigator becoming aware of the event.

Participant timeline {18}

The timeline for participant involvement is illustrated in Table 1 and figure 1.

Sample size {19}

Based on published literature, we conservatively estimate the 24-month vertigo control rate (Class A+B) to be 96% for the TSCP group and 85% for the ITG group. To detect this difference with a power of 80% ($\beta = 0.2$) at a two-sided significance level of 5% ($\alpha = 0.05$), a sample size of 102 patients per group is required. To account for a potential dropout rate of 20% over the 2-year follow-up period, we will enroll 128 patients per group, for a total sample size of 256 patients.

Recruitment {20}

Potential participants will be recruited from the outpatient Otolaryngology clinics across the 15 participating centers. Recruitment is scheduled to commence in November 2025 and will continue until the target sample size has been randomized, which is anticipated to be completed by November 2026.

Assignment of interventions: randomisation

Sequence generation: who will generate the sequence {21a}

A biostatistician independent of the study team will generate the randomization sequence, with a total of 256 allocation numbers created.

Sequence generation: type of randomisation {21b}

Participants will be randomly assigned to either the experimental (TSCP) group or the control (ITG) group at a 1:1 ratio, using a randomized block design with varying block sizes.

Allocation concealment mechanism {22}

To ensure allocation concealment, an independent third party will prepare sequentially numbered, opaque, sealed envelopes. Each envelope will contain a card indicating the treatment assignment. These envelopes will be distributed to each participating center and will be opened in order by the site coordinator only after a participant has been confirmed eligible and has provided written informed consent.

Implementation {23}

After confirming eligibility and obtaining consent, the site coordinator will be assigned the next sequential allocation for that center. This will be achieved by taking the next numbered, sealed envelope in the sequence, which will then be opened to reveal the treatment assignment. The coordinating center will monitor the sequence of used envelopes to ensure protocol adherence. Enrolling personnel will not be involved in envelope preparation and will have no access to the randomization list.

Assignment of interventions: blinding

Who will be blinded {24a}

This trial will have an open-label design, as blinding of participants and treating clinicians is not feasible due to the distinct nature of the interventions. To mitigate the risk of bias, a blinded outcome assessment will be implemented. All personnel performing and interpreting audiological and vestibular function tests, as well as the trial biostatisticians, will be blinded to treatment group allocation.

How will be blinding be achieved {24b}

Blinded outcome assessment is implemented in this study. All technicians performing and interpreting audiological and vestibular examinations are blinded to participants' treatment allocation. Study subjects are instructed not to disclose their assigned intervention, and outcome assessors have no access to grouping information. Data analysis is conducted by independent biostatisticians using blinded datasets with coded group identifiers (e.g., Group A vs Group B), who remain blinded throughout the study until statistical analysis is finalized and the database is locked.

Procedure for unblinding if needed {24c}

Not applicable. As this is an open-label trial, participants and treating clinicians are not blinded to the

intervention, hence no unblinding procedure is required.

Data collection and management

Plans for assessment and collection of outcomes {25a}

A standardized data collection protocol will be implemented across all participating centers. The following baseline and demographic parameters will be collected for all participants prior to randomization: age (years), gender (male/female), weight and height, duration of MD (years), history of prior treatments, and a detailed vertigo history (average monthly frequency of definitive spells over the preceding 6 months). Baseline clinical assessments will include pure-tone audiometry, speech discrimination scores, video Head Impulse Test (vHIT), bithermal caloric testing, Vestibular Evoked Myogenic Potentials (VEMPs), and scores from all patient-reported outcome questionnaires. For participants in the Triple Semicircular Canal Plugging (TSCP) group, the following intraoperative data will be gathered: operation time (minutes), estimated blood loss (mL), and the occurrence of any intraoperative complications. For participants in the Intratympanic Gentamicin (ITG) group, procedural data will be recorded, including the dose of gentamicin administered and any immediate adverse reactions during or after the injection. Longitudinal data collection for all primary and secondary endpoints will be conducted through a standardized assessment protocol at six pre-specified time points: baseline (pre-intervention), followed by systematic post-intervention evaluations at months 1, 3, 6, 12, and 24, ensuring comprehensive temporal coverage of clinical outcomes throughout the 2-year follow-up period.

Plans to promote participant retention and complete follow-up {25b}

To mitigate the risk of data loss, a dedicated study coordinator has been designated to conduct regular follow-ups through telephone calls, text messages, or alternative communication channels, while simultaneously monitoring participant compliance and providing ongoing support throughout the research period.

