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The Protective Role of Zinc Sulfate in Temporary Noise-induced Threshold Shift: a Randomized Clinical Trial Study

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Abstract

Background: Exposure to excessive sound leads to hearing loss. Temporary threshold shifts are defined as threshold shifts that return to baseline levels in the hours to weeks after excessive sound exposure.

Aim: This study aimed to examine the zinc sulfate protective effect following noise exposure.

Methods: Fifty-two participants with normal audiograms at baseline were randomly assigned to control and intervention groups. First, a distortion product otoacoustic emission test (DPOAEs) was carried out as the baseline assessment, then the intervention group received zinc sulfate supplement capsules for one month and placebo capsules were given to controls. To induce a transient hearing shift, an ABR test was performed. The ABR test was done with 90 dB of sound stimuli for each ear. This input stimulus was a noise exposure that induces a temporary reduction in hearing, in fact, a transient hearing shift has occurred. Then, both groups had a DPOAE test and a follow-up assessment. Signal/noise ratio and DP (distortion product) levels were measured to evaluate the effect of zinc supplement use on transient hearing shift.

Results: Comparing the results of the distortion product otoacoustic emission test before and after the auditory brainstem response testing showed significant differences between intervention and control groups ($p < 0.05$). Moreover, the differences in signal/noise ratio between the intervention group before and after ABR testing and also in the control group were significant ($p < 0.05$).

Conclusion: Daily zinc sulfate supplement might protect against thetransient hearing shift.

Conflicts of Interest: The Authors declare no conflicts of interest.

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Introduction

Noise-induced hearing loss has been recognized for centuries. Although exposure to excessive sound leads to hearing loss, the value of the hearing shift and the final recovery depends on the characteristics of the affected patient and the sound. Temporary threshold shifts (TTS) are defined as threshold shifts that return to baseline levels in the hours to weeks after excessive sound exposure. However, the majority of the TTS improve during the time but a notable permanent threshold shift (PTS) may occur due to more serious injuries. TTS with repeated exposures to noise such as occupational exposure may evolve to a permanent hearing loss. Thus, noise-induced threshold shift can be defined as the PTS that remains after a period of recovery (1). Noise is an important occupational health hazard and noise-induced hearing loss (NIHL) is a common occupational disease. NIHL could result in decreased quality of life because of social isolation and difficulties in communication with others (2-5). Exposure to

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high intensity noise results in increased levels of oxygen free radicals in the cochlea through mitochondrial overactivity, exposure to an increased level of glutamate in intercellular junctions and ischemia. If produced free radicals overcome the protective intraocular antioxidant system, which is mainly composed of glutathione, they might lead to some damage to proteins, lipids, and DNA, which ultimately would result in hairy cell injury. Based on the assumption that oxidative stress has a significant contribution to noise-induced cochlear injury, many pharmacologic strategies primarily in animal models have been developed to strengthen the cochlear innate protective mechanism. Many studies examined the antioxidant agents' and related compounds' effect on noise-induced cochlear disorders (6- 8). The antioxidants, including zinc, role in prevention and treatment of noise-induced trauma has attracted much attention (9- 11). Given the increase of job positions in industries and firms with noise pollution, finding a solution for the prevention of NIHL is of critical importance. Several studies reported that ABR resulted in a temporary reduction of hearing (12-14). In this study, we investigate the effect of zinc sulfate supplements on the temporary reduction of DPOAE immediately following auditory brain stem response (ABR) testing.

Methods

Design overview

This study was a randomized, double-blind trial. The study was approved by the University Research Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.879), and randomized clinical trial registry (IRCT20200926048841N3). All participants provided written informed consent.

Setting and participants

The study was conducted at the Department of otolaryngology and head and neck surgery, Taleghani Hospital, from January 2016 to June 2016. In this trial recruitment participants were volunteer staff of our day clinic. The demographic information, patients' past medical history, drug history, and occupational history were recorded. Patients who had no hearing loss, underlying conditions, or renal disorder were included. At baseline serum Blood urea nitrogen (BUN), creatinine, and zinc level were measured for all participants to ensure they can be given the zinc sulfate supplement daily. Those with normal values were included in the study.

