European Archives of Oto-Rhino-Laryngology (2019) 276:3287–3293
https://doi.org/10.1007/s00405-019-05635-x

OTOLOGY

Comparison of the protective efficacy between intratympanic dexamethasone and resveratrol treatments against cisplatin-induced ototoxicity: an experimental study

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Received: 25 May 2019 / Accepted: 4 September 2019 / Published online: 17 September 2019

Abstract

Purpose The main aim of this study was to compare the efficacy of intratympanic administration of dexamethasone and resveratrol in preventing cisplatin ototoxicity by measuring acoustic brainstem response (ABR) and distortion product otoacoustic emission (DPOAE).

Methods Forty rats (80 ears) were divided into five groups. Cisplatin was administered intraperitoneally to the first group ($n=8$). Group 2 ($n=8$) received cisplatin after resveratrol had been administered intratympanically. Group 3 ($n=8$) received cisplatin after dexamethasone had been administered intratympanically. Group 4 ($n=8$) received cisplatin after sodium chloride (NaCl) had been given intratympanically. Group 5 ($n=8$) received cisplatin after dimethylsulfoxide (DMSO) had been given intratympanically. ABR and DPOAE tests were performed on all groups before and 72 h after the procedure.

Results ABR threshold values in rats that received dexamethasone and resveratrol were found to be less affected than those observed in the other post-cisplatin groups. ABR-IV and ABR-I–IV interval values were significantly reduced in rats that had been given dexamethasone and resveratrol compared to the other groups. After cisplatin treatment, otoacoustic emission (OAE) amplitudes were significantly decreased in Groups 1, 4, and 5 for all frequencies, while OAE values were sustained in the resveratrol and dexamethasone groups (Groups 2 and 3). At OAE frequency 5652, dexamethasone was more significantly associated with protective than resveratrol was, while no significant difference was found between the two groups at other OAE frequencies.

Conclusion In conclusion, intratympanic dexamethasone and intratympanic resveratrol treatments may provide a significant protection against cisplatin-induced ototoxicity.

Keywords Cisplatin · Dexamethasone · Intratympanic · Ototoxicity · Resveratrol

Introduction

Ototoxicity is the cellular degeneration and dysfunction of the cochlea and vestibular organs caused by various medications and chemicals [1, 2]. Its effects may be temporary or permanent. Cisplatin (Cis-diamminedichloroplatinum) is an antineoplastic agent that is commonly found in medications causally associated with ototoxicity. Cisplatin is mainly used in the treatment of malignant diseases, including head and neck tumors, and cancers of the urogenital system, central nervous system, respiratory system, and esophagus [3]. The ototoxic effects of cisplatin are evidenced by DNA damage, reactive oxygen species, ion channel blockage, and lipid peroxidation [4]. Cisplatin increases the formation of reactive oxygen derivatives in the cochlea [4, 5]. The clinical picture shows irreversible, bilateral, sensorineural hearing loss, which initially involves high-frequency sounds and subsequently low-frequency sounds, including speech. While follow-up tests for ototoxicity, audiometry, DPOAE, and ABR may be performed, there is no standard treatment for the prevention of cisplatin-induced ototoxicity.

Steroids are among the medications that have been shown to be effective in preventing cisplatin ototoxicity, limiting

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the generation of reactive oxygen species in the inner ear [6]. In patients with sudden hearing loss, Meniere's disease, and autoimmune inner ear diseases, intratympanic rather than systemic use of steroids has the advantage that the systemic side effects of steroids can be avoided, while relatively higher steroid concentration may be achieved in the perilymph.

Resveratrol is a polyphenol molecule with numerous antioxidant properties. The efficacy of resveratrol in preventing cisplatin ototoxicity has been demonstrated in several studies [7–9]. Resveratrol inhibits ototoxicity with its antioxidant effect by reducing reactive oxygen radicals [9]. In this study, DPOAE and ABR outcomes were used to compare the relative efficiency of intratympanic dexamethasone and intratympanic resveratrol in preventing cisplatin ototoxicity.

