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ORIGINAL ARTICLE

Comparison of Intratympanic Oxytocin and Dexamethasone in Cisplatin Ototoxicity: An Experimental Study

Burak Mustafa Taş[1] · Gökçe Özel[2] · Musa Azman[1] · Işıl Çakmak Karaer[3] · Rahmi Kılıç[4]

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Abstract

Although it is widely used, there is still no valid treatment for ototoxicity caused by the antineoplastic drug cisplatin. In this study, we aimed to investigate the efficacy of intratympanic resveratrol and intratympanic dexamethasone treatment in cisplatin-induced ototoxicity. We also compared intratympanic atosiban (oxytocin antagonist) and oxytocin in cisplatin ototoxicity. In this study, 30 rats (60 ears) were used by separating into 5 groups. Cisplatin, oxytocin, dexamethasone, atosiban and 0.9% NaCl were administered intraperitoneally to all groups separately. Auditory Brainstem Response and Distortion Product Otoacoustic Emission tests were performed on all groups before and 72 h after the procedure. Pre-treatment values were higher than post-treatment values in all groups ($p < 0.001$). There was no significant prolongation of the post-treatment Auditory Brainstem Response I-IV interval in the oxytocin and dexamethasone groups ($p > 0.05$). There was no significant decrease in the frequencies of 2832 and 4004 after treatment in the oxytocin and dexamethasone group compared to pre-treatment in Distortion Product Otoacoustic Emission. As a result, it has been shown that intratympanic oxytocin may be an option that can be used in the treatment, although it is not as effective as dexamethasone in preventing cisplatin ototoxicity.

Keywords Atosiban · Cisplatin · Dexamethasone · Ototoxicity · Oxytocin

Introduction

Cisplatin (cis-diamminedichloroplatinum) is a commonly used antineoplastic agent. Cisplatin is mainly used in the treatment of many malignant diseases [1]. Cisplatin causes ototoxicity that may be even permanent with high toxic damage to the inner ear [2]. Cisplatin reduces glutathione by producing reactive oxygen radicals and inhibits the activity of antioxidant enzymes [3]. Follow-up tests for ototoxicity, audiometry, Distortion Product Otoacoustic Emission (DPOAE) and Auditory Brainstem Response (ABR) may be performed.

Oxytocin is a neurohypophyseal peptide hormone synthesized in the hypothalamus. It is the stimulation of the uterine contractions and myoepithelial contractions in the mammary gland. Many studies have shown the antioxidant and anti-inflammatory effects of oxytocin [4, 5]. Oxytocin prevents apoptosis by reducing consumption of glutathione and superoxide dismutase [6]. Atosiban is a reversible oxytocin receptor and can decrease uterine contractions. Atosiban may reduce the antioxidant activity of oxytocin by binding to oxytocin receptors [7].

Steroids were shown to limit the effect of reactive oxygen species in the inner ear[8]. Therefore, it is used in cisplatin ototoxicity [8]. Although intratympanic dexamethasone is used in various diseases, they have advantages such as less side effects and higher concentration in the perilymphatic area compared to systemic steroids.

In our study, it was aimed to evaluate the effectiveness of oxytocin and dexamethasone, which have known

✉ Burak Mustafa Taş
mbtass@hotmail.com

1 Department of Otorhinolaryngology, Division of Head and Neck Surgery, Kırıkkale University School of Medicine, Kırıkkale, Turkey

2 Gökçe ÖZEL ENT Clinic, Ankara, Turkey

3 Department of Otorhinolaryngology, Division of Head and Neck Surgery, Malatya Training and Research Hospital, Malatya, Turkey

4 Ankara Training and Research Hospital Otorhinolaryngology Clinic, Ankara, Turkey

antioxidant activities, against cisplatin ototoxicity in intratympanic use.

Materials and Methods

This study was carried out with the ethics committee approval of Experimental Animal Research Center of … (No: 14/20). A total of 30 female, adult, healthy, 3-month-old Albino-Wistar rats (60 ears) were used in our study. Rats were kept in an environment in experimental Animal Research Center where the temperature was $22^0C \pm 2^0C$, humidity 65–70%, with 12-hour light/12-hour dark and a free access to food and water, in addition to medication application times. External and middle ear examinations of the rats were performed under anesthesia. Ears with plugs were cleaned and rats with infection in the external auditory canal, opacification and perforation in the tympanic membrane and those with an infection in middle ear were excluded from the study.