Randomization and interventions

On inclusion, patients were randomly assigned to two groups with a remote computer-generated code using dedicated software. (http://www.randomization.com). All participants underwent a DPOAE test in the audiology services of Taleghani Hospital at baseline. The patients with a normal audiogram, normal ear canal, and normal acoustic reflex who had within normal range serum zinc level and normal renal function were randomly assigned to the control or intervention group. The patients in the intervention group received 300 mg zinc sulfate supplement capsules (produced by Alhavi Drug Company) while the patients in the control group received identical placebo capsules. All participants were instructed to use their daily capsules with lunch meals. To induce a transient hearing shift, an ABR test was performed for each ear. The intensity of the input stimulus was initially set at 90 dB and sequentially attenuated in 10 dB steps down to a threshold level was reached. This input stimulus was a noise exposure that induces a temporary reduction in hearing, in fact, a transient hearing shift have occurred. The ABR test lasted approximately 30 minutes. Then, immediately after ABR analysis, a DPOAE test was performed for follow-up assessment.

Thus, DPOAEs were obtained at baseline (before intervention) and immediately after ABR analysis. Signal/noise ratio and DP

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(distortion product) levels were measured to evaluate the protective effect of zinc supplement use on transient hearing shift. Researchers and the study statisticians were masked to treatment allocation. All audiometric values were measured and compared with baseline values.

DPOAE testing

In DPOAE, recordings are the recording of otoacoustic emissions generated in the inner ear in response to known frequencies, f1 and f2. The sound frequencies are produced by small probes that were placed in the ear canal. These probes send the sound frequencies to the tympanic membrane then with a little delay; the otoacoustic emission generated is recorded by sensors on the probes.

In this method, the details of response amplitude increase and DPOAE levels or frequencies intensities which could be considered as generated OAE compared with noise floor (in this study 6 dB) were defined. 15, 16 In this study, all audiometric measurements were performed in a silent room by standard OAE measuring devices. The primary tone frequency ratio (f2/f1) was 1.22 with the same level of 65db.DPOAES generated by the primary tones were recorded by the device's microphone and the most prominent DPOAE in humans, whichisfdP=2f1-f2 was used. The frequency ranges used in this study were the standard audiometric range of 1-8 kHz. Distortion Product Otoacoustic Emissions were obtained by applying the Signal Processing System (System 2, Tucker-Davis Technologies, Alachua, FL).

A probe microphone (ER-10C, Etymotic Research, Elk Grove, IL) is applied to calibrate, generate stimuli, and to record emissions. The forward pressure level (FPL) technique was used for Calibration.

ABR testing

A commercial system (System 3, Tucker-Davis Technologies, Alachua, FL) was used for ABR testing. The input stimulus intensity was set at 90 dB HL and sequentially attenuated in 10 dB steps down to 10 dB below the threshold. Responses were collected from electrodes inserted through the skin at the ipsilateral mastoid, vertex, and contralateral mastoid.

Statistical Analysis

All data were analyzed using, IBM SPSS Statistics for Windows, Version 20.0. All variables were reported as mean ± SD. Paired t-test and Chi-square tests were used. A two-sided P-value of ≤0.05 was deemed as a statistically significant threshold.

Results

Demographic findings: A total of 52 subjects (26 in the intervention group and 26 in the control group) participated with 18 men (34.6%) and 34 women (65.4%). In the intervention group, 8 participants were female (61.5%) and 5 were male (38.5%) while in the control group 9 were female (62.2%) and 4 were male (30-8%). The mean age in the intervention group were 29.5±0.73 years and in the control group 26±0.98 years. The mean age of all participants was 27.8±0.7. The mean age of men was 29.2±1.3 and the mean age of women was 27.0±0.7. The difference was not significant.

The DPOAE test results and signal/noise ratio at 1000 Hz frequency.

