*The Laryngoscope*


# Round Window Membrane Vibration May Increase the Effect of Intratympanic Dexamethasone Injection

Soon Hyung Park, MD; In Seok Moon, MD, PhD

**Objectives/Hypothesis:** We investigated whether the round window membrane (RWM) vibration can facilitate dexamethasone perfusion via the RWM in patients with sudden hearing loss.

**Study Design:** Prospective study.

**Methods:** We first performed an in vitro study using a semipermeable membrane. In the subsequent in vivo study, 20 mice were randomized into two groups: an intratympanic dexamethasone injection (ITDI)-only group, and an ITDI with RWM vibration group. Concentration of dexamethasone was investigated using high performance liquid chromatography. Third, we performed a prospective clinical study. Fifty-five refractory sudden hearing loss patients were divided into two groups: those who received ITDI only (n = 36) and those who received ITDI with RWM vibration (n = 19). Final hearing assessments were conducted 2 months after salvage treatment.

**Results:** In the in vitro study, the concentration of dexamethasone increased with vibration time with the peak concentration observed at 3 minutes of vibration. In the in vivo study, ITDI with RWM vibration resulted in a significantly higher perilymph concentration of dexamethasone (7.68 ± 3.13 μg/ml) than that in the ITDI-only group (2.66 ± 1.73 μg/ml). In a clinical setting, the overall improvement in hearing was similar between the two groups. However, when we compared the speech discrimination score between the two groups, we found that the relative discrimination gain in the ITDI with RWM vibration group (18.11 ± 23.54%) was higher than that in the ITDI-only group (7.00 ± 15.54%) ($P = 0.042$).

**Conclusion:** RWM vibration can enhance the effect of intratympanic dexamethasone injection and is a viable treatment option for sudden hearing loss.

**Levels of Evidence:** N/A.

**Key Words:** Round window, intratympanic, vibration, sound, sudden hearing loss.

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## INTRODUCTION

Sudden hearing loss (SHL) is considered a syndrome and not a diagnosis.[1] There is no standard treatment protocol, but the most widely accepted treatment regimen is steroids.[2,3] The mechanism of action of steroids in the inner ear is unclear, but a higher perilymphatic concentration of steroids is associated with greater hearing recovery.[4]

In 1999, Parnes[5] reported that intratympanic injection resulted in higher steroid concentrations in the cochlea than oral or intravenous injection. Intratympanic dexamethasone injection (ITDI) offers the potential for direct delivery of high concentrations of steroid to the inner ear while avoiding systemic effects[5,6]; many studies have confirmed that ITDI provides at least some benefit in patients with refractory sudden hearing loss.[7–9]

To design a minimally invasive, cost-effective method to enhance the effect of intratympanic steroid injection, we hypothesized that vibration of the round window membrane (RWM) could potentially increase the transport of steroid into the inner ear. External sound stimulation can induce ossicular chain movement and generate oval window vibration. The resulting perilymphatic waves then cause the RWM to vibrate (Fig. 1). Based on this hypothesis, we investigated the effects of RWM vibration on the transportation of dexamethasone via the RWM and also evaluated the therapeutic efficacy of ITDI with RWM vibration generated by external sound stimulation on refractory SHL.

## MATERIALS AND METHODS

### *In Vitro Study*

To evaluate the effect of vibration of the RWM on dexamethasone transport and to determine the optimal vibration time, we designed two different sizes of L-shaped acrylic tubes (Acrylchoika Co., Seoul, Republic of Korea). Semipermeable membrane (cellophane, Happyschool, Republic of Korea) was inserted between the tubes and the tubes were connected together (Fig. 2A). Semipermeable has characteristic that allows certain molecules or ions to pass through it by diffusion. Dexamethasone solution at 10 mg/mL was created by mixing dexamethasone

Additional Supporting Information may be found in the online version of this article.

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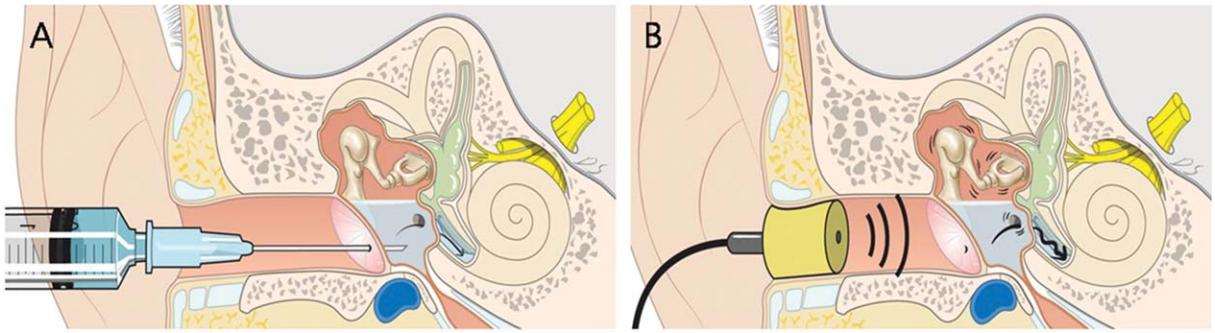


