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Efficacy of Systemic Methylprednisolone and Intratympanic Dexamethasone in Rats with Noise İnduced Hearing Loss

Gürültüye Bağlı İşitme Kaybı Olan Sıçanlarda Sistemik Metilprednizolon ve İntratimpanik Dexametazonun Etkinliği

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ABSTRACT Objective: To evaluate the audiological and electron microscopic (EM) effects of systemic methylprednisolone and intratympanic dexamethasone (IT DXM) in rats with noise induced hearing loss. **Material and Methods:** Thirty-one adult female Wistar albino rats were randomized into 3 groups as Group I (n=8), Group II (n=11) and Group III (control, n=12). The animals were exposed to white noise at a frequency of 1-10 kHz and 110 dB sound pressure level for 8 hours in a free environment. Distortion product otoacoustic emission (DPOAE) measurements were performed before and after the noise. Group I received 0.8 mg/day IT DXM and Group II had 1 mg/kg/day intraperitoneal methylprednisolone for 7 days. Intraperitoneal saline solution was administered to Group III. DPOAE tests were repeated on the 7th and 21st days. After animals were sacrified on the 21st day, their cochleas were examined under EM. Statistical analysis was performed for the DPOAE measurements. **Results:** Measurement of the first day to 7th and 21st days were compared in all groups separately. Statistical significant recovery was observed in the frequencies of 5,000-6,000 Hz ($p<0.05$) in Group I and in the frequencies of 6,000-8,000 Hz ($p<0.05$) in Group II. The measurements were similar in control group for all frequencies on the 1st, 7th and 21st days ($p>0.05$). Groups I and II showed more stable and larger number of stereocilia compared to Group III on EM examination. **Conclusion:** IT DXM and systemic methylprednisolone are effective at certain frequencies in noise induced hearing loss. The combined use of both methods may provide additional benefits.

Keywords: Hearing loss, noise-induced; injection, intratympanic; otoacoustic emissions; spontaneous

ÖZET Amaç: Çalışmamızda, gürültüye bağlı işitme kaybı gelişen sıçanlarda, sistemik metilprednizolon ve intratimpanik (İT) deksametazonun odyolojik ve elektron mikroskopik (EM) etkilerinin değerlendirilmesi amaçlandı. **Gereç ve Yöntemler:** Otuz bir adet erişkin dişi Wistar albino sıçan Grup I (n=8), Grup II (n=11) ve Grup III (kontrol, n=12) olmak üzere 3 gruba randomize edildi. Tüm sıçanlara 1-10 kHz frekansında, 110 dB şiddetinde 8 saat boyunca kesintisiz, homojen karakterde gürültü verildi. Gürültü öncesi ve 1 gün sonrası "distortion product otoakustik emisyon (DPOAE)" ölçümü yapıldı. Birinci gruba 7 gün boyunca 0,8 mg/kg İT deksametazon, 2. gruba 7 gün 1 mg/kg/gün intraperitoneal metilprednizolon uygulandı. Üçüncü gruba ise 7 gün boyunca intraperitoneal yolla serum fizyolojik verildi. DPOAE ölçümleri 7 ve 21. günde tekrarlandı. Sıçanlar 21. günde sakrifiye edilerek kokleaları çıkartıldı ve EM inceleme yapıldı. Ölçümler ise istatistiksel analize tabi tutuldu. **Bulgular:** Tüm grupların 1. gün ölçümü ile 7 ve 21. gün ölçümleri ayrı ayrı karşılaştırıldı. Grup I'de 5.000 ile 6.000 Hz frekanslarda istatistiksel anlamlı iyileşme gözlendi ($p<0,05$). Grup II'de ise 6.000 ile 8.000 Hz frekanslarda istatistiksel anlamlı iyileşme gözlendi ($p<0,05$). Kontrol grubunda ise 1. gün ile 7 ve 21. gün ölçümleri benzer olarak izlendi ($p>0,05$). Elektron mikroskopide Grup I ve Grup II'de Grup III'e göre stereosilya sayısı ve bütünlüğü kalitatif olarak daha fazla izlendi. **Sonuç:** İT deksametazon ve sistemik metilprednizolon gürültüye bağlı işitme kaybı tedavisinde belirli frekanslarda etkilidir. Her iki metodun kombine kullanımı ek yarar sağlayabilir.