The mean level of DPOAE (DP level) at 1000 Hz frequency was 6.04±0.36dB before sound exposure and -1.73±0.68dB after exposure. The paired t-test showed a significant difference (p <0.0001). The mean DPOAE level at 1000Hz frequency was 7.14±0.26dB before exposure and 5.48±0.4dB after exposure; the difference was significant (p <0.0001) (shown in Figure 1 and Table 1). A comparison of signal/noise ratio at 1000HZ frequency showed that 19.2% of participants in the intervention group had a ratio at 1000HZ frequency showed that 19.2% of participants in the intervention group had a ratio <6 (positive test), while 61.5% of control had positive results. The Chi-square test

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showed a significant difference (p <0.002) and the Pearson coefficient was 9.665.

The DPOAE test results and signal/ noise ratio at 2000 Hz frequency.

The mean DPOAE Level at 2000 Hz frequency was 6.5± 0.29 dB before exposure and - 3.6±0.53dB after exposure, in the control group, the difference was significant (p <0.0001). The mean DPOAE level at 4000 frequency in the intervention group was 5.77+0.19 dB before exposure and 2.1±0.47 dB after exposure. The difference was not significant (p <0.53). An independent t-test showed no significant difference before exposure (p=0.59) while after exposure the difference was significant (p <0.0001) (shown in Figure 3 and Table 1). A comparison of signal/noise ratio at 4000 Hz frequency showed that in the intervention group, 15.4% had a ratio <6, while 84.6% of the control group had the same positive results. The chi-square test showed a significant difference (p <0.0001, Pearson coefficient =24.923), (Table 2).

Table 1. Mean level of DPOAE before and after intervention in control and intervention group

		Mean DPOAE				Std. Error Mean			
		1000Hz	2000Hz	4000Hz	8000Hz	1000Hz	2000Hz	4000Hz	8000Hz
Control	Before	6.04	6.50	4.21	1.56	0.36	0.29	0.36	0.33
	After	-1.73	-3.61	11.93	-11.97	0.68	0.53	0.64	0.67
Case	Before	7.14	7.10	5.77	2.99	0.26	0.21	0.19	0.26
	After	5.48	6.53	2.10	1.27	0.40	0.43	0.47	0.45

Table 2. Signal /noise ratio after intervention in control and intervention group

	Signal/Noise							
	Negative				Positive			
	1000Hz	2000Hz	4000Hz	8000Hz	1000Hz	2000Hz	4000Hz	8000Hz
Control	10 (38.5%)	6 (23.1%)	4 (15.4%)	3 (11.5%)	16 (61.5%)	20 (76.9%)	22 (84.6%)	23 (88.5%)
Case	21 (80.8%)	21 (80.8%)	22 (84.6%)	22 (84.6%)	5 (19.2%)	5 (19.2%)	4 (15.4%)	4 (15.4%)

The DPOAE Test results and signal noise ratio at 8000 Hz frequency

The mean DPOAE Level at 8000 Hz frequency was 1.56± 0.33 dB before exposure and - 11.97±0.67 dB after exposure, in the control group, the difference was significant (p <0.0001). The mean DPOAE level at 8000 frequencies in the intervention group was2.99±0.26dB before exposure and 1.27±0.45 dB after exposure. The difference was not significant (p <0.58) (shown in Fig. 4 and Table 1).

An independent t-test showed no significant difference before exposure (p=0.069) while after exposure the difference was significant (p <0.0001). A comparison of signal/noise ratio at 8000 Hz frequency showed that in the intervention group, 15.4% had a ratio <6 while 88.5% of the control group had the same positive results. The chi-square test showed a significant difference (p <0.0001, Pearson coefficient =27.810).

Repeated measures ANOVA test showed that DP levels at frequencies of 1000,2000,4000, and 8000Hz before exposure and after

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exposure in the control group were significantly different from the same measurements in the intervention group (p <0.0001). Also, repeated measures ANOVA test showed that signal/ noise ratio at 1000,2000,4000, and 8000Hz frequencies before and after exposure in the control group were significantly different from the same measurements in the intervention group (p <0.0001).