Fig. 1. After intratympanic dexamethasone injection (A), round wind vibration was generated using 90 dB of sound stimulation (B). We hypothesized that stapes vibration induced by sound stimulation may increase round window membrane permeability and increase the dexamethasone concentration in the cochlear perilymph.

21-phosphate disodium salt (100 mg; Sigma–Aldrich, Steinheim, Germany) with 0.9% NaCl. Artificial perilymph containing (in mM) 150 NaCl, 3.6 KCl, 1 $MgCl_2$, 0.7 $CaCl_2$, 5 glucose, and 10 HEPES at pH 7.4 was prepared. We put 1.5 ml of dexamethasone solution in the smaller diameter tube and 3.5 ml of artificial perilymph in the other tube (Fig. 2A). We used a vibrating razor (Proglide, Gillette, China) as the vibrator (Fig. 2B). It has 95Hz–105Hz frequency and less than 0.7 mm amplitude (patent number: WO2013002925 A2).The vibrator was contacted to the tube at the side of the artificial perilymph for 0, 1, 2, 3, 5, and 10 minutes. Thirty minutes after fluid administration, 200 $\mu$l of artificial perilymph was sampled from the bottom of the tube using a micropipette. The concentration of dexamethasone in perilymph samples was determined immediately in the laboratory using high performance liquid chromatography (HPLC). These experiments were repeated in triplicate for each vibration time, and the mean concentration was evaluated.

### *In Vivo Study*

We used 6-week-old, male ICR mice (supplied by Orient-Bio, Gapyeong, Korea) weighing approximately 29∼36 g. Twenty mice were randomized into two groups: an ITDI-only group (n = 10), and an ITDI with RWM vibration group (n = 10). All animal experiments were approved by the Institutional Animal Care and Use Committee of Yonsei University Health System (No. 2013-0026).

Animals were anaesthetized by intraperitoneal injection of xylazine hydrochloride (23.32 mg, Rompun; Bayer Korea LTD, Ansan, Republic of Korea, 10 mg/kg) and tiletamine/zolazepam (125 mg/125 mg, Zoletil 50; Carros, France, 30 mg/kg).

Dexamethasone solution at 40 mg/mL was created by mixing dexamethasone 21-phosphate disodium salt (100 mg; Sigma–Aldrich) with 0.9% NaCl. All mice received 10 μl of dexamethasone solution in the anteroinferior quadrant of the left tympanic membrane using a finely crafted glass capillary tube (connected via a sterile scalp vein set to a 1-mL syringe) (Fig. 3A–C). After dexamethasone administration, mice in the RWM vibration group were exposed to 90 dB SPL noise for 3 minutes using a sound box with a high frequency reproducer (Electro-Voice, Buchanan, MI) (Fig. 4A). Mice in both groups were laid in the right decubitus position in quiet conditions for 30 minutes after the ITDI; the duration and position that the mice were placed in were based on previous reports.[7–9] Then mice were sacrificed, and the surgical procedure described below was performed.

A postauricular incision was made and the bulla was exposed and opened under sterile conditions. The round window located in the superior portion of the stapedial artery was easy to find (Fig. 3D). The middle ear cavity was washed with sterile water three times. To evaluate the accuracy of perilymph sampling, verapamil solution at 10 $\mu$g/mL was created by mixing verapamil hydrochloride (1g; Sigma-Aldrich) with artificial perilymph. Ten microliters of verapamil solution was preloaded into a microcathetertip (20 $\mu$l, Eppendorf, Germany) before perilymph sampling. One microliter of perilymph was sampled through the round window using the prepared microcatheter tip with verapamil solution connected to a micropipette (Fig. 3D).The concentration of dexamethasone in the perilymph samples was analyzed immediately in the laboratory using HPLC. The concentration of verapamil was also analyzed to evaluate technical consistency.