Drug Application

All rats underwent general anesthesia with 60 mg/kg intraperitoneal (i.p) ketamine hydrochloride (Ketalar, Eczacibasi Parke-Davis, Istanbul, Turkey) and 10 mg/kg i.p xylazine HCl (Alfazyn, Alfas International B.V., Woerden, The Netherlands) before the procedures.

The groups were formed as follows: Group 1 (cisplatin) ($n=6$), Group 2 (oxytocin) ($n=6$), Group 3 (dexamethasone) ($n=6$), Group 4 (atosiban) ($n=6$) and Group 5 (0.9% NaCl (sodium chloride)) ($n=6$). Group 5 was designated as the control group. 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, 5 I.U./ml oxytocin (Synpitan Forte, Deva Ltd, Istanbul, Turkey) was administered intratympanically in a dose of 0.05 ml to both tympanic membranes of each rat under the microscope. In Group 3, 4 mg/ml dexamethasone ampoule was administered intratympanically in a dose of 0.05 ml to both tympanic membranes of each rat under the microscope. In Group 4, 7.5 mg/ml oxytocin (Tractocile, Ferring Pharmaceuticals, Saint-Prez, Switzerland) was administered intratympanically in a dose of 0.05 ml to both tympanic membranes of each rat under the microscope. In Group 5, 0.9% NaCl 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. Based on previous publications, ABR and DPOAE were performed when there was no residual drug in the middle ear (after 72 h) [9].

Distortion Product Otoacoustic Emission (DPOAE)

Distortion product otoacoustic emission recordings were taken with the Otodynamics OAE System device (Otodynamics Ltd, Hatfield, United Kingdom). Measurements were made before and 72 h after the medication administration. With the probe used for DPOAE, pure sound stimuli at 2 different frequencies (f1 and f2) were given simultaneously and the strongest emission in the cochlea was found with the formula 2f1-f2. These acoustic responses were obtained via the microphone inside the probe. The procedures were made in a quiet environment. The frequencies of 1416, 2002, 2832, 4004 and 5652 kHz were measured in DPOAE.

Auditory Brainstem Response (ABR)

Auditory brainstem response recordings were taken with the Interacoustics Eclipse EP15 (Interacoustics A/S, Middelfart, Denmark). Measurements were made before and 72 h after the medication administration. Newborn ear probes were inserted into the ear from the external ear canal of the measured side. Subdermal stainless-steel monops needle electrodes were placed on vertex (positive), mastoid region (negative) and dorsum (earth). Stimulations were produced in the first 10 milliseconds and all clicks were filtered (from 100 to 3000 Hz). Stimulation level started at 11 pps from 100 dB hearing level and reduced by 10 dB every step. Hearing threshold was defined as the visible, reproducible ABR produced at the lowest stimulation intensity. An average of 1500 click/stimulus was applied for all levels. The ABR I, ABR IV and ABR I-IV interval and threshold values were used in the measurements.

Statistical Analysis

SPSS Statistics 24.0 (IBM SPSS Inc, Chicago) program was used for statistical analysis. Descriptive statistics related to continuous data were stated as mean ± standard deviation. The statistical value of $p<0.05$ was considered significant. Kolmogorov-Smirnov test and Shapiro–Wilk test were used as normality tests. Pre-treatment ABR I-IV interval values in Group 3, pre-treatment ABR threshold values in Group 3, pre-treatment 5652 frequencies values in Group 2 and post-treatment 2002 frequencies values in Group 1 were not normally distributed. Normally distributed data were compared with Paired Sample t-test. Comparison of normally distributed data between the groups was assessed with Independent samples t-test. Data without normal distribution were compared with Wilcoxon signed ranks test. Mann-Whitney U test was performed on the data that was not normally distributed among groups.