Anahtar Kelimeler: İşitme kaybı, gürültüye bağlı; enjeksiyon, intratimpanik; otoakustik emisyonlar; spontan

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Noise induced hearing loss is a common problem, causing sensorineural hearing loss and labor loss. Unfortunately, social life has recently and nowadays brought people the problem of noise induced hearing loss, such as nightclubs, listening to music with high-end headphones or working in an industrial area. This problem most affected the workers of the industrial revolution before World War II. Occupational noise, in particular is a significant risk factor for workers of many ages, ranging from 7% to 21% (average 16%) of the adult-onset hearing loss worldwide.[1]

Research continues on the pathophysiology and treatment of acoustic trauma or noise induced hearing loss. Clinical human studies are generally based on the identification of risk factors in large groups. Animal studies are important in preclinical research.

Noise causes a lot of damage to the cochlea, but the outer hair cells are the most damaged. However, in more severe noises, the pathology may progress to inner hair cell death, loss of nerve fibers, and damage to stria vascularis.[2] A high level noise causes acute edema in the stria vascularis, which is associated with intermediate cell loss.[3] Glucocorticoids clearly have protective effects through the glucocorticoid receptor signaling pathway.[4]

Since the glucocorticoid receptor was detected in the human inner ear, corticosteroids have been used for in inner ear disease such as autoimmune inner ear disease, tinnitus and Meniere's disease.[5-7] Methods of administration of drugs vary. We aimed to compare the the results obtained with the treatment options in practical clinical use and application methods of glucocorticoids by creating noise-induced hearing loss in animals.

MATERIAL AND METHODS

The research protocol was approved by the Kocaeli University Ethics Committee for Animal Experiments (date: June 18, 2013, number: KOU HAYDEK 6/1-3013) and was performed according to the ethical standards of the Helsinki Declaration and in adherence to Turkish law and regulations. All animals have received humane care in compliance with the Guide for the Care and Use of Laboratory Animals.

ANIMALS

Forty female Wistar albino rats weighing 200-230 g from Kocaeli University experimental medical research and scientific training laboratory were used because of their similarity about well defined temporal bone anatomy and hearing physiology. The animals were maintained on a 12:12 h light:dark cycle at 22 °C with free access to food and water.

EXPERIMENTAL PROCEDURES

All the animals were anesthetized with xylazine (10 mg/kg) and ketamine (80 mg/kg) by intraperitoneally. Otoscopic examination and distortion product otoacoustic emission (DPOAE) assessment was performed and those with normal data obtained were included in the trial. After awakening in the cages, the animals were exposed to 110 dB sound pressure level (SPL) white (broadband) noise (1-10 kHz) with a sound stimulator and sound amplifier for 8 hours. The exposure levels measured at the 4 positions in each cage varied by <1 dB.

Twenty-four hours after the noise exposure, all the animals had the 2nd DPOAE measurement and data showed that they had had hearing loss. They were then randomly divided into intratympanic dexamethasone (IT DXM) (Group I), systemic methylprednisolone (Group II), control group (%0.9 NaCl-Group III). In Group I; under ether anesthesia the tympanic membrane of the right ear was visualized under an operating microscope and 0.8 mg dexametasone (Onadron® 8 mg, İ.E Ulagay, Turkey) in 0.2 cc (4 mg/mL) volume was injected trough inferior the rear quadrant using a dental needle once a day for 7 days. In Group II animals received 1 mg/kg methylprednisolone (Prednol ®, Mustafa Nevzat, Turkey intraperitoneally without anesthesia once a day for 7 days. Twenty mg methylprednisolone was diluted with 40 cc with saline and 1 cc was injected by insulin injector. Group III received the same volume saline solution intraperitoneally for 7 days to compare Group II and to mask any effects of intraperitoneal inflammation.

During the study all the animals were examined every day and Group I was planned as n=16 against the possibility of otitis. On the 2nd day 5 of them de-

veloped otitis media due to licking or perforation of the injection site and also 3 of them died. In Group II one animal died. We think the cause of death was anesthesia in Group I and peritonitis in Group II. So 8 animals were excluded from the study. Thereby the number of groups were; n=8 in Group I, n=11 in Group II, n=12 in Group III.