Materials and methods

Animal care and treatment

This study was carried out with the ethics committee approval of the Experimental Animal Research Center of Kırıkkale University in February 2014 and number 2014/87. Our work has been supported by Kirikkale University Scientific Research Projects Coordination Unit (Project number: 2014/019). A total of 40 female, adult, healthy, 3-month-old Albino–Wistar rats (80 ears) were used in our study. The rats were kept in a suitable temperature and humidity environment in which they could access food and water at will. The rats' ears were inspected, and if present, plugs were removed, while rats with infection in the external auditory canal, opacification, and perforation in the tympanic membrane, or an infection in the middle ear were excluded from the study. The rats were otoscopically examined under anesthesia.

Anesthesia and drug application

The animals were randomized into five groups using the simple randomization technique. Eight experimental animals (rats) were used in each group. The groups were formed as follows: Group 1 (cisplatin group) ($n=8$), Group 2 (resveratrol group) ($n=8$), Group 3 (dexamethasone group) ($n=8$), Group 4 (sodium chloride (NaCl) group) ($n=8$), and Group 5 (DMSO group). Group 4 was designated as the control group and Group 5 was added to elucidate the possible interventional effect of dimethylsulfoxide (DMSO), which is a diluent of resveratrol. All rats underwent general anesthesia, with the intraperitoneal (i.p.) administration of 60 mg/kg ketamine hydrochloride (Ketalar ®, Eczacibasi Parke-Davis, Istanbul, Turkey) and 10 mg/kg xylazine HCl (Alfazyn®, Alfas International B.V., Woerden, The Netherlands) before the procedures. In Group 1, 15 mg/kg i.p. cisplatin (Cisplatin DBL, Hospira Australia Pty Ltd. Victoria, Australia) was administered via slow infusion. In Group 2, 20 mg/ml resveratrol (R5010, Sigma–Aldrich, Taufkirchen, Germany) was administered intratympanically in a dose of 0.05 ml to both tympanic membranes of each rat under the microscope. A 4 mg/ml dexamethasone ampoule was administered intratympanically in a dose of 0.05 ml to both tympanic membranes of each rat in Group 3 under the microscope. In Group 4, 0.9% NaCl was administered intratympanically in a dose of 0.05 ml to both tympanic membranes of each rat under the microscope. In Group 5, DMSO (resveratrol solvent) was administered intratympanically in a dose of 0.05 ml to both tympanic membranes of each rat under the microscope. In Groups 2, 3, 4, and 5, i.p. 15 mg/kg of cisplatin was given 30 min after the administration of medication. The doses were determined based on the previous studies [7, 10].

ABR measurements

The rats in all experimental groups were anesthetized with 10 mg/kg xylazine (Alfazyn®, Alfas International B.V., Woerden, The Netherlands) and 60 mg/kg ketamine (Ketalar®, Eczacibasi Parke-Davis, Istanbul, Turkey) in recording the baseline ABR data at the beginning of the study and the final ABR measurements carried out 72 h after the treatment. The animals were examined under anesthesia and were confirmed to have normal external auditory canals and tympanic membranes before the baseline and final audiometric measurements. The rats under general anesthesia were warmed up using an electrical heater to stabilize their normal body functions. During the tests, the room temperature was maintained at 21 °C. ABR recordings were captured using the Interacoustics Eclipse EP15 device (Interacoustics A/S, Denmark). Ear probes for newborn hearing screening were inserted via the external ear canal of the measured side. Subdermal stainless steel monops needle electrodes were placed on the vertex (positive), mastoid (negative), and dorsum (earth). Impedances were checked to ensure that the electrodes' impedance was less than 2 kΩ. Stimulations were produced in the first 10 ms. Stimulations were produced in the first 10 ms and the responses were filtered from 100 to 3000 Hz. The stimulation level started at 11 pps from 100 dB HL (decibels Hearing Level) and was reduced by 10 dB at every step. The hearing threshold was defined as the lowest stimulation intensity at which visible, reproducible ABR response was produced. Responses corresponding to 1500 click stimuli were averaged to produce single response at each stimulus intensity**.** ABR-I, ABR-IV, ABR-I–IV interval, and threshold values were used in the measurements. All interventions and measurements were performed by the same single examiner.