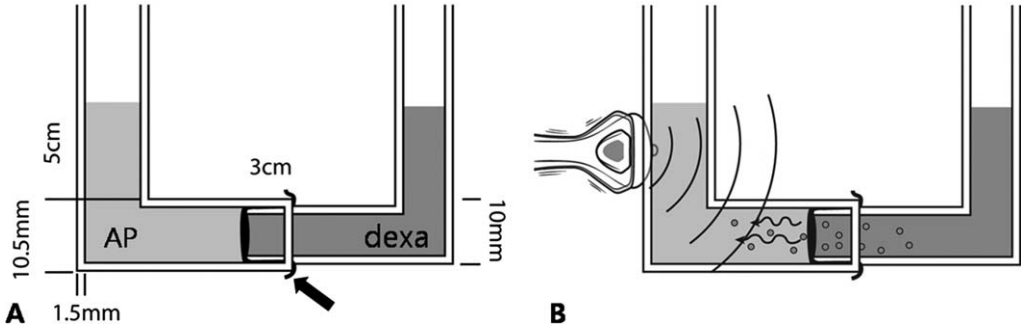


Fig. 2. Size and shape of the acrylic tube. Semipermeable membrane was inserted between the tubes (arrow). Dexamethasone solution (DEXA) and artificial perilymph (AP) were administrated each side of the tube (A). Vibration was applied at the side of the artificial perilymph (B).

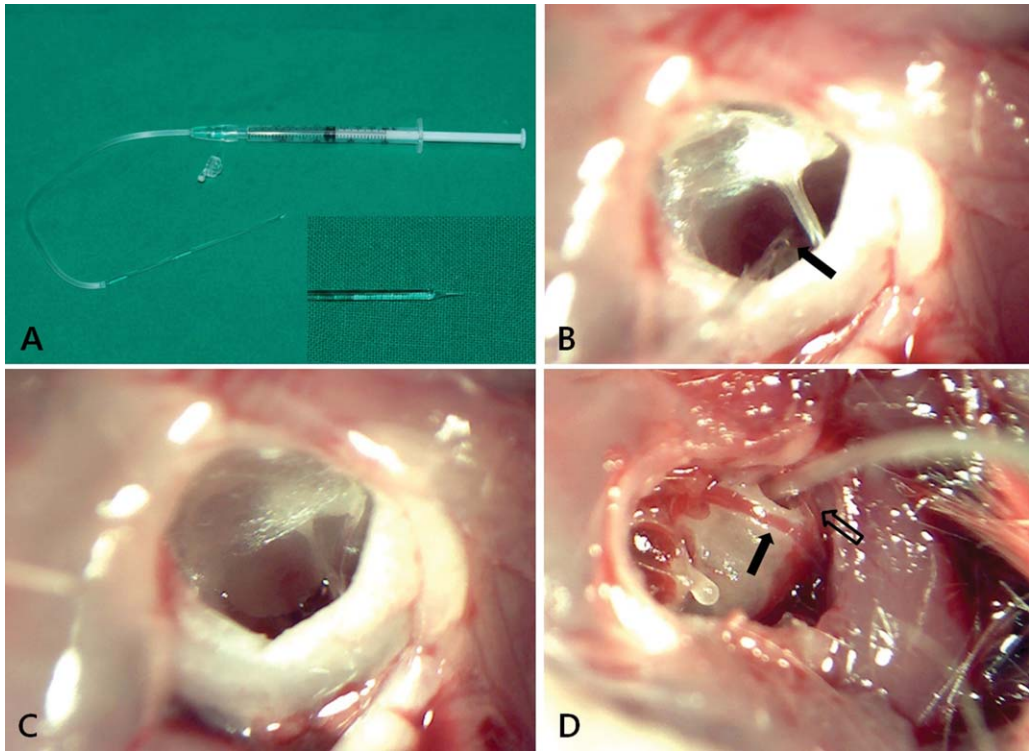


Fig. 3. To perform intratympanic injection, a finely crafted glass capillary tube connected via scalp vein set to a 1-ml syringe was prepared (A). A puncture was made at the anteroinferior quadrant of the mouse tympanic membrane using the glass capillary tube (arrow) (B). After the injection, the middle ear filled with dexamethasone and bulging of the tympanic membrane was identified (C). The round window (box arrow) was noted just above the stapedial artery (arrow). A microcatheter tip was inserted through the round window membrane and perilymph sampling was performed (D).

