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Intratympanic injection of human umbilical cord mesenchymal stem cell derived small extracellular vesicles for refractory sudden sensorineural hearing loss: a Phase 1 trial

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Abstract

Background Refractory sudden sensorineural hearing loss (RSSNHL) remains a therapeutic challenge with limited effective treatment options. Human umbilical cord mesenchymal stem cell-derived small extracellular vesicles (hucMSC-sEVs) have demonstrated otoprotective and regenerative potential in preclinical studies. This Phase 1 trial evaluated the safety of intratympanic hucMSC-sEVs in patients with RSSNHL.

Methods This single-center, open-label, single-arm clinical study enrolled RSSNHL patients between June and September 2025 (ChiCTR2500103765). Participants received intratympanic hucMSC-sEVs for five consecutive days across four dose cohorts, ranging from 8×10^8 to 1×10^{11} particles/mL. Follow-up assessments were conducted at 1, 2, 4, and 8 weeks after treatment, during which adverse events (AEs) were recorded, and hearing outcomes were evaluated.

Results Twelve of the thirteen enrolled patients completed the 8-week follow-up. Intratympanic administration of hucMSC-sEVs was well tolerated across all dose levels, with no dose-limited toxicity or serious AEs. The most common AEs were ear pain (5/12), ear fullness (3/12), and transient dizziness (2/12), all characteristic of intratympanic injection and resolving without intervention.

Conclusions In this Phase 1 study, intratympanic hucMSC-sEVs were well tolerated and showed preliminary signals of hearing improvement. Responses were observed only in patients receiving lower dose levels (8×10^8 and 4×10^9 particles/mL) and in those treated within a shorter disease window (≤ 22 days). These exploratory findings require confirmation in larger controlled trials.

Trial Registration This study was registered on June 5, 2025, at Chinese Clinical Trial Registry (ChiCTR2500103765).

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Keywords Sensorineural hearing loss, Small extracellular vesicles, Mesenchymal stem cells, Refractory, Phase 1 trial

Introduction

Sudden sensorineural hearing loss (SSNHL) is an acute inner ear disorder characterized by a rapid onset of unexplained hearing decline [1]. Despite extensive research, its underlying mechanisms remain poorly understood [2]. SSNHL imposes a substantial functional and psychosocial burden, particularly in individuals with severe-to-profound hearing loss [3]. Although glucocorticoids constitute the current first-line therapy [4], their therapeutic effect is limited, and many patients fail to achieve meaningful recovery. For patients who do not respond to steroid therapy, a condition often referred to as refractory sudden sensorineural hearing loss (RSSNHL), effective treatment options remain scarce, underscoring an urgent unmet clinical need [5].

Mesenchymal stem cell (MSC) based therapies have gained attention as a potential approach for auditory restoration, with increasing evidence indicating that their therapeutic effects are largely mediated through secreted small extracellular vesicles (sEVs) [6–8]. The translation of sEVs-based therapies into the clinic is supported by a growing body of evidence on their safety profile and regenerative mechanisms [9, 10]. Preclinical studies have demonstrated that MSC-sEVs exert robust otoprotective effects across multiple models of auditory injury, including noise trauma and ototoxic drug exposure, by mitigating oxidative stress, reducing apoptosis, and preserving the function of hair cells and spiral ganglion neurons [11–13]. Intratympanic administration provides a direct and minimally invasive route for delivering sEVs to the inner ear while limiting the systemic side effects [14, 15]. In our previous rat study, we further showed that intratympanic MSC-sEVs can successfully reach the cochlea and effectively attenuate spiral ganglion neuron degeneration [16]. These findings collectively provide a strong biological and translational rationale for evaluating intratympanic sEVs therapy in humans.

In light of these preclinical data and the unmet clinical need in RSSNHL, we conducted a clinical study evaluating intratympanic delivery of human umbilical cord mesenchymal stem cell-derived small extracellular vesicles (hucMSC-sEVs) as a potential therapeutic approach. We hypothesized that intratympanic administration of hucMSC-sEVs would be safe and well-tolerated, with the potential to support auditory recovery. This Phase 1 trial was therefore designed to systematically evaluate the safety of this novel therapeutic strategy.