DPOAE measurements

DPOAE recordings were captured using the Otodynamics OAE System device (Otodynamics Ltd., UK). Measurements were taken before and 72 h after the medications had been administered. With the probe used for DPOAE, pure-tone stimuli at two different frequencies ($f1$ and $f2$) were given simultaneously, and the strongest emission from the cochlea was observed with the formula $2f1–f2$. The acoustic stimulus consisted of two simultaneous continuous pure tones of different frequencies: $f1$ and $f2$ ($f2/f1 = 1{:}22$). The intensities were $L1$ and $L2$ for tones at frequencies $f1$ and $f2$, respectively, with $L1$ minus $L2 = 10$ dB SPL ($L1 = 65$ dB SPL, $L2 = 55$ dB SPL). DPOAEs were measured from 1.0 to 6.0 kHz. These acoustic responses were obtained via the microphone inside the probe. The frequencies of 1416, 2002, 2832, 4004, and 5652 kHz were measured in DPOAE. The recordings were performed in an isolated quiet environment and the rats were monitored until they were completely sedated and remained motionless with regular spontaneous breathing, to minimize the noise contamination originating from the environment or the muscular activity of the animals. The plastic tubing adapters that presented the optimum fit to the external auditorycanal were attached to the emission probe and a closed cavity was formed by placement of the probe into the external auditory canal.

Probe verification

To verify that the probe assembly was acoustically sealed to the ear canal and that neither of the tube phones was being blocked, white noise was delivered to the ear canal through each of the two transducer channels independently. A fast-Fourier Transform (FFT) was computed on the white noise. The spectrum of the white noise was examined to ensure that spectrum levels were flat below 1000 Hz and that levels were similar across channels. This technique was repeated at intervals throughout the experiment to check that no changes in probe position had occurred.

Probe calibration test

For the calibration, the test on a probe was repeated to ensure that the values are within ± 0.5 dB. If the response has changed, the probe was refitted, and test was repeated. If repeat tests have produced the same values, these records were accepted as a reference, so that any future change in probe performance could be noted.

Determination of DPAOE

In the DPOAE mode, if a signal was present that was greater than − 5 dB SPL and greater than 2 dB SNR at any frequency point, then the equipment may be producing an artifact. Therefore, the presence of DPAOE is determined.

Statistical analyses

Statistical analyses were performed using the SPSS software for Windows, version 16.0. Normality for continuous variables in the groups was determined by the Kolmogorov–Smirnov test. The normally distributed variables ($P > 0.05$) were compared using a one-way ANOVA test. The variables with non-normal distributions were compared using the Kruskal–Wallis H test. For multiple comparisons between the groups, the Tukey test and the Conover test were used where appropriate. A paired sample t test and Wilcoxon signed-rank test were used to compare the pre- and post-treatment ABR and DPOAE values in each group. A value of $P < 0.05$ was considered statistically significant.

Results

ABR and DPOAE analyses were performed on all groups before and after the above-mentioned interventions. No significant difference was observed between the pre-treatment ABR values, ABR-I–IV interval, and ABR threshold values of the groups (Table 1, $P > 0.05$).

After cisplatin administration, ABR-I values were significantly reduced in rats that had been treated with resveratrol (Group 2) than in the other groups (Table 2). ABR-IV values

Table 1 Comparison of pre-treatment ABR-I, ABR-4, ABR-1–4, and ABR threshold values of groups

Parameter	Group 1 (cp)	Group 2 (res)	Group 3 (dexa)	Group 4 (saline)	Group 5 (dmso)	*P*
Pre-treatment ABR-1	1.28 ± 0.24	1.25 ± 0.19	1.46 ± 0.37	1.23 ± 0.33	1.24 ± 0.25	0.150
Pre-treatment ABR-4	4.27 ± 0.20	4.17 ± 0.12	4.27 ± 0.16	4.27 ± 0.16	4.29 ± 0.18	0.285
Pre-treatment ABR1-4 interval	2.98 ± 0.34	2.92 ± 0.22	2.80 ± 0.39	3.03 ± 0.42	3.05 ± 0,34	0.292
Pre-treatment ABR threshold Med (min–max)	25 (20–30)	25 (20–30)	25 (20–30)	25 (20–30)	25 (20–25)	0.272

