A new method for restoration of sensorineural hearing loss: a prospective clinical study

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Summary

Background
Sensorineural hearing loss, one of the most common diseases, has historically been regarded as an incurable and irreversible condition. The number of people with hearing loss has grown rapidly in recent years, because of the prevalence of environmental noise and the increase in the elderly population. Although hearing aids are provided as an alternative device to help hearing impaired people, no fundamental treatment is currently available. Several studies have shown that noise-induced hearing loss can be prevented by prior exposure to low-levels of acoustic stimuli, a procedure known as sound conditioning. However, to our knowledge, this is the first clinical study to evaluate the effects of sound conditioning on hearing restoration.

Methods
Nine patients with high-tone hearing loss were subjected to modified sound conditioning for 2 weeks. In all, 63 samples (i.e., frequency regions) were obtained from the patients. Acoustic stimuli consisted of frequency-modulated tone and amplitude-modulated narrow band noise. Behavioral hearing thresholds were compared before and after treatment to investigate the effects of modified sound conditioning.

Findings
Our findings demonstrate that modified sound conditioning improves hearing ability. On average, the behavioral hearing threshold decreased by 8.91 dB (i.e., approximately 15%) after sound conditioning for 2 weeks, followed by a 2 week break (p = 0.001, Wilcoxon’s signed-rank test with Bonferroni’s correction). Twelve of the 63 samples exhibited hearing improvements in excess of 15 dB, whereas 27 samples showed hearing improvements of 5 to 15 dB.

Interpretation
Modified sound conditioning may improve the hearing abilities of patients with sensorineural hearing loss.

Funding
Earlogic Korea Inc.

Introduction
Hearing loss is defined as a decrease in the ability to detect sound. There are three fundamental types of hearing loss, defined with respect to the part of the auditory system affected. These are conductive hearing loss, sensorineural hearing loss, and mixed hearing loss. Sensorineural hearing loss occurs when the inner ear (the cochlea) or the auditory nervous system is damaged. Such damage can result from a wide range of environmental and biological factors, including noise exposure, ototoxic drugs (i.e., drugs that are toxic to the auditory system), and aging. Hearing loss can also be classified by severity into mild, moderate, moderate-severe, severe, and profound hearing loss.
Hearing loss is now one of the most common diseases of man. More than 278 million people suffered from moderate to profound hearing loss in 2005, according to global estimates by the World Health Organization (WHO). In Europe, more than 15% of adults suffer from hearing disorders, including mild hearing loss. Despite numerous efforts to prevent noise exposure, the number of people with noise-induced hearing loss has grown rapidly in recent years because of the overuse of audio equipment and excessive exposure to loud noise in the workplace. In addition, the growing numbers of elderly people has resulted in a rapid increase in the prevalence of age-related hearing loss. Since there is no medical and surgical treatment for sensorineural hearing loss, most people with mild to moderate hearing loss are left without any treatment and typically suffer a reduction in quality of life. Hearing loss is also quite costly, as the annual cost of untreated hearing loss in the UK is estimated to exceed £13.5 billion, because of lost productivity. Over the past 20 years, a number of pharmacological interventions have been tried to prevent hearing loss or restore hearing ability. Although a small number of drugs with antioxidant activities were shown to prevent noise-induced hearing loss, no fundamental therapies have been clinically available. In the late 1990s, researchers discovered that acoustic stimuli slow progressive sensorineural hearing loss and exposure to a moderately augmented acoustic environment can delay the loss of auditory function. In addition, prolonged exposure to an augmented acoustic environment could improve age-related auditory changes. These ameliorative effects were shown in several types of mouse strains, as long as the acoustic environment was provided prior to the occurrence of severe hearing loss. In addition to delaying progressive hearing loss, acoustic stimuli could also protect hearing ability against damage by traumatic noise. In particular, a method called forward sound conditioning (i.e., prior exposure to moderate levels of sound) has been shown to reduce noise-induced hearing impairment in a number of mammalian species, including humans. Interestingly, recent report has suggested that low-level sound conditioning also reduces free radical-induced damage to hair cells, increases antioxidant enzyme activity, and reduces Cox-2 expression in cochlea and can, over a longer period of time, enhance cochlear sensitivity. Specifically, increased cochlear sensitivity was observed when distortion product otoacoustic emissions (DPOAEs) and compound action potentials (CAPs) were measured. In addition to forward sound conditioning, backward sound conditioning (i.e., the use of acoustic stimuli after exposure to a traumatic noise) has been shown to protect hearing ability against acoustic trauma and to prevent the cortical map reorganization induced by traumatic noise. Given the protective effects of sound conditioning, particularly with regards to enhanced cochlear sensitivity, we hypothesized that sound conditioning could restore hearing loss. To investigate this possibility, we applied modified sound conditioning to patients with sensorineural hearing loss. The results of our study showed that acoustic stimuli can indeed improve hearing ability. These findings will pave the way for more effective treatments of sensorineural hearing loss, particularly now when most patients with mild hearing loss are left behind treatment and demands for effective methods to cure hearing loss are urgent.