Methods

Study design and participants

This was a single-center, open-label, single-arm Phase 1 clinical trial designed to evaluate the safety of intratympanic hucMSC-sEVs injection for RSSNHL. The study protocol was approved by the Ethics Committee of Zhujiang Hospital, Southern Medical University (2025-KY-065-01). This trial was performed in accordance with the Declaration of Helsinki. The trial is registered on in the Chinese Clinical Trial Registry (ChiCTR2500103765).

Eligible participants met the following criteria: aged ≥ 18 years; hearing loss ≥ 20 dB at ≥ 2 contiguous frequencies, with < 15 dB improvement in pure-tone average (PTA) of the affected frequencies after ≥ 7 days of standard corticosteroid-based therapy and pre-treatment PTA > 60 dB HL; and cranial magnetic resonance imaging (MRI) confirming the absence of acoustic neuroma or other identifiable etiologies. We excluded persons with acute/chronic infectious inflammation, tympanic membrane perforation, middle ear effusion, or cholesteatoma in the affected ear; acoustic neuroma or other central nervous system disorders contributing to hearing loss; pregnancy or lactation; history of drug allergy and other conditions deemed unsuitable for enrollment by the investigator. All participants provided written informed consent and were prohibited from concurrent participation in other clinical trials.

Procedures

The hucMSC-sEVs used in this clinical trial were supplied by Guangdong Qianhui Biotechnology Co., Ltd. The product underwent quality-control testing, including particle size, particle concentration, particle-to-protein ratio, mycoplasma testing, sterility testing for bacteria/fungi, endotoxin testing, and replication-competent virus testing (Supplementary Materials). All tested parameters met the predefined release specifications for clinical use.

All enrolled patients completed comprehensive pre-treatment evaluations (Baseline, BL), including audiological tests (0.25–8 kHz pure-tone audiometry) and MRI to rule out concurrent conditions like middle ear space-occupying lesions, for confirmation of eligibility. PTA was calculated as the average of pure-tone thresholds at 0.5, 1, 2, and 4 kHz (standard audiometric frequencies for SSNHL evaluation). Baseline characteristics included PTA, blood routine, hepatic and renal function tests, tympanic membrane integrity, and middle ear pressure, all of which were completed before the first injection.

Thirteen patients were allocated to four sequential dose cohorts (Group A, $n = 4$; Groups B, C, and D, $n = 3$ each): Group A (1×10^{11} particles/mL), Group B ($2 \times$

10^{10} particles/mL), Group C (4×10^9 particles/mL), and Group D (8×10^8 particles/mL). Multiple dose levels were included to evaluate safety and tolerability across a dose gradient, and the highest dose was supported by preclinical safety data [16]. All patients received daily intratympanic injections of 0.3 mL assigned hucMSC-sEVs preparation into the affected ear for five consecutive days; injections were performed under otoscopic guidance via sterile puncture of the anteroinferior quadrant of the tympanic membrane. Post-injection, patients maintained a supine position with the head tilted 30–45 degrees contralaterally for thirty minutes, during which they must refrain from swallowing and chewing.

Patients were instructed to record adverse reactions and medication use in a diary card after each injection. Concomitant medications (e.g., ginkgo biloba preparations and vitamin supplements) were allowed if clinically necessary. Follow-up visits were conducted at 1, 2, 4, and 8 weeks post-treatment. At each visit, evaluations included audiometry, tympanometry, otoscopy, blood routine, hepatic and renal function tests.

Outcomes

The primary endpoint of this trial was to evaluate the safety and tolerability of intratympanic hucMSC-sEVs injection, including local and systemic adverse events during the consecutive five-day injection period and the 8-week follow-up; unsolicited but treatment-related AEs within the same period; serious adverse events throughout the entire study period; as well as clinically significant abnormalities in routine laboratory tests, otoscopy and tympanometry during the 8-week follow-up.

The secondary endpoint was preliminary efficacy, assessed by changes in PTA at baseline and weeks 1, 2, 4, and 8. As this was a Phase 1 trial, hearing outcomes were primarily evaluated according to the prespecified 1997 criteria from the Chinese Society of Otorhinolaryngology and the Editorial Board of the Chinese Journal of Otorhinolaryngology. To facilitate broader international comparability, outcomes were additionally categorized according to Siegel's criteria. For descriptive consistency across different reporting frameworks, we also present the proportion of patients with ≥ 15 dB improvement in PTA as an exploratory indicator of hearing improvement. The overall response rate was calculated as: (Cure + Marked Improvement + Improvement) / Total Number $\times 100\%$.