One-way ANOVA test and Kruskal–Wallis H test were used

Table 2 Comparison of post-treatment ABR-I, ABR-4, ABR-1–4, and ABR threshold values of groups

Parameter	Group 1 (cp)	Group 2 (res)	Group 3 (dexa)	Group 4 (saline)	Group 5 (dmso)	*P*
Post-treatment ABR-1	1.89 ± 0.24	1.64 ± 0.23[a]	1.84 ± 0.27	1.95 ± 0.26	1.96 ± 0.19	0.002
Post-treatment ABR-4	5.38 ± 0.33	4.48 ± 0.22μ	4.65 ± 0.26μ	5.46 ± 0.38	5.61 ± 0.54	**< 0.001**
Post-treatment ABR 1–4 interval Med (min–max)	3.33 (3.04–4.34)	2.88 (2.29–3.36) μ	2.78 (2.07–3.78) μ	3.28 (2.97–4.20)	3.40 (3.11–4.96)	**< 0.001**
[a]Post-treatment ABR threshold values Med (min–max)	70 (60–85)	52 (50–60) μ	55 (50–60) μ	72 (65–80)	70 (60–85)	**< 0.001**

One-way ANOVA test and Kruskal–Wallis *H* test were used

μ significantly different from others, and similar with each other

[a]Significantly different from others

were significantly reduced in rats that had been treated with resveratrol and dexamethasone than in the control (NaCl), DMSO, and cisplatin groups ($P < 0.001$). Similarly, the ABR-I–IV interval was significantly longer in the cisplatin, DMSO, and control groups than in rats that had been treated with dexamethasone and resveratrol ($P < 0.05$). In rats that had received resveratrol and dexamethasone after cisplatin administration, ABR-IV and ABR-I–IV interval values were similar. When the threshold values were examined, ABR threshold values after cisplatin administration were found to be less affected in rats that had been treated with dexamethasone and resveratrol ($P < 0.001$) (Table 2).

Cisplatin treatment was determined to significantly increase the ABR-I and ABR-IV values in all groups when the ABR test changes were evaluated before and after treatment in each group ($P < 0.001$) (Table 3). Although the ABR-I–IV interval was prolonged after treatment, this difference was not statistically significant in rats that had been treated with dexamethasone and resveratrol; however, it was statistically significant in rats receiving control treatment, DMSO, and cisplatin. Threshold values were found to increase significantly in all groups in response to the cisplatin effect ($P < 0.001$) (Table 3).

All groups were similar in terms of OAE values before the cisplatin treatment (Table 4, $P > 0.05$).

After the cisplatin had taken effect, OAE amplitudes decreased significantly in Groups 1, 4, and 5 for all frequencies, while OAE values were maintained in rats that had been treated with dexamethasone and resveratrol ($P < 0.001$) (Table 5). In addition, there was no significant difference between the protective effect of resveratrol and dexamethasone at frequencies of 1416, 2002, 2832, and 4004, while dexamethasone was found to provide significantly better protection than resveratrol at a frequency of 5652 (Table 5).

The variation of OAE amplitudes at different frequencies was examined in the groups themselves (Table 6). Accordingly, after the cisplatin administration, at frequencies of 1416, 2002, and 5652, a significant decrease was observed