Materials and Methods

The study protocol was approved by the Institutional Review Board of Samsung Medical Center. The study was conducted from November 2007 to March 2008.

Subjects

Patients with high-frequency hearing loss [i.e., above 1 kHz, as measured by conventional pure-tone audiometry (PTA)] and speech discrimination scores (SDS) above 70% were selected for participation in this study. Patients ranged in age from 20 years to 60 years and had access to e-mail.

Subjects were excluded if their hearing thresholds exceeded 70 dB HL at frequencies of 1, 2, 4, or 8 kHz, or if their speech recognition thresholds (SRT) differed from measured PTA thresholds by more than 10 dB. In addition, subjects were excluded if their SDS scores were below 70% (i.e., indicative of neuropathy), if acoustic tumors were confirmed by imaging analysis, or if they were shown to have middle ear diseases involving perforated tympanic membranes or effusion with no documented conductive hearing loss.

Materials
1. Pure tone audiometer for baseline measurement
Initial audiometric evaluations measured pure-tone air and bone conduction, as well as speech audiometry (SA), using a GSI 61 clinical audiometer (Grason-Stadler Inc., NH, USA). Patients with high tone sensorineural hearing loss were selected for the study if their speech discrimination scores exceeded 70%.

2. Micro-audiometric evaluation: AMA-PTA
Subjects were assessed using Automated Micro Audiometer-Pure Tone Audiometry, AMA-PTA (Earlogic Corp., CA, USA). AMA-PTA is a computer-controlled audiometer that carries out automated air and bone conduction tests with effective masking noise. AMA-PTA can perform air conduction audiometry at 6 frequencies in 2 minutes, and at 11 frequencies in 3 minutes. In addition, the audiometer performs “fine audiometry” over 1/3 octave (i.e., 17 frequencies) to 1/24 octave (i.e., 134 frequencies) band options, thereby reflecting the general structure of the cochlear filter as a function of frequency. Data from the AMA-PTA were analyzed to obtain targeted frequency bands.

3. Stimulus sounds
Stimulus sounds for conditioning were produced using the AMA-PTA Sound Generator (Version 5.2) and Sound Forge software (Version 8.0). Stimulus sounds included mixed sounds of frequency-modulated pure tones and amplitude-modulated narrow band noises. FM and AM sounds were modulated at frequencies of 0.125 to 8 Hz and 7 to 11 Hz, respectively. Since the levels of applied sounds were approximately 5 to 15 dB SL (i.e., ≤ 75 dB HL), sounds in these ranges are not acoustically harmful to humans.

Methods

1. Plan of test
Basic pure tone audiograms were analyzed to determine which octave bands to use in subsequent AMA-PTA tests (figure 1). After determining the test frequency range, AMA-PTA measurements with 1/24 octave band resolution were conducted three times (figure 2). Next, we determined the target frequency band for sound conditioning, ensuring that the range did not exceed the critical band of 1/3 octave (figure 3). A relevant sound conditioning wave file for each patient was selected from the sound file list (table 1) and e-mailed to the patient or a family member. The patient received the sound file, listened to the sound for 40 minutes twice per day (once in the morning and once in the evening) for 2 weeks, using the ear with poorer hearing ability. In cases where both ears had the same hearing thresholds, the right ear was selected for sound conditioning. Patients were allowed to use a personal computer, CD player, or MP3 player, as a listening apparatus. However, sound volume was categorized into the following levels, based on the subject’s feedback: (1) very quiet, (2) quiet, (3) regular, (4) loud, and (5) very loud, and all patients listened to the conditioning sound at level 1. The second hearing threshold measurement (i.e., 1/24 octave band AMA-PTA on the previous frequency range) was conducted three times after the initial 2 weeks of sound conditioning. After completing the second hearing measurement, each patient took a 2 week break. The third AMA-PTA test was conducted after the break to evaluate the durability of improved hearing ability. The overall procedure used in this study is summarized in figure 4.

2. Statistics
Thirteen patients were selected for participation in this study after we adopted a significance level of 0.05 and a statistical power of 0.8. The standard deviation was set at 7.1, and Wilcoxon’s signed-rank test with Bonferroni’s correction was used to assess differences in hearing thresholds.