Statistical analysis

This was an exploratory study with all analyses being descriptive in nature. All participants who completed the 2-month follow-up were included in the safety and exploratory efficacy analyses. Descriptive statistics were used to summarize baseline characteristics (e.g.,

demographic data, audiological indices) and 2-month follow-up data (safety and efficacy indicators). The normality of continuous variables was assessed using the Shapiro-Wilk test. Categorical variables were reported as counts (percentages), normally distributed continuous variables as mean $\pm$ standard deviation (SD); non-normally distributed continuous variables as median (interquartile range, IQR). The 95% confidence intervals (CIs) for medians (e.g., disease duration) were estimated using the binomial distribution-based exact method. For one participant (S003) with missing baseline audiological data at 125 Hz and 8 kHz, adjacent-frequency interpolation was implemented (125 Hz replaced by 250 Hz; 8 kHz replaced by 6 kHz), given the clinical feasibility of audiological testing. All statistical analyses were conducted using SPSS 25.0 software.

Results

Patient characteristics

A total of twelve patients with RSSNHL were enrolled in this Phase 1 study (Fig. 1). Patient characteristics are listed in Table 1. The median age was 40 years (range, 22–67 years), and 6 patients (50%) were male. The affected ear was evenly distributed between the right (6/12) and left (6/12) sides. The mean pre-treatment PTA of the affected ears was 88.17 ± 14.62 dB HL, consistent with severe-to-profound hearing loss. Disease duration ranged from 8 to 366 days, as all patients had received ≥ 7 days of glucocorticoid therapy without improvement. Participants were assigned to the four dose cohorts, with three patients in each group: Group A (1×10^{11} particles/mL), Group B (2×10^{10} particles/mL), Group C (4×10^9 particles/mL), and Group D (8×10^8 particles/mL). All patients received intratympanic administration of hucMSC-sEVs once daily for five consecutive days.

Safety

Intratympanic administration of hucMSC-sEVs was well tolerated at all tested concentrations. No dose-limiting toxicities, serious AEs, or treatment-related abnormalities were observed. Nine of twelve patients (75%) experienced a total of ten AEs. All events were classified as Grade 1 according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0) and resolved spontaneously. The most frequent AEs were procedure-related, including ear pain in five patients and ear fullness in three patients; two patients reported transient dizziness lasting only minutes.

Otoscopy demonstrated complete healing of tympanic membrane puncture sites in all patients (Figure S1). No tympanic membrane perforation, middle ear effusion, or infection occurred. Tympanometry confirmed stable middle ear function throughout follow-up, with all valid tympanometric peak pressure values falling within the