On the day 7 and 21 DPOAE assessment was repeated for all the animals and hearing results were recorded.

DETERMINATION OF DPOAES

After an otoscopic examination to rule out possible middle ear pathologies, DPOAEs were recorded using the smallest probe (Otodynamics Ltd, London, United Kingdom). Cubic difference distortion products ($2F_1$-F_2) were performed in the general diagnostic mode and the F1/F2 frequency ratio was set as 1.22 to obtain most powerful responses. In the input output (I/O) modality, both measurements of threshold and over threshold of I/O functions were performed using primary sound tones decreasing from 80 dB.

Measurements were performed in 4,004, 4,358, 4,761, 5,188, 5,652, 6,165, 6,726, 7,336, 7,996 Hz frequencies. DPOAE amplitude above 3 dB noise thresholds was considered significant. DPOAE amplitudes were analyzed statistically.

DISSECTION AND HISTOLOGIC ANALYSIS OF THE COCHLEA

On the day 21, animals were sacrificed by decapitation under anaesthesia inducted by intraperitoneal injection of 100 mg/kg ketamine. Temporal bones were dissected and right cochleas of the animals were harvested. Only 2 samples of each group were fixed in 4% glutaraldehyde and than decalcificated with formic acide and than prepared for transmission electron microscopy (TEM) regarding the assessment of outer hair cell structure using standard procedures. These samples were examined with Zeiss Leo 906 E TEM (Germany)

STATISTICAL ANALYSIS

The SPSS (SPSS, version 13.0 for windows; SPSS Inc, Chicago, Illinois, USA) was used to perform statistical calculations. Audiological results were compared with nonparametric 2 related (Wilcoxon) and 2 independent samples (Mann-Whitney U) tests. Differences were accepted statistically significant at a p value <0.05.

RESULTS

DPOAE

DPOAE levels were recorded in each animal before the exposure to noise and on days 1,7 and 21 after noise. All the animals had hearing loss in all frequencies after the noise exposure. All the groups were statistically similar in Mann-Whitney U test performed before the acoustic trauma and after.

Hearing threshold levels improved in all groups between the 1st and 7th days (Figure 1). There was also an increase in DPOAE results between days 1 and 21 (Figure 2). These results were not statistically significant in the control group (Group III).

Group I showed statistically significant improvement at frequencies between 5,000 Hz-6,000 Hz between the days 1 and 7 and between days 1 and 21 with Wilcoxon test ($p<0.05$) (Figure 3) (Table 1).

DPOAE results were statistically significant at of 6,000-8,000 Hz frequencies between 1st and 7th days and between 1st and 21st days in Group II ($p<0.05$) (Figure 4) (Table 2).

HISTOMORPHOLOGIC ASSESMENT

Right ears of animals were analysed in all groups. All animals underwent right temporal bone dissection, and stapedotomy and cochlea resection were performed. The oval window was drilled to allow the fixative to enter the inner ear. The obtained cochleas were placed in 10% neutral formalin solution for fixation. The tissues were then taken to hydrochloric acide+formic acide solution (Biodec R® Bio-Optica Milano, Italy) for decalcification, and then kept there for 16 hours. Histological tissue follow-up procedures were applied to the materials and embedded in paraffin blocks. Three µm thick sections were obtained with Leica Microtome, (United States of America). Sections were passed through xylene and 3-stage alcohol, followed by hematoxylin and then with eosin. H&E stained sections were evaluated and caspase-3 immunostaining was performed.

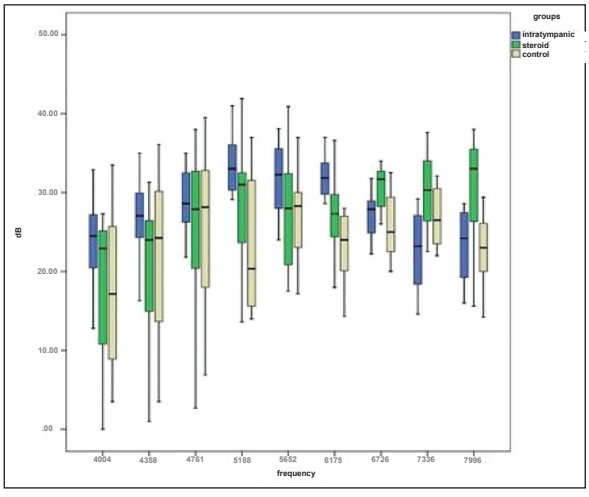

FIGURE 1: The mean of the emission measurements of all 3 groups at day 7 post-traumatic and the highest and lowest measurements, respectively, are shown.