Table 3 Intra-group comparison of ABR and threshold values of each groups

Parameter	Group 1 (cp)	Group 2 (res)	Group 3 (dexa)	Group 4 (saline)	Group 5 (DMSO)
Pre-treatment ABR-I	1.28 ± 0.24	1.25 ± 0.19	1.46 ± 0.37	1.23 ± 0.33	1.24 ± 0.25
Post-treatment ABR-I	1.89 ± 0.24	1.64 ± 0.23	1.84 ± 0.27	1.95 ± 0.26	1.96 ± 0.19
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Pre-treatment ABR-IV	4.27 ± 0.20	4.17 ± 0.12	4.27 ± 0.16	4.27 ± 0.16	4.29 ± 0.18
Post-treatment ABR-IV	5.38 ± 0.33	4.48 ± 0.22	4.65 ± 0.26	5.46 ± 0.38	5.61 ± 0.54
p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Pre-treatment ABR-I–IV interval	2.98 ± 0.34	2.92 ± 0.22	2.80 ± 0.39	3.03 ± 0.42	3.05 ± 0,34
Post-treatment ABR-I–IV interval Med (min–max)	3.33 (3.04–4.34)	2.88 (2.29–3.36)	2.78 (2.07–3.78)	3.28 (2.97–4.20)	3.40 (3.11–4.96)
P	0.001	0.301	0.910	0.003	0.002
Pre-treatment threshold values Med (min–max)	25 (20–30)	25 (20–30)	25 (20–30)	25 (20–30)	25 (20–25)
Post-treatment threshold values Med (min–max)	70 (60–85)	52 (50–60)	55 (50–60)	72 (65–80)	70 (60–85)
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Paired Sample T Test and Wilcoxon Rank test were used

Table 4 Comparison of pre-treatment DPOAE values of groups

Parameter	Group 1 (cp)	Group 2 (res)	Group 3 (dexa)	Group 4 (saline)	Group 5 (DMSO)	*P*
OAE1416 (ort ± SD)	5 (3.6–5.7)	5 (3.3–5.9)	4.6 (3.7–5.5)	4.2 (3.6–5.5)	4.6 (3–5.5)	0,267
OAE2002 (ort ± SD)	9.28 ± 0.87	8.99 ± 0.98	9.28 ± 0.96	9.55 ± 0,78	9.24 ± 1.06	0.572
OAE2832 (ort ± SD)	16.90 ± 1.46	16.55 ± 1.84	16.64 ± 2.05	16.68 ± 2.25	16.40 ± 2.19	0.968
OAE4004 (ort ± SD)	20.41 ± 2.67	20.50 ± 1.28	19.73 ± 1.93	19.46 ± 1.51	20.98 ± 2.11	0.190
*OAE5652 (ort ± SD)	27.5 (20–29.2)	25.8 (22.4–29.2)	26.5 (20–29.2)	26.5 (21.8–30.8)	27.5 (20–29.2)	0.895

One-way ANOVA test and Kruskal–Wallis *H* test were used

Table 5 Comparison of post-treatment DPOAE values of groups

Parameter	Group 1 (cp)	Group 2 (res)	Group 3 (dexa)	Group 4 (saline)	Group 5 (DMSO)	*P*
OAE1416	2.98 ± 0.67	4.38 ± 0.69[a]	4.16 ± 0.73[a]	2.87 ± 0.66	2.31 ± 0.52	< 0.001
OAE2002	6.81 ± 1.50	7.90 ± 1.17[a]	7.95 ± 0.92[a]	6.80 ± 0.70	6.60 ± 0.78	< 0.001
OAE2832	11.60 ± 1.19	15.30 ± 2.421[a]	16.48 ± 2.03[a]	11.96 ± 1.02	11.60 ± 1.66	< 0.001
OAE4004	11.80 ± 0.99	17.73 ± 2.57[a]	18.88 ± 2.96[a]	11.37 ± 2.11	12.60 ± 1.08	< 0.001
OAE5652	13.29 ± 1.62	18.83 ± 1.97[b]	21.33 ± 2.40[b]	14.01 ± 3.43	12.04 ± 1.28	< 0.001

One-way ANOVA test was used

[a]Significantly different from others, and similar with eachother

[b]Significantly different from others

Table 6 Comparison of pre-treatment and post-treatment DPAOE values within each group