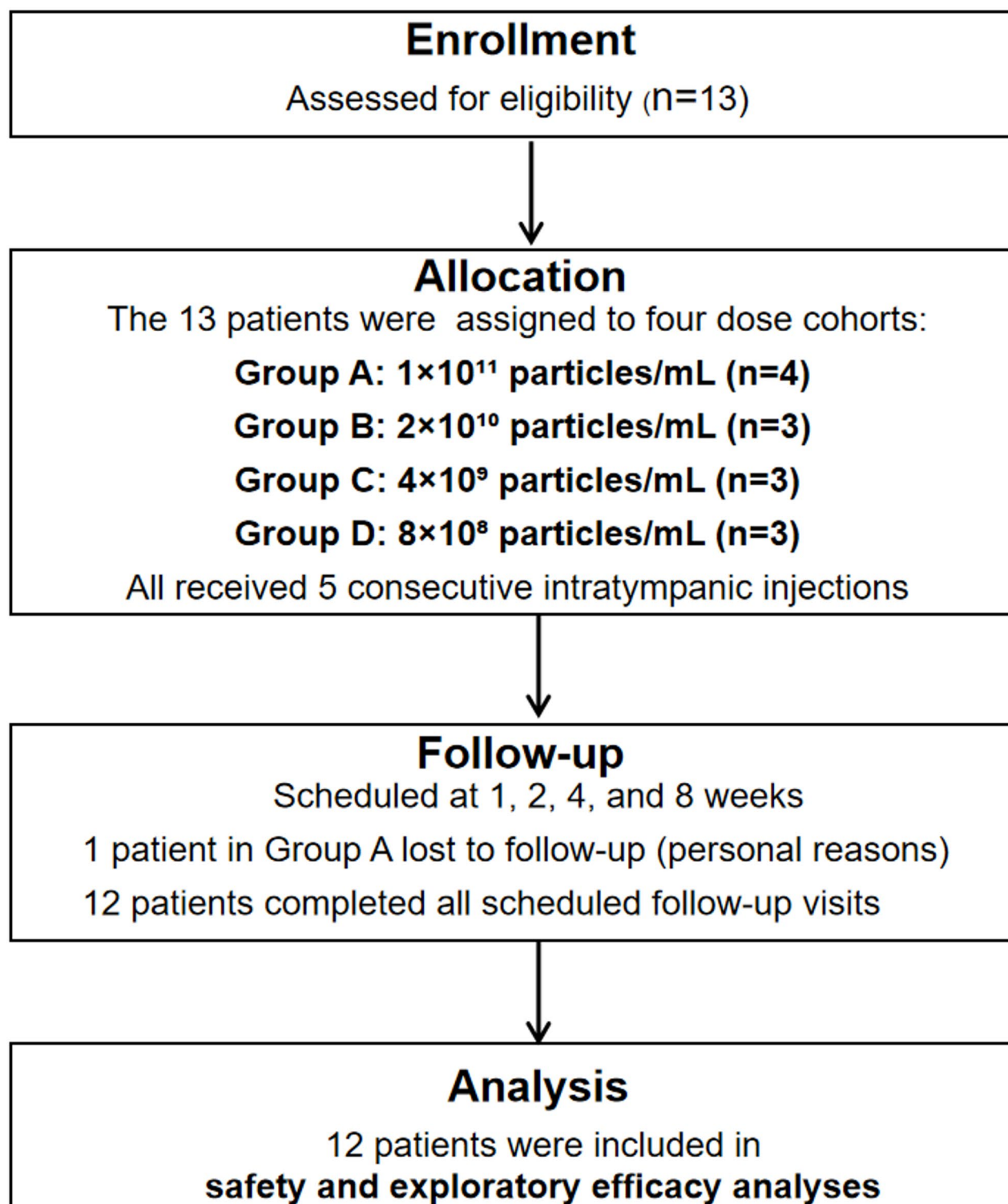
**Fig. 1** CONSORT flow diagram

Table 1 Patients Characteristics

Patient	Sex	Age	Disease duration	Affected ear	Pre-PTA (dB HL)	Otologic complications	Treatment group
S002	F	40 yr	91 d	Left	76	Tinnitus	B
S003	F	32 yr	21 d	Left	106	Tinnitus, Vertigo	C
S004	F	51 yr	366 d	Right	88	Tinnitus, Vertigo	A
S005	F	47 yr	22 d	Right	96	Tinnitus	D
S006	M	45 yr	65 d	Left	85	Tinnitus	A
S007	M	52 yr	12 d	Right	106	Tinnitus, Vertigo	C
S008	M	67 yr	60 d	Left	61	Tinnitus, Vertigo	D
S009	M	22 yr	8 d	Right	88	Tinnitus	C
S010	M	30 yr	11 d	Right	86	Tinnitus	D
S011	F	23 yr	33 d	Right	79	Tinnitus	B
S012	F	39 yr	47 d	Left	111	Tinnitus	B
S013	M	53 yr	38 d	Left	76	Tinnitus	A

Table 2 Tympanometric peak pressure (TPP) at each follow-up visit (daPa)

Group	ID	Baseline	Week 1	Week 2	Week 4	Week 8
A	S004	NA	-17	69	-31	-55
	S006	3	-31	-4	-12	-3
	S013	-6	-2	-2	-19	-28
B	S002	NP	NP	-47	-111	NP
	S011	0	-7	-7	-6	-8
	S012	-1	-19	-4	-2	-1
C	S003	-11	1	-20	-5	0
	S007	-2	-6	-4	-1	-4
	S009	NA	-27	-1	-8	-21
D	S005	-1	-1	2	3	2
	S008	NP	-70	NP	-4	-61
	S010	-7	-14	NP	-22	4

NP = not performed; NA = not available

physiological range (Table 2). Hematologic, hepatic, renal indices, and glucose levels remained within normal limits without clinically meaningful changes from baseline (Fig. 2). Overall, no local or systemic safety concerns were identified during the study period.