Data management {26}

An electronic Case Report Form (eCRF) will be utilized to capture all clinical observation data for each patient. Investigators are responsible for ensuring the completeness, validity, and reliability of the data, as well as for the timely completion and electronic signature of the eCRF. An explanation must be provided for all missing data. At the conclusion of the trial, the electronic database will be locked. To ensure trial quality, standardized training on all trial procedures will be delivered via

multicenter web-based meetings. This training will cover all core processes, including participant recruitment, randomization, perioperative management, surgical techniques, eCRF completion, outcome assessment, data management, and the handling of serious adverse events. This ensures procedural consistency and the reliability of study results across all centers. Periodic data monitoring will be conducted by an independent third party to identify missing data and potential discrepancies or errors. Any data queries identified during this process will be resolved by the data management team. Furthermore, trial progress meetings will be held quarterly. Any amendments to the protocol will adhere to Good Clinical Practice (GCP) principles and maintain the ethical standards of this randomized controlled trial.

Confidentiality {33}

Patient identifiable information will be strictly accessible to authorized study physicians, while all collected data will be de-identified and securely stored in password-protected encrypted storage systems with access restricted to authorized study personnel

Statistical methods

Statistical methods for primary and secondary outcomes {27a}

The primary endpoint, the proportion of patients with effective vertigo control at 24 months, will be compared between the two groups using the Chi-squared test or Fisher's exact test, as appropriate. A relative risk with a 95% confidence interval (CI) will be calculated. For secondary continuous outcomes, between-group differences will be analyzed using independent t-tests or Mann-Whitney U tests. Repeated measures data will be analyzed using linear mixed-effects models to account for intra-patient correlation over time, with treatment group, time, and their interaction as fixed effects. Time-to-event data (balance recovery) will be analyzed using Kaplan-Meier curves and compared with the log-rank test. All statistical tests will be two-sided, with a p-value < 0.05 considered statistically significant.

Who will be included in each analysis {27b}

Three study populations are predefined for statistical analyses. The Full Analysis Set (FAS), covering all randomized patients receiving assigned intervention and analyzed per randomized grouping under the intention-to-treat (ITT) principle, serves as the dataset for primary efficacy analysis. The Per-Protocol (PP) Set, consisting of participants who obtain allocated treatment, have assessable primary

outcome data, and finish no fewer than two of the Month 1, Month 3 and Month 6 scheduled visits, is adopted for primary endpoint sensitivity analysis and all secondary outcome assessments, with only PP subjects possessing corresponding available data included in respective secondary endpoint analyses. In addition, all patients exposed to any portion of investigational treatment form the Safety Analysis Set, where safety indicators are analysed based on patients' actual received treatment.

How missing data will be handled in the analysis {27c}

All enrolled patients that underwent one of the two interventions under investigation will be assessed using an intention-to-treat analysis in each group. Per-protocol analysis will be performed as a secondary analysis. Missing values will be imputed through the multiple imputation method.

Methods for additional analyses (e.g. subgroup analyses) {27d}

While the study is not primarily powered for subgroup analyses, exploratory subgroup analyses may be conducted based on key baseline clinical characteristics (e.g., age, disease duration, or baseline hearing level). The specific variables and statistical methods for these exploratory subgroup analyses will be fully detailed in the Statistical Analysis Plan (SAP) prior to database lock and unblinding

Interim analyses {28b}

No interim analyses are pre-planned.

Protocol and statistical analysis plan {5}

The study protocol will be publicly accessible upon its publication in Trials. The core statistical analysis plan has been directly integrated into the Statistical methods section of this submitted protocol. A more comprehensive, standalone Statistical Analysis Plan (SAP) will be finalized by the trial biostatistician prior to the completion of patient follow-up and database lock. This full SAP will be available from the corresponding author upon reasonable request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {3d}

The trial will be coordinated and overseen by two main functional groups to ensure rigorous day-to-day management and high-level scientific governance. The Project Management Group (PMG), based at the lead institution (Shandong Provincial ENT Hospital), provides day-to-day organizational support. Comprising central trial coordinators, clinical research associates, a lead data manager, and the central biostatistician, the PMG is responsible for managing the electronic Data Capture (eDC) system, tracking multicenter participant recruitment, resolving clinical data queries, ensuring protocol adherence across all 15 participating centers, and organizing logistics for site monitoring. To maintain smooth trial operations, the PMG will hold regular meetings once a month throughout the duration of the trial.