### *High Performance Liquid Chromatography*

Dexamethasone standards were prepared by diluting the stock drug solution (1,000 g/mL in 50% methanol). A comparator curve was calculated by diluting the dexamethasone stock solution in artificial perilymph to final concentrations of 0.5, 1, 5, 10, and 100 $\mu$g/mL dexamethasone. Dexamethasone concentrations were measured by high performance liquid chromatography (HPLC, Agilent 1100 series, Agilent Technologies, Santa Clara, CA) (Fig. 4B). Perilymph samples were washed twice with 20$\mu$L artificial perilymph and then put in a tube with a

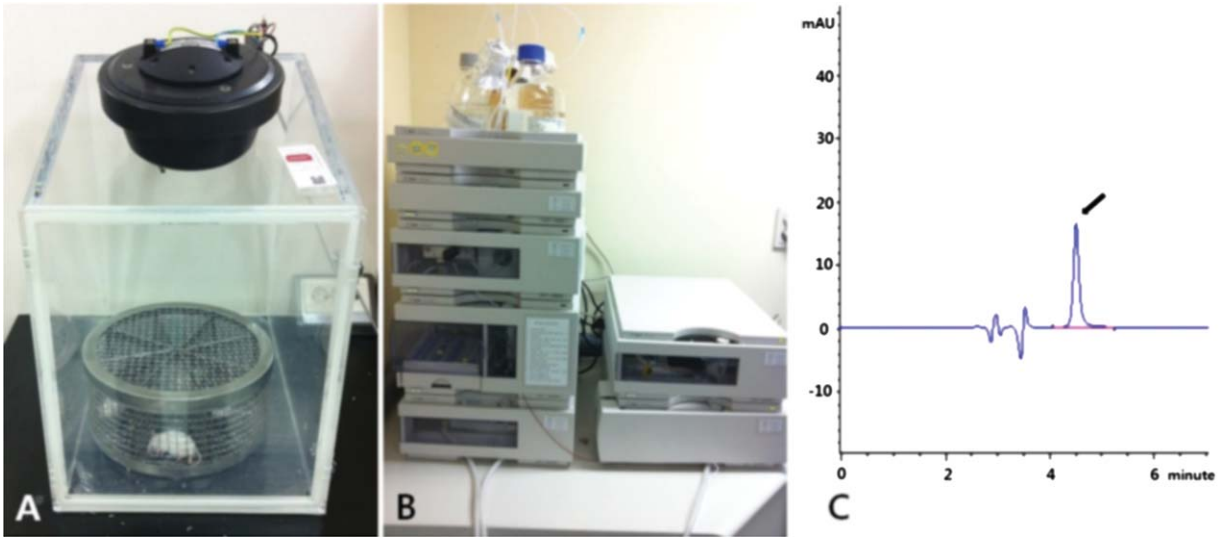


Fig. 4. 90 dBL SPL of noise was applied to mice using a sound box with a high frequency reproducer (A). High performance liquid chromatography (Agilent Technologies, Santa Clara, CA) (B) was used to measure the concentration of dexamethasone. Chromatography revealed the peak concentration of dexamethasone in the cochlear perilymph of mice (arrow, C).

cap. The mixture was vortexed followed by centrifugation at 13,000 rpm for 5 minutes. A 10-$\mu$L aliquot was injected to HPLC for analysis.

The mobile phase was 50 mM ammonium formate: acetonitrile: formic acid (70:30: 0.05, v/ v/v) at a flow rate of 1.0 mL/minute, and the detection wavelength was 245 nm. Separation was performed on a Hypersil Gold C18 column (4.6 $\times$ 250 mm, internal diameter 5 $\mu$m, ThermoFisher Scientific, Waltham, MA) at 30°C. Using this technique, the peak concentration of perilymphatic dexamethasone was detected by chromatography (Fig. 4C).

### *Clinical Study*

From January to December 2012, 159 SHL patients presented to our hospital within 7 days of disease onset. Histories, physical examination, pure-tone audiometry, speech audiometry, and impedance audiometry were conducted for each patient. Auditory brainstem response latency and temporal magnetic resonance imaging were selectively performed to rule out retrocochlear pathologic findings. Mean hearing thresholds were expressed as the average of the 0.5-, 1.0-, 2.0-, and 3.0-kHz hearing thresholds (4-tone average). All patients were initially treated identically. Approximately 1 mg/kg of prednisolone (5 mg/tablet, Solondo; Yuhan Corp., Seoul, Republic of Korea) was administered orally for 5 days and then tapered, and patients received 750 mg of acyclovir intravenously (250 mg/vial, Zovirax; Dong- Ah Pharmaceutical, Seoul, Republic of Korea). Furthermore, 500 ml of volume expander (500 ml/bag, Voluven, Fresenius Kabi, Germany) was infused for 5 days. Of the treated patients, 67 had no therapeutic response after more than 2 weeks of treatment. Patients who demonstrated no improvement (< 10 dB change) 2 weeks after treatment was initiated (within 3 weeks from disease onset) were defined as refractory to initial treatment. With approval from the institutional review board of Yonsei University Medical Center (No. 4–2012-0531), the 55 patients who agreed to participate in this study were enrolled consecutively.