Preliminary efficacy

Preliminary exploratory analyses were conducted in the twelve patients who completed all follow-up assessments. Five patients showed a PTA improvement of ≥ 15 dB at the end of follow-up (Fig. 3A). Hearing threshold changes across frequencies suggested that improvement was observed at multiple tested frequencies in some patients (Fig. 3B).

At the group level, PTA trends over time are shown in Fig. 4A. Groups A and B showed limited overall change after treatment. In contrast, patients in Groups C and D appeared to show greater reductions in PTA over the follow-up period, which was generally consistent with the individual frequency-specific changes shown in Fig. 4B. Within these two groups, all three patients in Group C and two of three patients in Group D showed PTA improvement meeting the ≥ 15 dB criterion. Given

the small sample size and uncontrolled study design, these findings should be interpreted cautiously and are described here only as exploratory observations rather than evidence of a definite dose-response relationship or treatment efficacy. In addition, two patients in Groups A and C reported reductions in vertigo-related VAS scores from 50 to 60 to 20 and 25, respectively, accompanied by subjective alleviation of symptoms to a mild level.

Individual-level PTA trajectories (Supplementary Figure S2) showed heterogeneity in hearing outcomes across patients. While little overall change was observed in Groups A and B, some patients in Groups C and D showed gradual PTA reductions over the 8-week follow-up, with improvement observed as early as week 1 in certain cases.

Correlation analysis

Correlation analyses (Fig. 5A) showed that age and pre-treatment PTA were not significantly associated with hearing improvement. In contrast, relatively lower huc-MS-C-sEVs concentrations and shorter disease duration were significantly correlated with greater PTA recovery. Disease-duration plotting (Fig. 5B) revealed that all

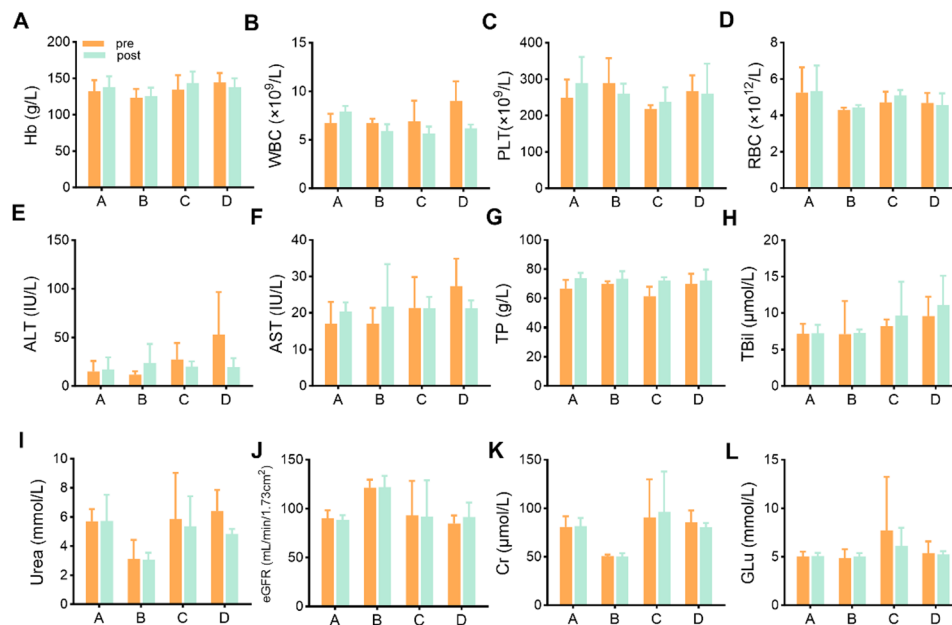


Fig. 2 Systemic laboratory indices before and after intratympanic administration of hucMSC-sEVs. **A** Hemoglobin; **B** White blood cell count; **C** Platelet count; **D** Red blood cell count; **E** Alanine aminotransferase; **F** Aspartate aminotransferase; **G** Total protein; **H** Total bilirubin; **I** Urea; **J** Estimated glomerular filtration rate; **K** Creatinine; **L** Glucose. Dose groups: A = 1×10^{11} B = 2×10^{10} ; C = 4×10^9 ; D = 8×10^8 particles/mL ($n = 3$ per group)