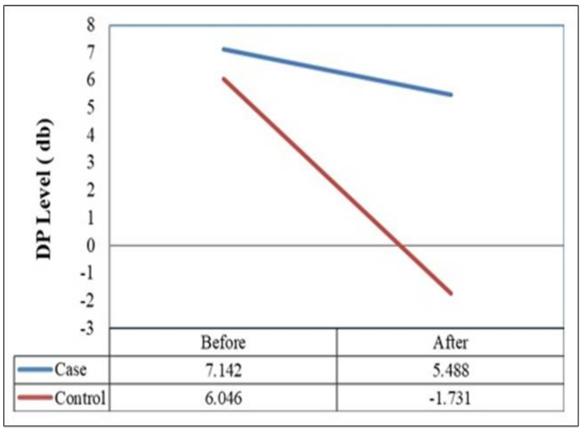

Figure 1. The mean level of DPOAE in control and intervention groups before and after the intervention (1000Hz).

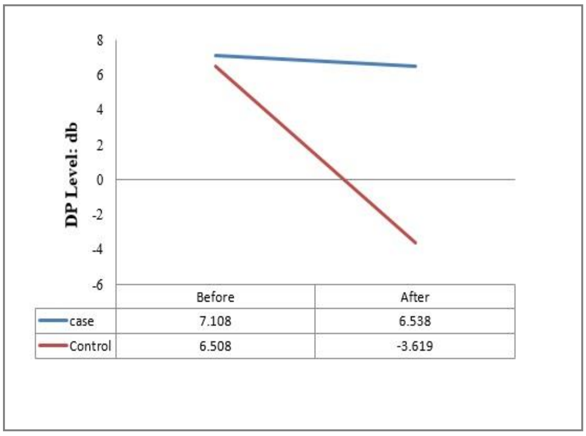

Figure 2. Mean level of DPOAE in control and intervention groups before and after the intervention (2000Hz).

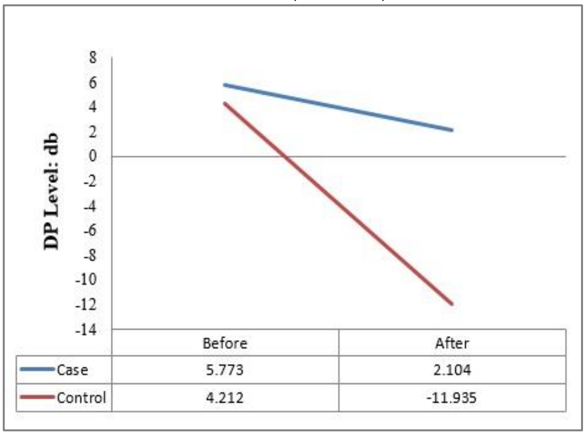

Figure. 3. Mean level of DPOAE in control and intervention groups before and after intervention (4000Hz).

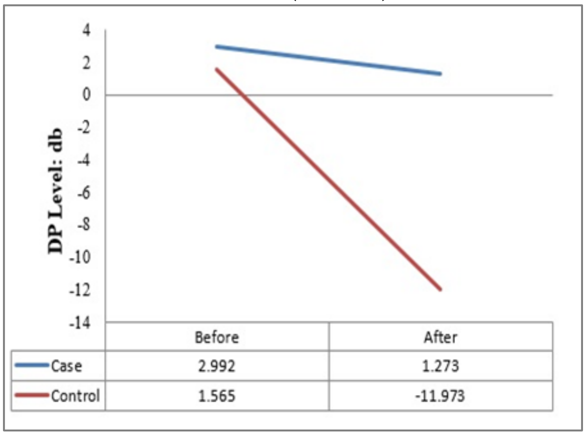

Figure 4. The Mean level of DPOAE in control and intervention groups before and after the intervention (8000 Hz).