Role of the funding source
The study sponsors had no role in the study design, data collection, analysis, interpretation, or dissemination, or in the decision to submit this paper for publication. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results
Of the 13 patients who agreed to participate in this study, 4 patients did not conform to the study protocol or failed to meet eligibility requirements. Therefore, data were analyzed from the remaining nine patients. Behavioral hearing thresholds for each
Patient were obtained at seven frequency regions. It is important to note that hearing thresholds obtained at each frequency were analyzed as individual results, because of the frequency specificity of the auditory system. For that reason, each frequency region was considered to be a single sample. To rule out the possibility of bias arising from test-retest variation, we repeated the behavioral hearing test (i.e., pure-tone audiometry) three times for each sample and adopted the average value as a hearing threshold of the corresponding sample. As a result, 63 hearing thresholds (i.e., 7 frequency regions × 9 patients) were obtained in every session.

To examine overall changes in hearing abilities as a result of modified sound conditioning, we calculated the grand average of the 63 hearing thresholds for each session and compared the grand averages before and after sound conditioning (Figure 5). The grand average before modified sound conditioning was 59.80 dB HL, and this value decreased to 50.89 dB HL after patients underwent 2 weeks of modified sound conditioning followed by a 2 week break. Thus, 8.91 dB of significant improvement in hearing ability was achieved (p = 0.001, Wilcoxon’s signed rank test with Bonferroni’s correction). In addition, a comparison of the grand averages from post-1 (i.e., after performing modified sound conditioning) and post-2 (i.e., 2 weeks after modified sound conditioning is stopped) sessions revealed that improvements in hearing ability could be maintained for at least 2 weeks after the conclusion of sound conditioning (p = 1.000, Wilcoxon’s signed rank test with Bonferroni’s correction).

To investigate the distribution of hearing improvement, we calculated the magnitude of improvement in each sample by subtracting the post-2 average from the pre-treatment average, and grouped the results by the extent of improvement (Table 2). The results showed that 2 weeks of modified sound conditioning improved hearing ability in 52 of 63 samples. Among the 52 samples, 39 exhibited more than 5 dB of improvement. Surprisingly, 12 samples achieved improvements of greater than 15 dB.

To examine intra-patient improvement in hearing ability, we compared the pre-treatment patient average with the post-2 patient average (Table 3), where ‘patient average’ refers to the average hearing thresholds of seven samples of the corresponding patient. Significant improvements in hearing ability were observed in 7 of the 9 patients (i.e., patients A through F and H). Among the seven patients, one (i.e., patient B) exhibited more than 40 dB of hearing improvement.

Although we obtained averages of three repeated tests and used these values as representative hearing thresholds, we still could not rule out the possibility of bias resulting from test-retest variations. Therefore, we reanalyzed the effects of modified sound conditioning after excluding samples that displayed more than 10 dB of test-retest variability (i.e., standard deviation) in any session. Consistent with our previous findings, these results also suggested that modified sound conditioning improves hearing ability (Figure 6). The grand average before modified sound conditioning was 60.80 dB HL, and this value decreased to 54.13 dB HL after sound conditioning. Thus, 6.67 dB of significant improvement in hearing ability was achieved (p = 0.001, Wilcoxon’s signed rank test with Bonferroni’s correction) after undergoing 2 weeks of modified sound conditioning followed by a 2 week break. Comparison of post-1 and post-2 grand averages confirmed that improvements in hearing ability could be maintained for at least 2 weeks after the conclusion of sound conditioning (p = 1.000, Wilcoxon’s signed rank test with Bonferroni’s correction).

**Discussion**

Hearing loss has long been considered to be an irreversible phenomenon, as it is linked to hair cell death and the auditory hair cells of the mammalian inner ear do not regenerate. However, a number of recent studies have found that hearing loss does not necessarily result from hair cell death, as loss of outer-hair cell electromotility can reduce hearing ability by as much as 40 dB. In addition, noise-induced permanent hearing loss can result from damage to the cochlear amplifier, which is a main function of outer-hair cells. In light of these observations, we sought to explore more effective methods of hearing restoration.