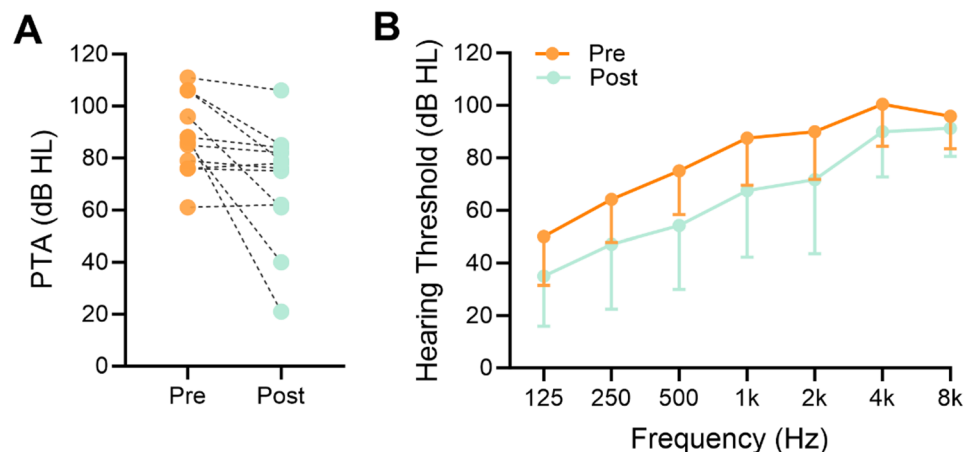


Fig. 3 Hearing outcomes. **A** Individual changes in PTA before and after treatment. **B** Mean hearing thresholds across frequencies (125 Hz–8 kHz) before and after treatment. Error bars indicate standard deviation

responders were clustered within an early therapeutic window of 22 days, whereas patients with longer disease courses showed little or no improvement. Dose–response analysis (Fig. 5C) further demonstrated that clinically meaningful gains occurred only in the lower-dose cohorts (Groups C and D), with three patients achieving marked PTA improvements exceeding 30 dB. A post hoc sensitivity analysis excluding S004 showed a similar overall pattern, with greater mean PTA improvement in lower-dose cohorts C and D and a preserved association between shorter disease duration and greater hearing improvement.

Discussion

This study demonstrates that intratympanic administration of hucMSC-sEVs is safe and well tolerated in patients with RSSNHL. No dose-limiting toxicity, serious adverse events, or treatment-related organ dysfunction occurred during follow-up. All adverse events were grade 1 and procedure-related, resolving spontaneously without intervention, underscoring both the safety of hucMSC-sEVs and the feasibility of the intratympanic delivery route.

Although not powered for efficacy evaluation, this trial provides preliminary signals of therapeutic benefit. A distinct dose–response pattern was observed, with