High-level oversight is provided by the Trial Steering Committee (TSC), which retains ultimate authority for scientific governance and administrative oversight of the trial. This multidisciplinary body, comprising sponsor representatives, independent clinical experts, biostatisticians, independent adjudicators, and participating principal investigators, oversees all aspects of trial design, implementation, analytical methodology, and data interpretation. Furthermore, the TSC is responsible for approving major protocol amendments and making final decisions regarding the continuation or early termination of the trial. The TSC will meet formally once a year, with additional ad-hoc meetings convened as necessary if critical safety or operational issues arise.

Composition of the data monitoring committee, its role and reporting structure {28a}

The independent Data Monitoring Committee (DMC) consists of one independent biostatistician and multiple discipline-specific clinical experts who are entirely external to the trial research team, trial sponsor and funding body with no relevant conflicts of interest. The DMC undertakes scheduled interim data reviews throughout the trial period to assess participant safety and verify the reliability of trial efficacy outcomes. All formal findings and recommendations from the DMC will be submitted in written reports to the Trial Steering Committee as its designated reporting pathway. Full detailed DMC charter is appended as a supplementary document of this trial protocol.

Frequency and plans for auditing trial conduct {29}

The steering committee will convene annually, the Project Management Committee monthly, and the Data & Safety Monitoring Board quarterly.

Protocol amendments {31}

Any important amendments to the protocol—such as changes to eligibility criteria, interventions, outcomes, or the statistical analysis plan—will first be discussed and agreed upon by the Trial Steering Committee. Subsequently, the proposed amendment will be submitted to the central ethics committee at Shandong Provincial ENT Hospital for formal review and approval. No amendment will be implemented until written approval has been received from the ethics committee. Upon approval, the lead investigator will ensure that all site principal investigators are notified of the changes. The protocol will be updated with a new version number and date, and the trial registry record will be amended accordingly. If an amendment directly affects participant care, safety, or the nature of their consent, participants will be informed of the changes and re-consented as required by the ethics committee.

Dissemination policy {8}

The outcomes of the trial will be disseminated through peer-reviewed publications. The trial has been registered at clinicaltrials.gov (ChiCTR2500108599). The final trial results will be published in a peer-reviewed journal. Furthermore, results will be presented at appropriate national and international conferences. Relevant information about the trial and its results will be disseminated to patient groups and by social media.

Discussion

This study is designed to address a critical knowledge gap in the management of intractable Meniere's disease. By employing a robust, multicenter, randomized controlled design, it will provide high-quality evidence on the comparative effectiveness and safety of a function-preserving surgery (TSCP) versus a widely used ablative therapy (ITG). The choice of ITG as the active comparator is deliberate and multifactorial. ITG represents a current standard of care and a guideline-recommended therapy in the US, Europe, and Asia for patients who have failed conservative management, making the results of this trial directly relevant to real-world clinical practice[4,19,20].

The decision not to include a sham surgery control group was made after careful ethical and methodological consideration. First and foremost, exposing patients to the inherent risks of general anesthesia and a transmastoid surgical approach without the potential for therapeutic benefit was deemed ethically untenable, especially when an effective active treatment is available[22]. Furthermore, the primary aim of this trial is not to establish the efficacy of TSCP against placebo, but rather to conduct a pragmatic comparison against a widely accepted active treatment to inform clinical

decision-making. Sham-controlled trials are exceedingly rare in otologic surgery for vertigo, and there is no broad consensus recommending them as a standard design[22,24]. The nature and magnitude of the placebo effect in surgery are themselves subjects of significant debate, with potential for confounding by methodological artifacts[25]. Therefore, selecting ITG as the active comparator provides a clinically meaningful and ethically sound framework to determine the relative merits of TSCP for this challenging patient population.

The primary strength of this trial is its prospective, randomized methodology, which minimizes selection bias and enhances the internal validity of the findings. The multicenter design increases the generalizability of the results to a broader patient population and clinical settings. Furthermore, the comprehensive battery of outcome measures, including objective vestibular function tests and validated patient-reported outcome measures, will provide a holistic view of the treatment effects beyond simple vertigo control.