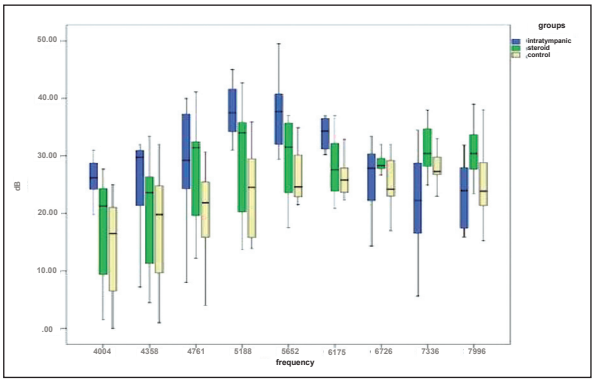

FIGURE 2: Emission averages of all 3 groups at day 21 post-traumatic, with the highest and lowest measurements distributions.

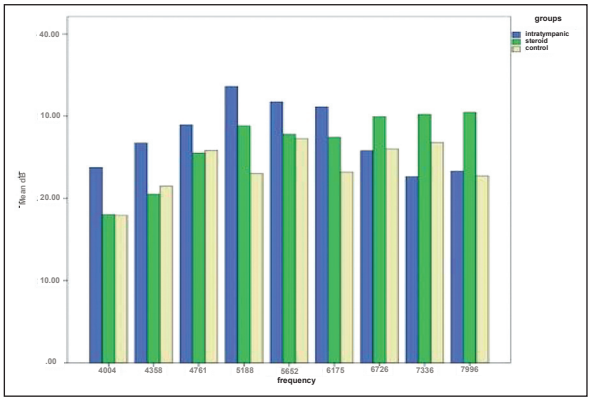

FIGURE 3: Bar graph of all groups at day 7 posttraumatic. While statistical significance was observed at 5,000 Hz and 6,000 Hz in the non parametric Wilcoxon test performed in the intratympanic group, a significant difference was observed between 6,000-8,000 Hz in the systemic steroid group ($p<0.05$). There was no significant difference in the control group ($p>0.05$).

We aimed to demonstrate apoptosis with caspase-3 staining, but caspase-3 expression was not present in any group. Consequently, we did not consider the immunohistochemistry staining results for this study.

Two samples from each group were prepared for electron microscopic examination. After temporal bone dissection, tissues were fixed in 4% glutaraldehyde solution. After decalcification in formic acid, TEM procedure was followed. One mm^3 trimmed tissue samples were fixed in 4% glutaraldehyde in +4 degrees for 2 hours. Then respectively after primary washing, secondary fixation and secondary washing and dehydration was applied. Samples were then stained for 1 hour at +4 degrees. Secondary dehydration was performed by removing water from the tissue in ethyl alcohol solutions at +4 °C. After infiltration and embedding, it was kept in a 60 °C oven for 24 hours and polymerization was achieved. Semi-thin sections of 1 micron thickness were taken on the slide from the plasticised tissue blocks with ultramicrotome and stained with toluidine blue. The zone was checked in the light microscope and the block was shaved for ultrathin section removal. Sections were taken to copper grids and citrate/uranyl acetate contrasting was performed. The images in the grids were transferred to digital media after they had been examined under transmission electron microscope.

In the transmission electron microscopic examination, it was observed that stereocilia formation was degenerated and the number of stereocilia decreased in control group. Since the budget of the study was not sufficient, only 2 samples could be sent. Therefore, it is not sufficient to reach a precise definition of histopathological changes. Organ of corti, tectorial membrane, spiral ganglion, outer hair cell entirety and stereocilia formation was better in Group I and Group II than control group (Figure 5, Figure 6, Figure 7).