Patients refractory to initial treatment received ITDI. We have demonstrated the effectiveness of ITDI as a salvage treatment in previous studies, and we used the same schedule and protocol for ITDI salvage treatment as described in our previous studies.[8,9] Two weeks after initiating treatment, audiologic evaluation was performed. Patients who showed no improvement (< 10 dB change) were enrolled in this study and underwent ITDI injection with or without round window membrane vibration. The final hearing result was evaluated after at least 2 months of salvage treatment.

We divided patients into two groups: those who received ITDI only (n = 36) and those who received ITDI with RWM vibration (n = 19). Patients who were admitted between May 2012 and October 2012 were treated by ITDI only. Patients who were admitted between January to April and November to December underwent ITDI with RWM vibration as a salvage therapy. Salvage treatment was initiated 2 weeks from the starting day of initial treatment (within 3 weeks of disease onset), and patients received ITDI every other day for a total of five treatments. Local anesthesia was administered to patients in the supine position. They were instructed to avoid swallowing during injection and to tilt their head 30 to 40 degrees to the healthy side so that the round window membrane would be bathed for 30 minutes. Tympanic puncture was performed under microscopy with a 24-gauge spinal needle at the junction between the posteroinferior and posterosuperior quadrants; undiluted dexamethasone (5 mg/ml, Dexa-S; Il-Sung Pharmaceutical, Seoul, Republic of Korea) was injected. The volume of liquid injected ranged from 0.4 to 0.5 ml. After injection, patients were observed for 30 minutes after positioning, as described in previous reports.[7–9] In the RWM vibration group, after the same procedure was followed as described above, 90 dB HL external click sound stimulation was applied for 3 minutes using an auditory brainstem response device (Navigator Pro, Bio-logic, San Carlos, CA) (Supplement 1).

The final hearing result was defined as the last measured hearing result after at least 2 months of salvage treatment. Hearing improvement were defined based on Siegel's criteria (Table I).[10] We also compared the relative hearing gain (RHG; hearing difference between presalvage and final pure-tone threshold)[9] and relative discrimination gain (RDG; discrimination difference between presalvage and final speech discrimination score) between the two groups. RHG was also analyzed according to frequency.

### *Statistics*

Significant differences between groups were determined using power analysis, Fisher's exact test, the independent $t$ test, or the paired $t$ test with $P < 0.05$ defined as the cutoff value for statistical significance. Statistical analyses were performed using SPSS v16.0 (SPSS Inc., Chicago, IL).

## RESULTS

### *In Vitro Study*

Chromatography measurements were used to determine the peak concentration of dexamethasone in artificial perilymph. Mean dexamethasone concentration of artificial perilymph increased gradually according to vibration time and reached a peak concentration after 3 minutes of vibration (Fig. 5). Paradoxically, after stimulation for more than 5 minutes, the concentration of dexamethasone decreased slightly. Based on these results, we considered 3 minutes to be the optimal time of vibration and used this time span in following experiments.

### *In Vivo Animal Study*

The dexamethasone concentration in cochlear perilymph samples from 20 mice was determined using HPLC. The dexamethasone concentrations are shown in

TABLE I.
Siegel's Criteria (1985).

| Type | Hearing Recovery |
|---|---|
| I. Complete recovery | Patients whose final hearing level was better than 25dB, regardless of the size of gain |
| II. Partial Recovery | Patients who showed more than 15dB of gain and whose final hearing level was between 25 and 45dB |
| III. Slight Recovery | Patients who showed more than 15dB of gain and whose final hearing level was poorer than 45dB |
| IV. No Improvement | Patients who showed less than 15dB of gain or whose final hearing level was poorer than 75dB |

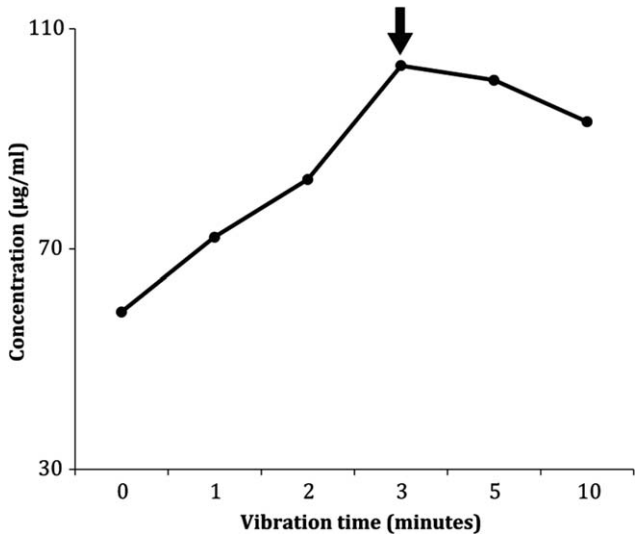


Fig. 5. Dexamethasone concentration according to vibration time. Three minutes of vibration resulted in the peak concentration of dexamethasone (arrow).