A potential limitation is the open-label design, which is unavoidable given the nature of the interventions. This could introduce performance bias from clinicians and reporting bias from patients. To mitigate this, we have incorporated several strategies, most importantly the blinding of objective outcome assessors and the use of patient-completed diaries for the primary endpoint, which are collected prior to the follow-up consultation.

The results of this trial have the potential to significantly impact the treatment algorithm for intractable MD. If TSCP is shown to be superior in vertigo control while demonstrating significant advantages in preserving hearing and balance function, it could become the preferred treatment for this challenging condition, shifting the paradigm from ablative to preservative strategies.

Trial status

Recruitment will be started in Nov 30, 2025, and is expected to be completed by Nov 30, 2026. The estimated study completion date is Nov 30, 2028. The current protocol version: 1.2, Dec 10, 2025.

Abbreviations

AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
AE	Adverse Event
AFS	Aural Fullness Scale

BSS	Berg Balance Scale
CTCAE	Common Terminology Criteria for Adverse Events
cVEMP	Cervical Vestibular Evoked Myogenic Potential
DHI	Dizziness Handicap Inventory
eCRF	Electronic Case Report Form
FLS	Functional Level Scale
GCP	Good Clinical Practice
ITG	Intratympanic Gentamicin
ITT	Intention-to-Treat
MD	Meniere’s Disease
oVEMP	Ocular Vestibular Evoked Myogenic Potential
PP	Per-Protocol
PRO	Patient-Reported Outcome
PTA	Pure-Tone Average
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDS	Speech Discrimination Score
SOP	Standard Operating Procedure
THI	Tinnitus Handicap Inventory
TSCP	Triple Semicircular Canal Plugging

VADL	Vestibular Disorders Activities of Daily Living
vHIT	Video Head Impulse Test
VOR	Vestibulo-Ocular Reflex

Declarations

Acknowledgements

We would like to thank all the patients and staff who will participate in this trial.

Authors' contributions {3a}

D.Z. and H.W. conceived the study and contributed to design concept; X.L. and A.D. drafted this trial protocol. D.Z. served as the project director. Q.Z., Y.L. and other authors contributed to study design and proposal development. A.D. was the lead trial statistical methodologist. Artificial intelligence was used for language polishing during manuscript preparation. All authors read and approved the final manuscript. Future authorship for publications originating from this trial will be determined in accordance with standard ICMJE guidelines.

Sources of funding and other support {7a}

The trial is supported by the National Natural Science Foundation of China, No. 82471175, Natural Science Foundation of Shandong, No. ZR2024MH027. This study also receives internal funding from Shandong Provincial ENT Hospital. The fundings and hospital has no role in the study design; in the collection, management, analysis, and interpretation of the data; or in the writing of the manuscript

Availability of data and materials {6}

The final de-identified trial dataset, data dictionary and analytic code are obtainable from the corresponding author upon reasonable post-publication request; no contractual clauses restrict investigators' data access.

Ethics approval and consent to participate {30}

The central ethics committee at Shandong Provincial ENT Hospital's Ethics Committee, as well as the local ethics committees at all participating institutions, have approved this study protocol (Central Ethics Approval Reference Number 2025-058-01). All participants will provide written informed consent prior to any study-related procedures.

Consent for publication

Not applicable.

Competing interests {7b}

The authors declare that they have no competing interests.

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Table 1. Schedule of enrolment, interventions, and assessments

	STUDY PERIOD						
	Enrollment	Allocation	Post-allocation Follow-up				
TIMEPOINT	**Screening (-7)**	**Baseline (0)**	**Month 1**	**Month 3**	**Month 6**	**Month 12**	**Month 24**
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Randomization		X					
INTERVENTIONS:							
Triple Semicircular Canal Plugging (TSCP)		X					
Intratympanic Gentamicin (ITG)		X[1,2]					
ASSESSMENTS:							
Vertigo Diary		X	———	———	———		X
Questionnaire for Postoperative Balance Recovery		X		———	———	———	X
Pure-Tone Audiometry (PTA)		X	X	X	X	X	X
Speech Discrimination Score (SDS)		X	X	X	X	X	X
Video Head Impulse Test (vHIT)		X	X		X*	X	X
Caloric Testing		X	X		X*	X	X
VEMPs (c/o)		X	X		X*	X	X
Berg Balance Scale (BSS)		X	X	X	X	X	X
Dizziness Handicap Inventory (DHI)		X	X	X	X	X	X
Vestibular Disorders Activities of Daily Living (VADL)		X	X	X	X	X	X
Functional Level Scale (FLS)		X	X	X	X	X	X
Tinnitus Handicap Inventory (THI)	X		X	X	X	X	X
Aural Fullness Scale (AFS)	X		X	X	X	X	X
Gadolinium-Enhanced MRI of the Inner Ear	X						X
Adverse Event (AE) Monitoring	X		X	X	X	X	X