As previously mentioned, sound conditioning can protect the auditory system from noise-induced damage and slow the process of hearing loss. In this study, we verified another capability of sound conditioning: the hearing improvement effect. There are several clues relevant to the mechanism of hearing improvement produced by modified sound conditioning. It has been suggested that sound conditioning induces physiological or biochemical changes in outer-hair cells. As hearing loss can result from damage to outer-hair cells, it is possible that modified sound conditioning improves hearing ability by modulating the function of these cells. Likewise, it is possible that sound conditioning influences the mechanical coupling between the basilar membrane and outer hair cells. Secondly, the relationship between ROS (reactive oxygen species) and hearing loss should be taken into account. Recent studies have shown that noise exposure increases free radical production, which damages hair cells. ROS are also known to play a role in age-related hearing loss. Interestingly, there is some evidence that sound conditioning interferes with the adverse effects of ROS (i.e., by increasing cochlear antioxidant enzyme activity), and that low-level sound conditioning reduces free radical damage to hair cells. Thus, it is plausible that modified sound conditioning improves hearing ability by restoring ROS-induced hair cell damage. Future studies should explore the synergistic effects of modified sound...
conditioning and antioxidant drugs.
Although we used very low levels of acoustic stimuli (ranging from 5 to 15 dB SL), a few patients appear to have been negatively affected (table 2). However, we discovered that three samples, all of which had negative effects in excess of 10 dB, had very high levels of test-retest variability (i.e., standard deviations ≥ 20 dB). Therefore, the seemingly negative results may have been influenced by large transient threshold shifts. Interestingly, these three samples were all obtained from one patient (i.e., patient I).
Although we have not yet determined the source of the test-retest variation, it is clear that the transient hearing threshold shift did not result from the hearing test equipment or study methods, as the same patient experienced standard deviations of less than 3 dB in three other samples. Moreover, large test-retest variability (i.e., in excess of 20 dB) occurred in only 1 of the 56 samples from other patients.
Modified sound conditioning differs from conventional hearing aids, which amplify external sound, in that sound conditioning is designed to fundamentally improve hearing ability. In this study, patients underwent modified sound conditioning for 2 weeks. As the magnitude of hearing improvement may depend on the duration of sound conditioning, further studies should expand on our results by testing additional timeframes. In addition, the severity of hearing loss may influence the extent of improvement achieved via modified sound conditioning, as efficacy may depend on the pathological status of a damaged inner ear. Most of the patients in our study suffered from moderate or moderate-severe hearing loss before undergoing modified sound conditioning. Thus, future studies should investigate the efficacy of modified sound conditioning for various types of patients, including those with mild hearing loss.

Contributors

EK, SK(Seonwoo Kim) and SHH participated in the design of the study. SS participated in data collection. EK and SK(Seonwoo Kim) participated in data analysis. SK(Sangyeop Kwak) participated in developing AMA-PTA and provided technical advices. EK and SHH participated in writing the report. All authors have seen and approved the final version of the report.

Acknowledgments

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Conflict of interest statement

SHH is a consultant of Earlogic Korea Inc. SK(Sangyeop Kwak) is CEO of Earlogic Korea Inc. EK, SS, and SK(Seonwoo Kim) declares that they have no conflict of interest.

Figure Legends

Figure 1. Pure tone audiogram. Octave bands for AMA-PTA test were selected on the basis of such pure tone audiograms.
Figure 2. Micro audiogram of the AMA-PTA test with 1/24 octave resolution in the selected frequency range.
Figure 3. Selection of targeted frequency bands for sound conditioning.
Figure 4. Study protocol.
Figure 5. Changes in the grand averages of hearing thresholds. ‘Pre’ refers to grand averages before modified sound conditioning. ‘Post-1’ refers to grand averages after 2 weeks of modified sound conditioning. ‘Post-2’ refers to grand averages 2 weeks after the conclusion of modified sound conditioning. Statistical analysis was performed using Wilcoxon’s signed rank test with Bonferroni’s correction.
Figure 6. Changes in the grand averages of hearing thresholds. ‘Pre’ refers to grand averages before modified sound conditioning. ‘Post-1’ refers to grand averages after 2 weeks of modified sound conditioning. ‘Post-2’ refers to grand averages 2 weeks after the conclusion of modified sound conditioning. Statistical analysis was performed using Wilcoxon’s signed rank test with Bonferroni’s correction.
References

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Table 1. List of sound files

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Abbreviation: CF, center frequency; Oct., octave

Table 2. Improvements in hearing ability.

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<th>Hearing Improvement (HI, dB)*</th>
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*For each sample, hearing improvement was calculated by subtracting the post-2 average from the pre average. Results were grouped by the extent of improvement.
Abbreviations: HI, hearing improvement.

Table 3. Changes in patient averages.

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<th>Post-2 Patient Average (dB HL)</th>
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**Statistical analysis was performed using the paired T-test or the Wilcoxon’s signed-rank test (*).
Figure 4

Day 3: Pre test
Day 13: Sound conditioning
Day 20: Post test 1

Day 2: Sound conditioning
Day 13: Post test 1
Day 20: No sound conditioning

Pre test
Basic hearing test by PTA & SA
High resolution hearing test by AMA-PTA

For 2 weeks
Sound conditioning
Twice a day (i.e., morning, evening)
40 minutes for each time

Post test 1
High resolution hearing test by AMA-PTA

For 2 weeks
No sound conditioning

Post test 2
Basic hearing test by PTA & SA
High resolution hearing test by AMA-PTA

Figure 5

p=0.0010

59.80
Grand Averages
N=63 (9x7)

52.05
p=1.0000

50.89

Hearing Threshold (dBHL)

Pre
Post-1
Post-2
Figure 6

- Grand Averages
  N=47

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p=0.0010

p=1.0000