Table II. We could not detect dexamethasone in two samples (#5 and #16). We considered this to be due to technical error and excluded these results from the analyses. Mean dexamethasone concentration was $2.66 \pm 1.73$ $\mu$g/mL in the ITDI-only group and $7.68 \pm 30.13$ $\mu$g/mL in the ITDI with RWM vibration group. Dexamethasone concentration in the RWM vibration group was almost three times higher than that in the ITDI-only group, and this difference was statistically significant ($P < 0.001$). The concentration of verapamil was similar in all mice ($811.5 \pm 8$ $\mu$l/ml).

### *Clinical Study*

The 55 refractory patients were divided into two groups: those who received ITDI-only therapy (n = 36) and those who received ITDI therapy with RWM vibration (n = 19). There were no significant differences in age, sex, general condition, follow-up period, initial hearing threshold of the affected ear, or the presalvage hearing threshold between the two groups (Table III).

According to Siegel's criteria, the overall rate of pure tone improvement in the ITDI with RWM vibration group was 57.9% (11/19). This was not different from the improvement rate seen in the ITDI-only group, which was 38.9% (14/36) (Table IV). When patients who had "favorable" recovery were considered (Type I and II patients according to Siegel's criteria), no significant differences were observed between the ITDI with RWM vibration group (31.6%, 6/19) and the ITDI-only group (16.7%, 6/36).The RHG in the ITDI with RWM vibration group was $18.76 \pm 19.44$ dB HL (hearing level); this was not significantly different from the RHG of the ITDI-only group ($12.97 \pm 20.65$ dB HL). However, when we examined the speech discrimination score, we found that the ITDI with RWM vibration group had a significantly higher RDG ($18.11 \pm 23.54\%$) than the ITDI-only group ($7.00 \pm 15.54\%$) ($P = 0.042$; Table IV).

We also analyzed RHG according to frequency. The RHG according to frequencies is shown in Figure 6. High frequency hearing was significantly improved in the ITDI with RWM vibration group based on a paired *t* test. Compared between two groups, RHG at frequencies of 0.25, 0.5, 1.0, 2.0, and 3.0 kHz was not significantly different ($P > 0.05$), but the hearing change at 4.0 and 8.0 kHz was significantly different between the two groups ($P = 0.036$ & $P = 0.048$, respectively) (Fig. 6).

## DISCUSSION

The round window membrane is a three-layered structure that consists of an outer epithelium, a core of connective tissue, and an inner epithelium.[11,12] This membrane is in contact with the perilymph and functions to release mechanical energy.[13] It could also

TABLE II.
Dexamethasone Concentrations in Mice Cochlear Perilymph (in vivo study).

| | IDTI Only (n = 10) | | | ITDI With RWM Vibration (n = 10) | |
|---|---|---|---|---|---|
| Number | Conc. ($\mu$g/mL) | BW (g) | Number | Conc. ($\mu$g/mL) | BW (g) |
| 1 | 3.3 | 35 | 11 | 7.6 | 33 |
| 2 | 6.5 | 32 | 12 | 8.4 | 31 |
| 3 | 4 | 36 | 13 | 4.2 | 34 |
| 4 | 1.5 | 33 | 14 | 5.4 | 33 |
| 5 | – | 32 | 15 | 12.3 | 35 |
| 6 | 1.5 | 29 | 16 | – | 30 |
| 7 | 1.2 | 30 | 17 | 5.7 | 30 |
| 8 | 2.5 | 33 | 18 | 5.9 | 29 |
| 9 | 2 | 30 | 19 | 13.2 | 31 |
| 10 | 1.4 | 31 | 20 | 6.5 | 32 |
| Mean (Conc.) | $2.66 \pm 1.73$ | $P < 0.001$* | | $7.68 \pm 3.13$ | |
| Mean (BW) | | $32.1 \pm 2.23$ | $P = 0.816$ * | | $31.8 \pm 1.93$ |

BW = body weight; Conc. = concentration; ITDI = intratympanic dexamethasone injection; RWM = round window membrane.
*Independent *t* test was used.