Table 1 Comparison of ABR and threshold values pre- and post-treatment

Parameter	Group 1 (Cisplatin)	Group 2 (Oxytocin)	Group 3 (Dexamethasone)	Group 4 (Atosiban)	Group 5 (Control)
Pre-treatment ABR I	1.18 ± 0.27	1.20 ± 0.21	1.51 ± 0.36	1.24 ± 0.31	1.23 ± 0.11
Post-treatment ABR I	1.78 ± 0.23	1.69 ± 0.18	1.88 ± 0.29	1.95 ± 0.21	1.91 ± 0.19
p values	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Pre-treatment ABR IV	4.18 ± 1.35	4.11 ± 0.22	3.97 ± 1.36	4.56 ± 0.32	4.01 ± 0.72
Post-treatment ABR IV	5.44 ± 0.39	4.86 ± 1.12	5.69 ± 0.16	5.96 ± 1.48	5.88 ± 0.96
p values	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Pre-treatment ABR I–IV interval	2.96 ± 0.32	2.89 ± 0.18	2.69 ± 0.58	3.06 ± 1.31	3.01 ± 0.89
Post-treatment ABR I–IV interval	3.22 ± 0.42	2.92 ± 1.17	2.71 ± 0.93	3.20 ± 0.42	3.23 ± 1.71
p values	< 0.001	0.441	0.871*	< 0.001	< 0.001
Pre-treatment threshold values Median (min-max)	25 (20–25)	25 (20–30)	25 (20–30)	25 (20–30)	25 (20–25)
Post-treatment threshold values Median (min-max)	72 (60–85)	55 (50–60)	50 (45–60)	70 (65–80)	70 (65–80)
p values	< 0.001	< 0.001	< 0.001*	< 0.001	< 0.001

*: Wilcoxon signed ranks test was used. Data represent mean ± SD excluding threshold values. ABR, Auditory Brainstem Response

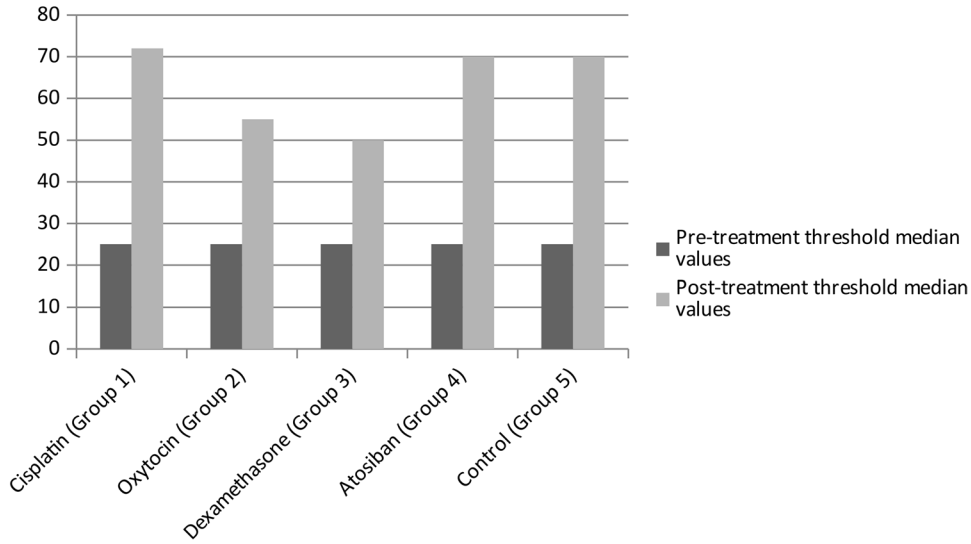

Fig. 1 The change in ABR pre- and post-treatment threshold median values of groups

Results

Auditory Brainstem Response Outcomes

ABR was performed to all groups before and after the procedure. Pre-treatment and post-treatment ABR values of the groups are given in Table 1. The change in ABR pre- and post-treatment threshold median values of group is given in Fig. 1. The post-treatment ABR I, ABR IV and ABR threshold values of the groups were found to be significantly higher than the pre-treatment values ($p < 0.001$). Similarly, a significant prolongation of ABR I-IV interval values was observed in Group 1, Group 4 and Group 5 ($p < 0.001$). There was no significant prolongation of the post-treatment ABR I-IV interval in the oxytocin and dexamethasone groups ($p = 0.441$ and $p = 0.871$) (Table 1).