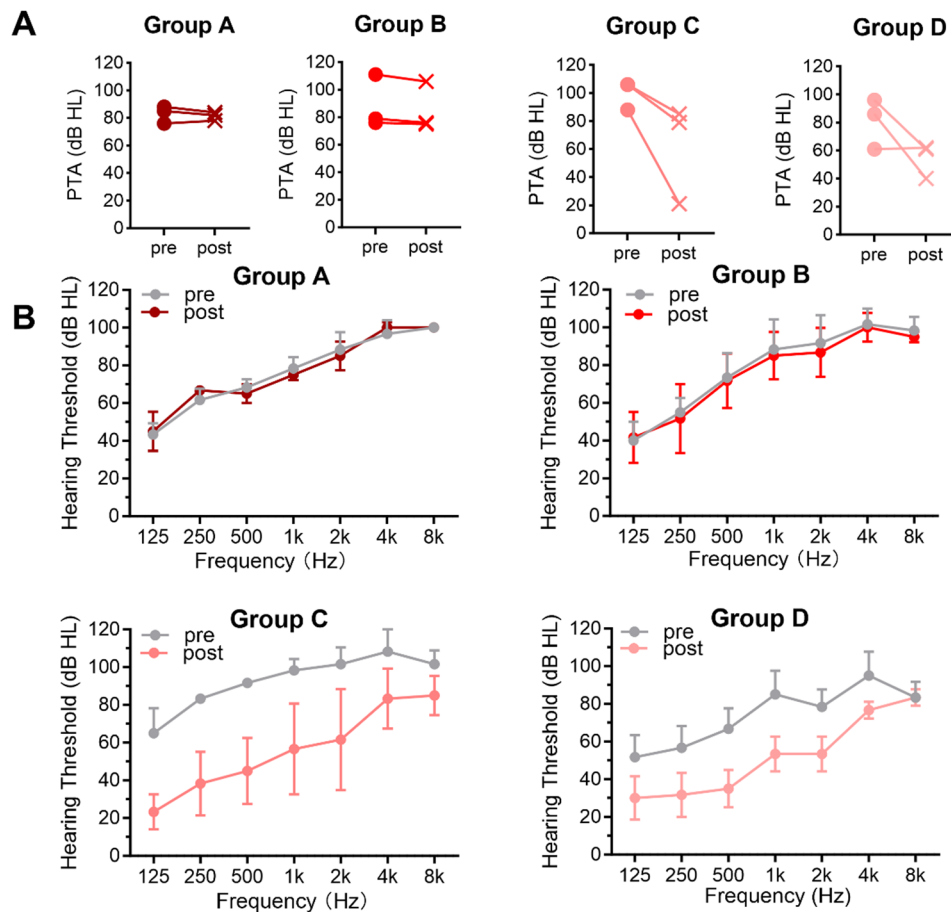


Fig. 4 Hearing outcomes at the group level. **A** PTA changes before and after treatment across the four dose cohorts. **B** Frequency-specific hearing thresholds (125 Hz–8 kHz) before and after treatment in each dose cohort. Error bars represent standard deviation

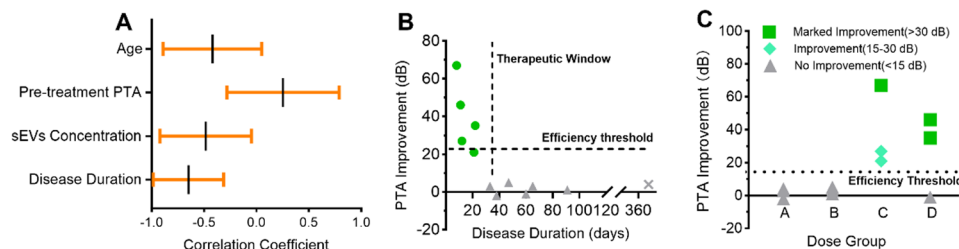


Fig. 5 Factors associated with hearing improvement. **A** Correlation analysis of clinical variables with PTA improvement. **B** Association between PTA improvement and disease duration. **C** Dose-response distribution of PTA improvement across the dose cohort

therapeutic benefit limited to the low-dose cohorts (8×10^8 to 4×10^9 particles/mL), whereas higher doses produced no measurable improvement. This inverted pattern aligns with recent preclinical studies. In an ischemic stroke model, low-dose EVs produced superior benefits compared with higher doses, including upregulation of neuroprotective factors such as BDNF [17]. Another mouse model of lung injury, survival improved with increasing dose only within a limited range, whereas doses above that range reduced survival [18]. Such findings suggest that higher doses may impair rather than

enhance therapeutic signaling, for example, through saturation of uptake or accelerated vesicle degradation [19, 20].