DISCUSSION

Noise induced hearing loss has been the subject of many studies and still has uncertain aspects. Although numerous studies have been done and proven,

TABLE 1: In Group I, at 5,000-6,000 Hz average and standard deviation results and 1st-7th day and 1st-21st day comparison p values respectively.

	DPOAE amplitudes (dB) (mean±SD)			p value	
Frequency (Hz)	1st day	7th day	21st day	1st -7th	1th -21st
5,138	24.8±5.49	33.6±4.10	37.8±4.82	0.012	0.012
5,652	21.1±6.02	31.7±4.90	37.5±6.47	0.012	0.012
6,175	20.1±5.42	31.1±4.78	35.3±5.75	0.012	0.012

DPOAE: Distortion product otoacoustic emission; SD: Standard deviation.

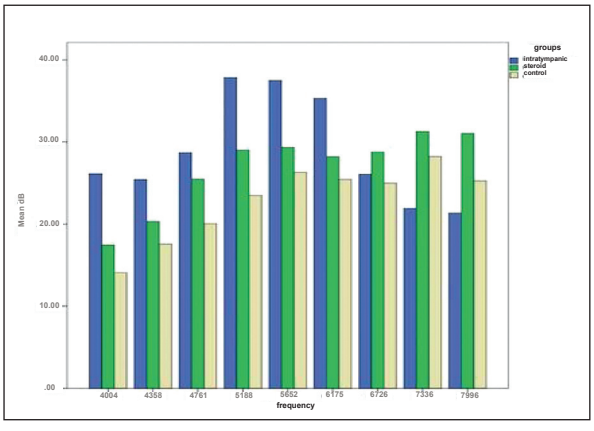

FIGURE 4: Bar graph of all groups at day 21 posttraumatic. While statistical significance was observed at 5,000 Hz and 6,000 Hz in the non parametric Wilcoxon test performed in the intratympanic group, a significant difference was observed between 6,000-8,000 Hz in the systemic steroid group ($p<0.05$). There was no significant difference in the control group ($p>0.05$).

researchers are still interested in. The mechanisms of noise induced hearing loss are diverse. Noise can cause both apoptotic cell death and necrotic cell death in the organ of corti. It increases the production of free radicals by triggering mitochondrial activity, and causes exitotoxic neuronal swelling. This process causes reactive oxygen species to cause cell damages in outer hair cells, stria vascularis and spiral ganglions.[8] They stimulate apoptotic pathways by damaging proteins, cellular lipids and DNA. Selective outer hair cell loss most often occurrs within 24 hours and continues for 2 weeks.

The damage from noise trauma depends on many factors. The frequencies most affected are 3.4 and 6 kHz, worse at 4 kHz. Continuous and increased noise intensity can cause serious damage.[9] Acoustic trauma is a sudden change in hearing that occurs suddenly as a result of exposure to a very loud and short-term sound. Noise-induced hearing loss is slow or delayed hearing as a result of continuous or intermittent noise. Acoustic trauma or noise induced hearing loss can lead to temporary threshold shift (TTS) or permenant threshold shift (PTS). There is no hair cell death in TTS but cochlear nerve terminals at their hair cell synapses show swelling and glutamate excitotoxicity within 24 h of exposure.[10-12] In PTS cochlear hair cell destruction or damage to their mechano-sensory hair bundles are seen.[13] So we exposed the animals to a sudden onset but long-lasting noise. In this way, we aimed to show the damage that will occur more clearly.

The first intratympanic drug injection was the lidocaine by Bárány in 1935 and streptomycin injection in 1956 by Schuknecht Meniere disease.[14,15] Among the agents examined for noise-induced hearing loss; corticosteroids, N-acetylsystein, salicylat, melatonin, tacrolimus, resveratrol etc.[16-19] To best of our knowledge, the current treatment for sudden sensorineural hearing loss is corticosteroid trheraphy. Therefore this agent can be used for acoustic trauma or noise induced hearing loss. Glucocorticoid receptors have been demonstrated in the human and rat inner ears.[20,21] The route of glucocorticoids is unclear. Intratympanic steroid treatment has been tried.[22] Parnes et al. studied hydrocortisone, dexamethasone, and methylprednisolone as orally, intratympanic and intravenously.[23] They found that all 3 drugs were better than systemic application in transition to cochlear fluids with topical application and methylprednisolone was the best. Today, both methylprednisolone and dexamethasone are used in intratympanic administration. We prefer dexamethasone in daily practice because of the burning sensation of methylprednisolone. In our study, we chose to proceed based on this application.