TABLE III.
General and Hearing Characteristics of the 55 Patients With Refractory Hearing Loss.

| Clinical Characteristics | ITDI Only Group (n = 36) | ITDI With RWM Vibration Group (n = 18) | *P* Value |
|---|---|---|---|
| Age (years) | 55.28 ± 15.98 | 53.68 ± 15.98 | 0.723* |
| Sex (M:F) | 19 : 17 | 9 : 9 | 0.538† |
| Ear (right:left) | 14 : 22 | 8 : 10 | 0.773† |
| Period from onset to visit (days) | 5.11 ± 4.01 | 6.32 ± 4.90 | 0.331* |
| Follow-up period (days) from salvage | 74.86 ± 25.77 | 67.84 ± 17.81 | 0.296* |
| Rates of systemic disease (n) | 18/36 (50.0%) | 9/18 (50.0%) | 1.000‡ |
| Primary hearing threshold (dB HL) | 75.75 ± 25.12 | 73.87 ± 21.52 | 0.605* |
| Presalvage hearing threshold (dB HL) | 72.19 ± 25.40 | 73.20 ± 22.98 | 0.886* |
| Presalvage SDS (%) | 39.92 ± 28.75 | 44.50 ± 32.80 | 0.714* |
| Presalvage hearing loss (moderate:M–S:severe:profound) | 10:12:3:11 | 5:4:5:4 | 0.302‡ |

There was no mild hearing loss.
*Independent *t* test was used.
†Chi square test was used.
‡Fisher's exact test.
ITDI = intratympanic dexamethasone injection; M–S = moderate–severe; RWM = round window membrane; SDS = speech discrimination score.

potentially participate in secretion or absorption. Similarities between the RWM of human and that of other species such as guinea pig, chinchilla, and cat have been documented.[14,15] Animal experiments have shown that the RWM behaves like a semipermeable membrane. Various antibiotics, antiseptics, arachidonic acid metabolites, albumin, toxins, and other compounds applied to the round window niche can enter the inner ear and cause inner ear changes.[11,16]

Anatomic obstructions to the passage of drugs across the round window membrane may be relatively low. Silverstein performed tympanostomy in 41 patients for intratympanic perfusion of medication and found that five patients (12%) had a completely or partially obstructed RWM.[17]Alzamil et al.[18] reported that of 202 temporal bones, 11% of the round window niches contained fibrous tissue or fat. Based on its semipermeable characteristics and high rate of sustained patency, there have been attempts to supply drugs through the RWM, and ITDI has become popular treatment modality for SHL.[4,9,19]

Many efforts have been made to enhance the effect of intratympanic steroid injection, such as mixing the steroid with hyaluronic acid or insulin like growth factor 1 (IGF-1) to enhance steroid absorption.[20–23] However, these approaches are expensive and their safety has not been definitively proven. Other methods such as the Silverstein wick and micro-catheter for sustained release of steroid have also been introduced.[24,25] However, these methods are more invasive than injection, and it is unclear whether sustained release is really more effective than pulse release of the steroid.

We hypothesized that the concentration of steroid inside the cochlea would increase if subthreshold vibrations were applied to the RWM, thereby increasing its permeability without inner ear damage. We think that the mechanism is as follows: First, we think that there is a stirring effect in the cochlear perilymph. Dexamethasone perfusion through the RWM depends of the concentration difference. Because of its stirring effect, if vibration is applied the cochlear perilymphatic dexamethasone is mixed evenly within a short time. This results in a relatively large concentration difference between the cochlear perilymph and intratympanic dexamethasone. As a result, dexamethasone perfusion can be facilitated. Second, vibration may affect active transport of RWM. RWM might also participate in secretion or absorption. The detailed mechanism remains still unknown, but we think that vibration of RWM may facilitate its active transport.

Studies have reported that permeability increases markedly when vibration lasting longer than a minute

TABLE IV.
Final Hearing Results After Salvage Treatment With Additional Analysis Based on Siegel's Criteria.

| Sigel's Type | ITDI Only (n = 36) | ITDI With RWM Vibration (n = 19) | *P* Value |
|---|---|---|---|
| I & II | 6 | 6 | 0.303* |
| I & II &III | 14 | 11 | 0.256† |
| Relative hearing gain (dB) | 12.97 ± 20.65 | 18.76 ± 19.44 | 0.318‡ |
| Relative discrimination gain (%) | 7.00 ± 15.54 | 18.11 ± 23.54 | 0.042‡ |

ITDI = intratympanic dexamethasone injection; RWM = round window membrane.
*Comparison of the rates of "favorable" recovery between groups. Fisher's exact test was used.
†Comparison of the rates of "any" recovery between groups. Fisher's exact test was used.
‡Independent *t* test was used.