Parameter	Group 1 (cp)	Group 2 (res)	Group 3 (dexa)	Group 4 (saline)	Group 5 (DMSO)
Pre-treatment OAE1416	5 (3.6–5.7)	5 (3.3–5.9)	4.6 (3.7–5.5)	4.2 (3.6–5.5)	4.6 (3–5.5)
Post-treatment OAE1416	2.90 (2.20–4.20)	4.50 (3–5.40)	4.10 (3–5.70)	2.85 (2.10–4.40)	2 (1.80–3.5)
P	< 0.001	0.01	0.003	< 0.001	< 0.001
Pre-treatment OAE2002	9.28 ± 0.87	8.99 ± 0.98	9.28 ± 0.96	9.55 ± 0.78	9.24 ± 1.06
Post-treatment OAE2002	6.81 ± 1.50	7.90 ± 1.17	7.95 ± 0.92	6.80 ± 0.70	6.60 ± 0.78
P	< 0.001	0.002	< 0.001	< 0.001	< 0.001
Pre-treatment OAE2832	16.90 ± 1.46	16.55 ± 1.84	16.64 ± 2.05	16.68 ± 2.25	16.40 ± 2.19
Post-treatment OAE2832	11.60 ± 1.19	15.30 ± 2.421	16.48 ± 2.03	11.96 ± 1.02	11.60 ± 1.66
P	< 0.001	0.083	0.832	< 0.001	< 0.001
Pre-treatment OAE4004	20.41 ± 2.67	20.50 ± 1.28	19.73 ± 1.93	19.46 ± 1.51	20.98 ± 2.11
Post-treatment OAE4004	11.80 ± 0.99	17.73 ± 2.57	18.88 ± 2.96	11.37 ± 2.11	12.60 ± 1.08
P	< 0.001	0.001	0.374	< 0.001	< 0.001
Pre-treatment OAE5652	27.5 (20–29.2)	25.8 (22.4–29.2)	26.5(20–29.2)	26.5 (21.8–30.8)	27.5 (20–29.2)
Post-treatment OAE5652	13.1 (10.1–17-1)	19 (15.5–21.9)	21.9 (15.1–24.1)	12.4 (9.9–20.5)	11.7 (10.7–15.5)
P	< 0.001	< 0.001	0.001	< 0.001	< 0.001

Paired sample *T* Test and Wilcoxon Rank test were used

in all groups after treatment. At a frequency of 2832, the pre- and post-treatment amplitudes were similar in rats that had been treated with resveratrol and dexamethasone; in the control, DMSO and cisplatin groups, post-treatment amplitudes were found to be significantly decreased. At a frequency of 4004, pre- and post-treatment measurements were similar in rats that had been treated with dexamethasone, whereas in all other groups, there was a significant decrease after treatment.

Discussion

Ototoxicity, balance disorder, and/or hearing loss occur due to the loss of function in the inner ear tissues caused by the use of chemical substances or medications. Approximately 130 ototoxic agents have been identified [11]. Cisplatin is a commonly used antineoplastic agent, and is among the most effective chemotherapeutic agents,

particularly in pediatric patients, with a cure rate of approximately 85% [4]. Cisplatin exacerbates DNA damage and lipid peroxidation by increasing the generation of reactive oxygen radicals [4, 5]. Blockage of the ion transition channels causes hyperpolarization and auditory threshold elevation [4]. Free-radical formation occurs as a result of decreased levels of intracellular glutathione, and thus causes changes in the antioxidant enzyme activity. The deterioration of the antioxidant defense system causes an increase in lipid peroxidation and thereby leads to apoptosis [5]. The clinical presentation of ototoxicity is bilateral, irreversible, and progressive sensorineural hearing loss at high frequencies [12]. Tinnitus is usually present as a temporary symptom. Cisplatin is irreversibly toxic to all cochlea, particularly the outer hair cells. Its vestibulotoxic effects are relatively rare. Cisplatin ototoxicity can be measured by audiometric examination, OAE measurements, and ABR [13, 14]. In addition, successful monitoring of ototoxicity and the association of frequencies with the clinical appearance may be ensured with DPOAE [15].