TABLE 2: In group II, at 6000-8000 Hz average and standard deviation results and 1st-7th day and 1st-21st day comparison p values respectively.

	DPOAE amplitudes (dB, mean±SD)			p value	
Frequency (Hz)	1st day	7th day	21st day	1st -7th	1th -21st
6,175	22.7±5.72	27.4±5.18	28.2±5.50	0.005	0.037
6,726	24.9±4.16	29.9±4.11	28.8±3.06	0.013	0.008
7,336	26.7±4.00	30.2±4.87	31.2±4.50	0.028	0.026
7,996	23.8±8.83	30.5±6.87	31.0±4.89	0.013	0.016

DPOAE: Distortion product otoacoustic emission; SD: Standard deviation.

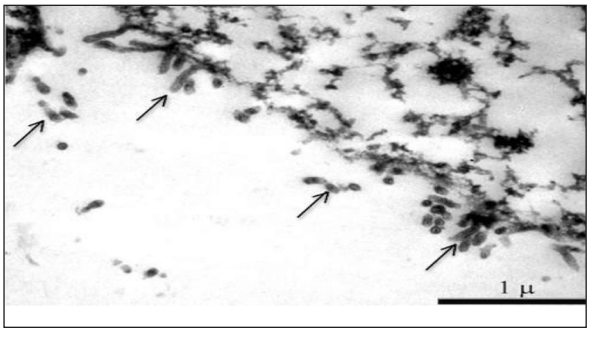

FIGURE 5: Transmission electron microscopic image of control group. The number of stereocilia (arrows) belonging to the outer hair cells were observed as decreased.

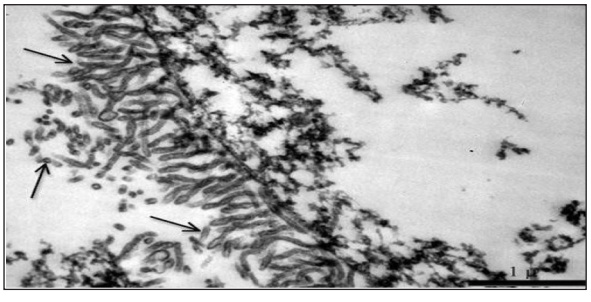

FIGURE 6: Transmission electron microscopic image of the systemic steroid group. The integrity and number of stereocilia (arrows) were preserved in the outer hair cells in the systemic steroid group.

Rat cochlea and human cochlea have some similarities and differences. In rats, the cochlea makes 3.25 or 4.25 turns. In humans, the number of turns is 2.5-2.75. The cochlea is consists of three tubular compartments, like the scala vestibular, and the tympanic ring are larger in proportion to the size of the temporal bone. The pars flaccida is absent in the eardrum.[24] Rats' cochleas are convenient for neurootologic studies including audiologic tests and histopathologic assessment.

We observed improvement in certain frequencies in the intratympanic group. These frequencies were 5,000-6,000 Hz. Ozdogan et al. in their study, showed thet the recovery was at 6,000 Hz on 14th day after acoustic trauma either.[25] Likewise Takemura et al. showed that direct infusion of different doses of dexamethasone into the inner ear was effective in reducing noise-induced trauma.[26] Another finding in our study was that the measurements in the systemic steroid group improved at high frequencies and the DPOAE values were statistically significant. Takahashi et al. studied the effect of methylprednisolone intraperitoneally after the exposing animals to 2 kHz pure tone of 110, 115 or 120 dB SPL for 10 minutes.[27] Doses were 6, 12 or 40 mg/kg for 7 days, and the compound action potential (CAP) threshold was examined on day 8. They found that the CAP threshold shift only improved after exposure to 110 dB SPL. In our study animals were exposed to 110 dB noise and