Disease duration also appeared to be a key determinant of treatment responsiveness. Consistent with the established concept that SSNHL is an otologic emergency, early intervention remains critical for optimizing recovery [21, 22], with most studies identifying an optimal treatment window of approximately 3 to 14 days after onset [23]. The present study enrolled patients who had already received corticosteroid therapy for more than 7

days without meaningful improvement and were therefore classified as having refractory SSNHL. Notably, therapeutic responses were still observed in patients with disease durations of up to 22 days. This finding suggests that sEV-based therapy may retain efficacy beyond the traditional treatment window and provides clinical evidence that could help refine the therapeutic boundaries of RSSNHL and define a feasible intervention window for future sEV-based strategies.

The pattern of frequency-specific recovery also merits attention. Improvements occurred most consistently at low-to-mid frequencies, with relatively limited gains at high frequencies. This distribution is physiologically plausible. The basal turn of the cochlea, responsible for high-frequency perception, is highly vulnerable to ischemic, metabolic, and oxidative stress and is therefore more prone to irreversible hair cell and neuronal loss [24–26]. In contrast, the apical and middle turns, which encode low-to-mid frequencies, often retain greater structural integrity even after substantial cochlear insult. A similar recovery pattern is commonly observed with intratympanic dexamethasone, where improvements typically occur at speech-relevant frequencies rather than the high-frequency range [27].

In addition to hearing improvement, two patients who presented with concurrent vertigo reported noticeable symptom relief following treatment. These improvements may reflect the broader neuromodulatory effects of hucMSC-sEVs on the inner ear microenvironment [28, 29]. Although exploratory, these observations raise the possibility that sEV-based therapy may provide functional benefits beyond auditory threshold restoration.

This study has several limitations. First, as an open-label, single-arm Phase 1 trial, it was primarily designed to evaluate safety and tolerability rather than efficacy. Therefore, any observed hearing improvement should be interpreted cautiously. Second, the sample size was small, particularly within each dose group, which limits the reliability of between-group comparisons. Third, the follow-up period was limited to 8 weeks, which is sufficient for preliminary safety assessment but not for evaluating the long-term durability of hearing recovery. Future controlled studies with larger sample sizes and longer follow-up are needed to further assess efficacy and optimize dosing. Nevertheless, the favorable safety profile and time-dependent response patterns provide a strong rationale for advancement to controlled clinical trials. Future studies should refine optimal dosing, characterize pharmacokinetics and biodistribution in the human inner ear, and explore biomarkers that may predict treatment responsiveness.

Abbreviations

RSSNHL Refractory sudden sensorineural hearing loss

hucMSC-sEVs	Human umbilical cord mesenchymal stem cell-derived small extracellular vesicles
AEs	Adverse events
MSC	Mesenchymal stem cell
sEVs	Small extracellular vesicles
PTA	Pure-tone average
MRI	Magnetic resonance imaging
CTCAE	Common terminology criteria for adverse events
VAS	Visual analogue scale

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13287-026-05136-9>.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Author contributions

FS designed the clinical study, recruited and treated patients; YHW treated patients and collected clinical data; YFZ, MQX, TMZ, SSJ, JQC, and JWB contributed to clinical coordination, patient follow-up, and data acquisition. ANC performed data analysis and contributed to the interpretation of results. HZZ supervised the study, provided overall project guidance, and contributed to data interpretation. FS, YHW, ANC, and HZZ drafted and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to privacy and ethical restrictions, individual patient-level clinical data are not publicly available. De-identified data may be provided after approval by the corresponding author and the relevant ethics committee, where applicable.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The project entitled “Intratympanic Injection of Human Umbilical Cord Mesenchymal Stem Cell Derived Small Extracellular Vesicles for Refractory Sudden Sensorineural Hearing Loss” was reviewed and approved by the Medical Ethics Committee of the Pearl River Hospital of Southern Medical University (Approval No. 2025-KY-065-01; approved 21 March 2025). Written informed consent was obtained from all participating patients (or their legally authorized representatives) for trial enrollment and use of their clinical data and samples. HucMSC-sEVs used in this study were provided by Guangdong Qianhui Biotechnology Co., Ltd. (Guangdong, China). According to the supplier, the human umbilical cord tissues were obtained under approved ethical protocols, and written informed consent was obtained from donors.

Consent for publication

The patients included in this study provided written informed consent for the publication of anonymized data in a scientific journal. No identifiable personal information is disclosed in this manuscript.

Competing interests

The authors declare no competing interests.

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