There was no significant difference between the groups' pre-treatment ABR I, ABR IV, ABR 1–4 interval and ABR threshold values ($p > 0.05$). The difference in ABR I values in the oxytocin and dexamethasone groups was found to be significantly less than in Group 1, Group 4 and Group 5 ($p < 0.001$). There was no difference between the oxytocin and dexamethasone groups in terms of ABR I values ($p > 0.05$). The difference in ABR IV values was not significant between the groups ($p > 0.05$). The difference in ABR I-IV interval values in the oxytocin and dexamethasone groups was found to be significantly less than in Group 1, Group 4 and Group 5 ($p < 0.001$). Although there was a significant increase in post-treatment threshold values in all groups, the median value in Group 2 and Group 3 was found to be affected less than the other groups ($p = 0.034$ and $p = 0.018$). There was no difference between the oxytocin and dexamethasone groups in terms of threshold values ($p > 0.05$). When the differences in the atosiban group were compared with Group 1 and Group 5, no significant difference was found ($p > 0.05$).

Table 2 Comparison of DPOAE values pre- and post-treatment

Parameter	Group 1 (Cisplatin)	Group 2 (Oxytocin)	Group 3 (Dexamethasone)	Group 4 (Atosiban)	Group 5 (Control)
Pre-treatment OAE-1416	5.12 ± 0.18	5.98 ± 1.24	4.59 ± 1.31	4.17 ± 1.91	3.98 ± 0.66
Post-treatment OAE-1416	2.21 ± 0.77	4.56 ± 1.11	3.58 ± 1.19	2.33 ± 1.24	2.07 ± 1.01
p values	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Pre-treatment OAE-2002	9.33 ± 1.86	9.37 ± 1.01	9.37 ± 0.88	9.98 ± 0.62	9.20 ± 1.01
Post-treatment OAE-2002	6.16 ± 1.11	7.91 ± 1.23	7.61 ± 0.97	6.80 ± 0.69	6.60 ± 0.18
p values	< 0.001*	< 0.001	< 0.001	< 0.001	< 0.001
Pre-treatment OAE-2832	15.87 ± 1.36	16.52 ± 2.41	15.88 ± 2.05	16.80 ± 2.71	16.27 ± 2.19
Post-treatment OAE-2832	11.52 ± 1.63	15.98 ± 1.31	15.27 ± 1.98	11.53 ± 1.65	11.30 ± 1.66
p values	< 0.001	0.335	0.411	< 0.001	< 0.001
Pre-treatment OAE-4004	21.08 ± 2.09	20.41 ± 1.66	19.73 ± 1.93	19.26 ± 1.44	20.25 ± 2.98
Post-treatment OAE-4004	12.11 ± 0.99	19.12 ± 3.07	18.8 ± 2.96	10.84 ± 2.18	12.38 ± 1.01
p values	< 0.001	0.454	0.469	< 0.001	< 0.001
Pre-treatment OAE-5652	28.12 ± 1.56	25.70 ± 2.09	25.85 ± 2.91	24.88 ± 3.41	28.45 ± 2.36
Post-treatment OAE-5652	13.1 ± 0.97	19.03 ± 3.14	20.69 ± 1.52	11.99 ± 2.72	11.71 ± 2.61
p values	< 0.001	< 0.001*	< 0.001	< 0.001	< 0.001

*: Wilcoxon signed ranks test was used. Data represent mean ± SD. OAE, Otoacoustic Emission