Discussion

In this study, 52 participants were randomly assigned to intervention and control groups. The mean age of all participants was 27.8 ± 0.7. At baseline a DPOAE test was conducted and the control and intervention group received placebo and zinc sulfate for one month, respectively. At one month both group had a DPOAE test after exposure to ABR sound stimulus of 90 dB intensity (as a sound stimulus). The results were recorded at 1000, 2000, 4000 and 8000 Hz frequencies. In this study, a temporally hearing loss induced byABR test was used as a simulation for the transient hearing shift to examine the antioxidant effect of zinc sulfate on ear protection. This temporary hearing loss had no long-term harm for patients and the degree of induced hearing loss was under control. For all participants, a sound stimulus of 90db was used to elicit an ABR. Our results showed a decline in DPOAE level and positive signal/noise ratios after ABR sound stimulus with 90 dB intensity at frequencies used in the control group comparing with the intervention

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group. In the control group who received a placebo, a decline in DPOAE level were observed after exposure to ABR sound stimulus in the range measured by DPOAE test, which suggested a free radical-mediated process; this decline in the control group base line and at the final stimulus exposure were significant in all frequency examined comparing with intervention group. While in the intervention group who received zinc sulfate, the induced hearing loss were well prevented; the different was significant. There was also a significant difference in hearing loss and signal /noise ratio in 1000, 2000, 4000, and 8000 Hz frequencies between the control and intervention groups. In addition, comparing at different frequency levels (1000, 2000, 4000, and 8000 Hz) between the control and intervention group (which showed the effect of antioxidants, zinc sulfate) by repeated ANOVA, DPOAE level measurement and signal/noise ratios showed significant differences. Therefore, this study showed the effectiveness of zinc sulfate use in prevention of transient hearing shift. Most studies of NIHL prevention used animal models and focused on n-acetylcysteine effect which showed promising protective effect against NIHL. Some of studies showed a decline in hearing loss in a group of animals who received n-acetylcysteine compared with controls after exposure to traumatic noise stimulus (17, 18). Moreover, Davis et al., showed that nacetylcysteine had no protective effect against NIHL. In their study the subjects used nacetylcysteine one hour before traumatic noise exposure and immediately after the exposure (19). In our study the participants in the intervention group used zinc sulfate for one month before exposure to sound stimulus which is much longer than other studies which mostly used only one dose of antioxidant agent. In another study by Kramer et al., the n-acetylcysteine effect was studied on people who attended a night club (exposure to traumatic high intensity sound and noise). The researcher examined the subject at entrance to club and at 2 hours of presence in the club. The intervention group received 900 mg of n-acetylcysteine at entering the club. These researchers found no protective effect of n-acetylcysteine against NIHL. Their observation might be explained at least to some extent by the fact that the level of traumatic noise and the participants' distance to the source of noises were not controlled for and the participants also smoked cigarettes and drank alcohol (20). In our study, we control for confounding factors through several measures. All participants were selected from the same working place (to have similar occupational exposure to noise) and their ages ranged from 18- 35 years; none of the participants smoked cigarettes or drank alcohol. The drug use was monitored on a weekly basis and sound stimulus for inducing hearing loss (ABR, 90dB) was well under control. On the other hand, a few studies examined the effect of other supplements on protection against NIHL. Vitamin E supplements were associated with a 14% decrease in NIHL (Risk ratio, 86%). The highest quintiles of vitamin E supplements showed a 47% risk reduction for moderate to severe hearing loss (>40 dB) compared with those at the lowest quintiles (21).

Few studies examined the zinc supplement's effect on protection against hearing loss (22, 23). Yang et al. showed that zinc gluconate uses in the intervention group led to improvements in sudden sensorineural hearing loss (SSNHL) compared with the control group. In their study, the patients in the control group received corticosteroids while the intervention group received both corticosteroids and zinc gluconate. They concluded that zinc antioxidant and anti-inflammatory effects resulted in decreased oxidative stress in the Cochlea of patients with SSNHL and could be a promising option for the treatment of this condition (22).

Conclusion

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Based on the fact that in our study the main confounding factors were well controlled and the antioxidant zinc sulfate was administered for one month, the findings of this study suggest that zinc supplement administration might protect against transient hearing loss in those who work in noise polluted environment.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethics

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