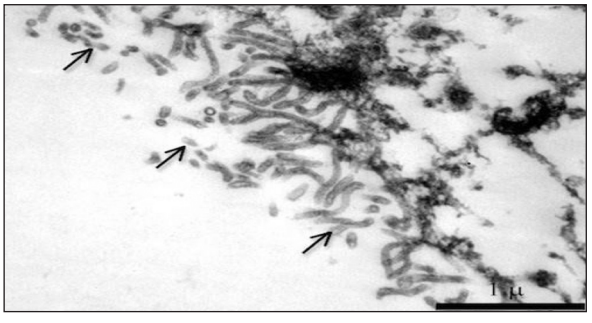

FIGURE 7: Transmission electron microscopic image of the intratympanic group. The stereocilia (arrows) of the outer hair cells of the animals in the intratympanic group are less in number and structure than the systemic steroids, but more than in the control group. It was also observed that their integrity was preserved.

our dose for the methylprednisolone 1 mg/kg for 7 days. Calculation of methylprednisolone as 1 mg/kg is widely used for systemic treatment in many clinics. Our findings are compatible with the literature.

Intratympanic drug administration has some advantages such as being an outpatient procedure, affecting only the affected ear etc. Chandrasekhar et al. studied dexamethasone concentrations in the perilymph after intratympanic and systemic administration in 40 guinea pigs.[28] IT DXM was found to be significantly higher than intravenous dexamethasone in perilymph levels. This feature of higher perilymph steroid concentration is beneficial in patients who are intolerant or contraindicated to systemic steroid.

Depending on the concentration, type or temperature of the drug, tympanic membrane perforation, vertigo and pain may ocur. Otitis media becomes a problem in aseptic conditions. These are the disadvantages of this method. While the incidence of otitis media due to intratympanic injection is rarely seen, permanent tympanic membrane perforation is not generally seen in humans.[29,30] In animal studies; death, otitis media and permanent tympanic membrane perforation are more common. Therefore greater attention should be paid to aseptic conditions in animal studies, and a larger number of animals in intratympanic injection groups than planned is required. Since we encountered the disadvantages mentioned above in the intratympanic injection groups in such studies conducted in our clinic before, we kept the number of this group higher than the others and paid attention to asepsis conditions. Despite all this experiences, we lost a large number of animals in our intratympanic injection group.

In our study, the audiologic improvement was achieved with intratympanic steroid injection at frequencies of 5,000-6,000 Hz, and with systemic steroid at frequencies of 6,000-8,000 Hz, according to DPOAE data. To be a pilot study, 2 cochlea samples from each group were analyzed by transmission electron microscopic examination for qualitative detection. However, the small sample size prevented us from obtaining quantitative data. In conclusion, both IT DXM group and systemic methylprednisolone group showed better preservation of organ of corti ultrastructure, outer hair cell morphology and stereocilia number compared to the control group. For this reason, it may be beneficial to use both methods in the earliest period of sudden hearing loss after acoustic trauma or exposure to severe noise.

CONCLUSION

The adverse effect of acoustic trauma on hearing threshold levels can be reversed by systemic or intratympanic steroid administration. In our study, IT DXM group and systemic methylprednisolone group showed improvement in the early period (7th day) at different specific frequencies. Therefore, combined treatment of intratympanic and systemic steroids can be used in the early phase of noise exposure. Of course, this theory should be supported by another study involving a combined therapy group.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sebla Çalışkan, Murat Topdağ;* ***Design:*** *Sebla Çalışkan, Murat Topdağ;* ***Control/Supervision:*** *Sebla Çalışkan, Murat Topdağ;* ***Data Collection and/or Processing:*** *Sebla Çalışkan, Kadri İla, Ahmet Kara;* ***Analysis and/or Interpretation:*** *Sebla Çalışkan, Murat Topdağ;* ***Literature Review:*** *Sebla Çalışkan;* ***Writing the Article:*** *Sebla Çalışkan;* ***Critical Review:*** *Murat Topdağ;* ***References and Fundings:*** *Sebla Çalışkan, Murat Topdağ, Kadri İla, Ahmet Kara;* ***Materials:*** *Sebla Çalışkan, Murat Topdağ, Kadri İla.*

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