Steroids are among the medications that have been proven effective in preventing cisplatin-induced ototoxicity [16]. The distribution of corticosteroid receptors in the inner ear is an indicator of the efficacy of corticosteroids on the cochlea [17]. Steroids prevent ototoxicity in the inner ear by preventing the generation of reactive oxygen species [16]. Palmer et al. [18] also demonstrated that dexamethasone and hydrocortisone reduce nitric oxide (NO)-induced cell damage.

Steroids can be administered intratympanically to protect against systemic side effects and to achieve high perilymph concentration [19]. Han et al. [20] reported that the combined steroid treatment was significantly better in meta-analyses comparing systemic steroid therapy with combined steroid therapy (intratympanic and systemic steroids). In an animal experiment, intratympanic administration of dexamethasone was reported to be effective for longer and more potent in cochlea compared to systemically administered dexamethasone [21].

Several studies have verified the efficacy of intratympanic steroid therapy with ABR or DPOAE. Hill et al. [22] demonstrated the protective effect of intratympanic dexamethasone in cisplatin ototoxicity by ABR in an animal experiment. In their study, Marshak et al. [23] demonstrated the protective effect of intratympanic steroids in cancer patients, particularly at high frequencies, with DPOAE.

Resveratrol, a polyphenol molecule, is naturally present in many fruits [24]. Resveratrol activates the antioxidant enzymes by gene modulation and mitigates the effect of reactive oxygen radicals [25]. Accordingly, resveratrol also reduces DNA damage caused by hydroxy radicals [26]. Several studies have demonstrated resveratrol's protective effect on the cochlea [7–9, 27, 28]. Erkan et al. [29] demonstrated that resveratrol provides significant protection in diabetic rat cochlea using DPOAE.

Increased reactive oxygen radicals caused by cisplatin and DNA damage can be reduced by resveratrol [7–9, 28]. Şimşek et al. [7] demonstrated the protective effect of resveratrol in preventing cisplatin ototoxicity, using ABR. In another study, the efficacy of resveratrol against cisplatin ototoxicity was demonstrated by DPOAE [28]. In their study, Garcia-Alcantara et al. administered resveratrol and *N*-acetyl cysteine in combination, and demonstrated that ototoxicity was reduced by antioxidant enzyme gene modulation [25].

The aim of this study was to demonstrate the protective effect of intratympanic dexamethasone and resveratrol against cisplatin ototoxicity using both ABR and DPOAE. The ABR-I–IV interval was prolonged in each group, but this difference was not statistically significant in rats that had been treated with dexamethasone and resveratrol, whereas significant prolongation was observed in the other groups. ABR thresholds were found to be less affected in rats that had been treated with resveratrol and dexamethasone than in other groups. DPOAE analysis revealed that, at a frequency of 5652, dexamethasone offered more significant protection than resveratrol, whereas no significant difference was observed between the same two groups at other OAE frequencies. It is well known that basal turn of cochlea is receptive to relatively higher frequencies, such as 5652. Higher protective effect of dexamehasone rather than resveratrol in this frequency which was observed in our study, may be explained by the anti-edema effect of dexamethasone on basal turn which cannot be attributed by resveratrol alone.

At a frequency of 2832, pre- and post-treatment amplitudes were similar in rats that had been treat with resveratrol and dexamethasone; in the other groups, amplitudes after treatment were found to be significantly decreased. At a frequency of 4004, pre- and post-treatment measurements were similar in rats that had been treated with dexamethasone.

Conclusion

There is currently no curative treatment for cisplatin ototoxicity. Therefore, future studies should focus on determining whether the agents used to prevent ototoxicity would reduce the antineoplastic effect of cisplatin.

In our study, the efficacies of intratympanically administered dexamethasone and resveratrol for the prevention of cisplatin ototoxicity were compared. The results indicate that both intratympanic applications were associated with significant preventative effects on cisplatin ototoxicity.

Funding The authors declare that this article did not receive any financial support during the research and authorship process.

Compliance with ethical standards

Conflict of interest The authors declare that they had no conflict of interest during the preparation and publication of this article.

Ethical approval This study was carried out with the approval of the ethics of the Experimental Animal Research Center of Kırıkkale University.

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