1: First injection for the ITG group.
2: Second injection for the ITG group, administered one week after the first injection, if criteria for withholding are not met.
*Optional

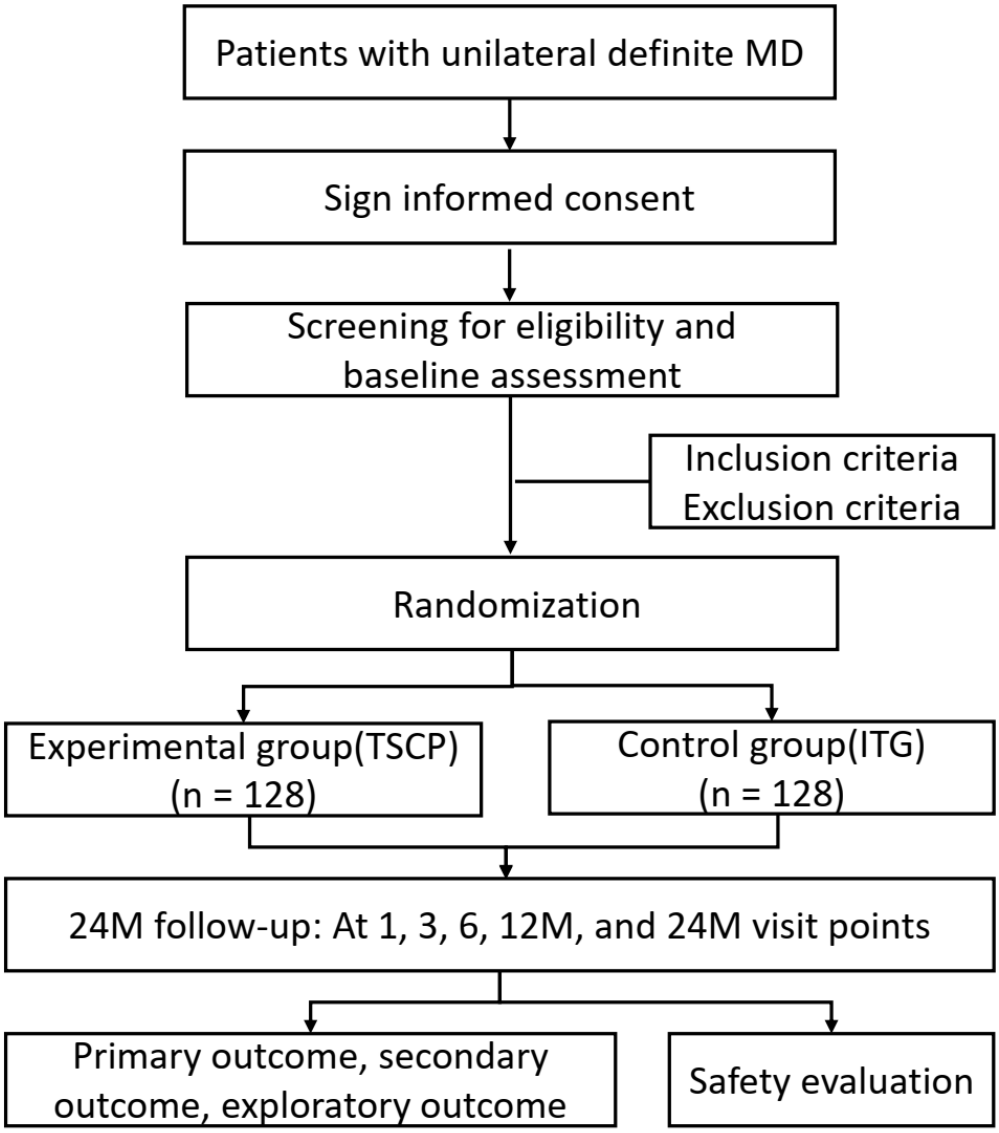

Figure 1. Flow diagram of the trial

Supplementary Files

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- SupplementalTable1.SPIRIT2013checklistofitemstoaddressinarandomizedtrialprotocol.docx