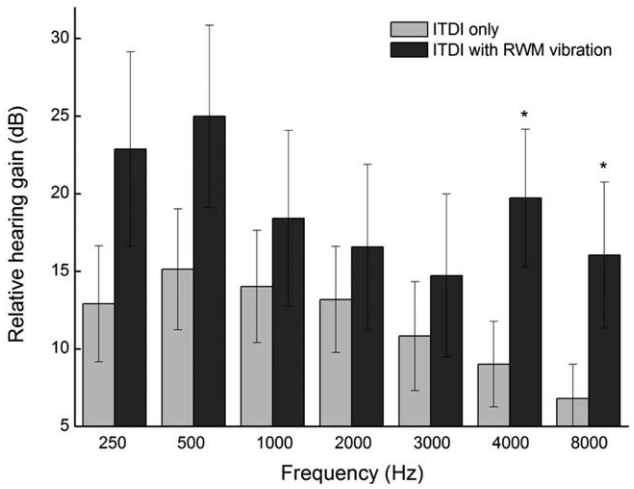


Fig. 6. Relative hearing gain according to frequency. The hearing gain at high frequencies (4000 Hz, 8000 Hz) was significantly higher in the intratympanic dexamethasone injection (ITDI) with round window membrane (RWM) vibration group than the ITDI group ($P = 0.036$ & $P = 0.048$).

occurs; thus, we investigated the effects of weak vibrations applied for longer than a minute.[26] Because RWM has much complicated structure and function, our in vitro study using semipermeable membrane cannot totally reflect the characteristics of RWM. However, we tried to investigate that vibration affects the permeability of the membrane. Furthermore, based on our study we tried to estimate optimal vibration time. We then found that 3 minutes was the shortest time required to markedly increase permeability. This pilot study helped us to minimize the number of mice sacrifice.

We used dexamethasone as the steroid because this is the steroid most widely used in a clinical setting for SHL treatment, and because it can most feasibly permeate through the RWM due to its liquid characteristics. As mentioned earlier, the concentration of dexamethasone in the inner ear was three times higher in animal experiments. But in a clinical setting, patients showed only slight improvement.

There are several reasons why we may have observed this difference between the animal experiments and those obtained in a clinical setting. First, because we examined refractory patients and some of them may have totally lost their potential to recover from hair cell damage, the steroid might have had no effect in some patients. Second, ITDI would have been a useless procedure in those patients for whom the RWM was not patent. Third, we used a relatively low concentration of dexamethasone (5 mg/ml) in the clinical study. However, the concentration of 5 mg/ml is standard in clinical practice because this has been proven to not adversely affect patients. Although RWM vibration is expected to increase the perilymphatic dexamethasone concentration in humans, this was not sufficient to make a significant difference in the hearing outcome according to Siegel's criteria. We examined 55 patients in this study who were refractory to the initial treatment. Taking the above reasoning into account, the roughly 60% recovery rate seen in the ITDI with RWM vibration group may indicate that almost every patient who has potential to recover responded to the treatment. To confirm the efficacy of this treatment, more data must be gathered, and changes in hearing should be evaluated in response not only to salvage treatment but also initial treatment.

The sound stimulation group showed a marked improvement in speech discrimination and a noticeable decrease in the pure tone threshold for high frequencies compared to the ITDI-only group. We attributed this to the anatomic closeness of the RWM to the basal turn that controls high frequency. The fact that high frequencies show a close relationship to speech discrimination may indicate an influence on the speech discrimination score improvement. Both the released mediator effect and the direct contact effect of a high concentration of steroid likely contributed to these results.

Our results indicate that when treating patients with refractory hearing loss with ITDI, vibration can increase absorption of steroid in the inner ear—and RWM vibration can be easily obtained. Therefore, we propose that music should be played in the procedure room after the injection as a cost-effective and noninvasive method to enhance the effects of ITDI.

## CONCLUSION

Experimental group receiving ITDI with RWM vibration treatment had a higher concentration of cochlear steroid, and patients who received ITDI with RWM vibration showed better hearing recovery than patients treated with ITDI only. Further studies evaluating sound intensity, frequency, and stimulation techniques for effective RWM vibration are required. Our results indicate that sound stimulation alone is an easy, noninvasive, and safe tool that may enhance the effectiveness of intratympanic steroid therapy.

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