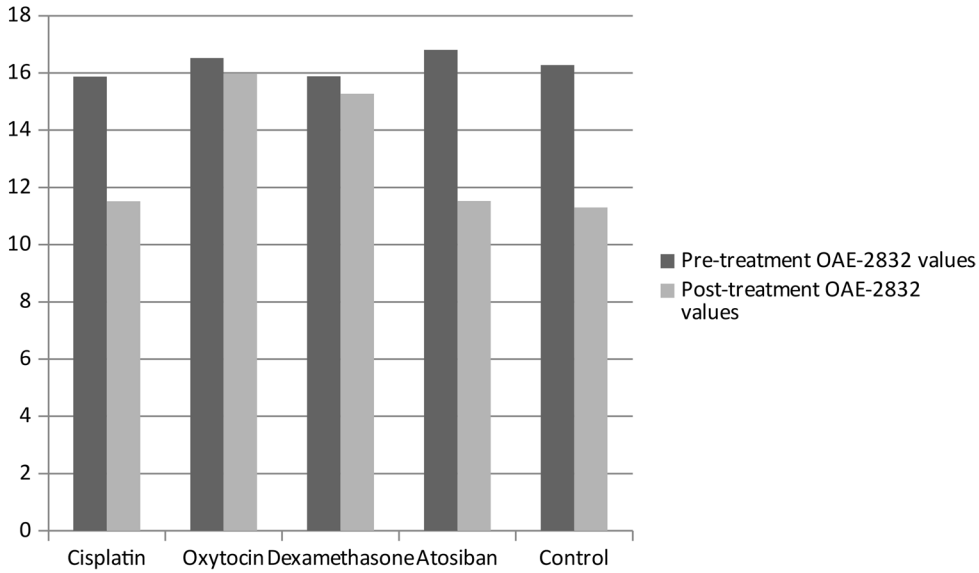

Fig. 2 Pre- and post-treatment changes in DPOAE 2832 frequency

Distortion Product Otoacoustic Emission Outcomes

DPOAE was performed to all groups before and after the procedure. Pre-treatment and post-treatment DPOAE values of the groups are given in Table 2. Pre-treatment values were higher than post-treatment values in all groups. Pre- and post-treatment changes in DPOAE 2832 and 4004 frequency are given in Figs. 2 and 3. There was a significant decrease in the 1416, 2002 and 5652 frequencies in all groups. There was no significant decrease in the frequencies of 2832 and 4004 after treatment in the oxytocin and dexamethasone group compared to pre-treatment (Table 2).

There was no significant difference between the groups' pre-treatment at frequencies of 1416, 2002, 2832, 4004 and 5652 ($p > 0.05$). When the oxytocin and dexamethasone groups were compared with the other groups in terms of changes in all frequencies, the difference in Group 2 and Group 3 was found to be significantly less than the other groups ($p < 0.001$). When the oxytocin and dexamethasone groups were compared with each other, no significant difference was observed between the two groups in terms of changes in all frequencies ($p > 0.05$). When the differences in the atosiban group were compared with Group 1 and Group 5, no significant difference was found ($p > 0.05$).

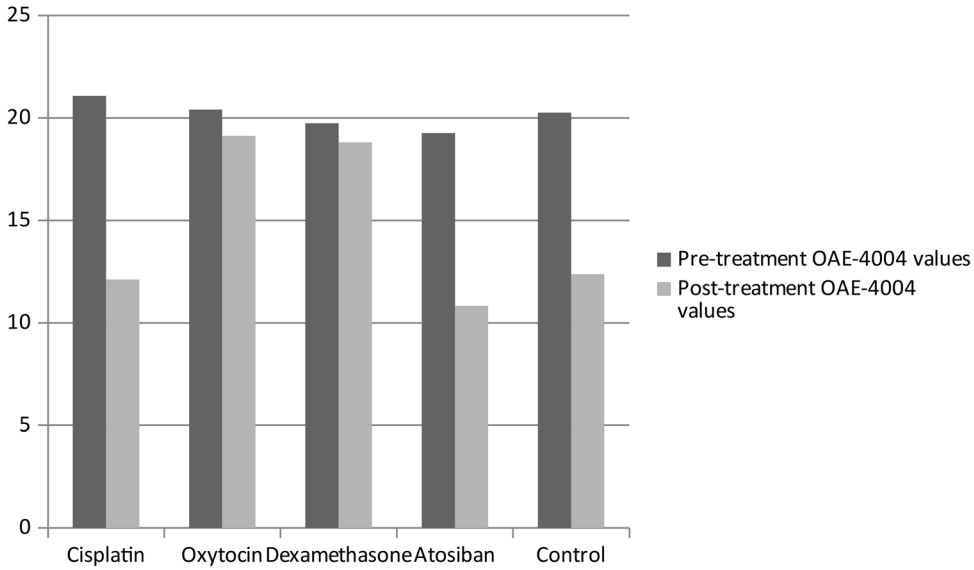

Fig. 3 Pre- and post-treatment changes in DPOAE 4004 frequency

Discussion

Cisplatin is one of about 130 ototoxic agents known to date [10]. Cisplatin enhances DNA damage and lipid peroxidation by increasing reactive oxygen radicals, furthermore blocking the ion transition channels causes hyperpolarization and auditory threshold elevation [11]. The deterioration in the antioxidant defense system causes an increase in lipid peroxidation and thereby leads to apoptosis in outer hairy cells [11]. Accordingly, cisplatin causes bilateral, irreversible and progressive sensorineural hearing loss. In our study, a prolongation in ABR values and a decrease in DPOAE frequencies were observed in each group given cisplatin.

Oxytocin receptors are found in many tissues [12, 13]. Kitano et al. reported that oxytocin receptor m-RNA is found in the inner ear [14]. The presence of oxytocin receptors in the inner ear makes oxytocin, which has anti-inflammatory and antioxidant properties, valuable for investigating ear diseases. In the study by Bekmez Bilmez et al., the protective effect of intratympanic and intraperitoneal oxytocin on cisplatin ototoxicity was demonstrated with DPOAE [15]. Especially in the group receiving intratympanic oxytocin, significantly less decrease in OAE values was observed compared to the intraperitoneal oxytocin group [15]. Akın Ocal et al. demonstrated the efficacy of intratympanic oxytocin in rats exposed to acoustic trauma with ABR and DPOAE [16]. In the study in which ABR thresholds were evaluated, no significant difference was found between the values on the 7th and 21st days after acoustic trauma and the values before acoustic trauma [16]. In our study, no significant prolongation was observed in the ABR I-IV interval value after cisplatin administration in the group receiving intratympanic oxytocin. Although the prolongation of the ABR I-IV interval was not significant in the oxytocin group, it was not as low as in the dexamethasone group. The difference in ABR I, ABR I-IV interval values in rats administered intratympanic oxytocin was found to be significantly less than the cisplatin, atosiban and control groups. When the dexamethasone and oxytocin groups were compared with the other groups, a significant increase was found in the ABR threshold values, but the increase in the dexamethasone group was less. In the group receiving oxytocin, there was no significant decrease in the post-treatment values at frequencies 2832 and 4004 compared to the pre-treatment values. In addition, the decrease in frequencies was significantly less than the cisplatin, atosiban and control groups. No difference was found when dexamethasone and oxytocin groups were compared with each other.

Atosiban is a reversible, competitive antagonist of the oxytocin receptor. Atosiban can reduce uterine contractions by decreasing intracytoplasmic calcium release and prostaglandin synthesis [17]. In many studies where oxytocin and atosiban are used together, it has been reported that atosiban reduces the anti-inflammatory and antioxidant effects of oxytocin [4, 18, 19]. Hussein and Mousa reported that in their study on acute myocardial injury in rats, atosiban decreased the antioxidant level increased by oxytocin [18]. Grzesiak et al. showed that atosiban given to pregnant women for tocolytic treatment increased oxidative stress [4]. In another study, oxytocin treatment was shown to alleviate stress-aggravated colitis, but atosiban reversed this effect [19]. In our study, no difference was observed between the atosiban, cisplatin and control groups for all values.

The efficacy of dexamethasone and methylprednisolone, which reduce reactive oxygen radicals, in cisplatin ototoxicity has been demonstrated in studies [20, 21]. Intratympanic steroid administration, which has no reported ototoxic effects, has the advantage of less side effects and higher

perilymphatic concentration compared to systemic steroid administration [22]. In a meta-analysis, it was reported that combined steroid therapy (intratympanic steroid and systemic steroid) was significantly better than systemic steroid therapy [23]. Dexamethasone loaded nanoparticles have been shown to be effective in cisplatin ototoxicity [21]. Rauch et al. compared oral prednisolone with intratympanic methylprednisolone in a multicentered, prospective, randomized study of 250 patients with the unilateral sensorineural hearing loss [24]. Intratympanic methylprednisolone administration was shown not to be more ineffective than oral prednisolone therapy [24]. In our study, no significant prolongation of the ABR I-IV interval value was observed in rats receiving intratympanic dexamethasone after cisplatin administration. The difference in ABR I, ABR 1–4 interval and ABR threshold values in rats administered dexamethasone was found to be significantly less than in the cisplatin, atosiban and control groups. There was no significant decrease in post-treatment values compared to pretreatment values in DPOAE frequencies of 2832 and 4004 in rats receiving dexamethasone. In addition, the decrease in frequencies was significantly less than in the atosiban, cisplatin and control groups. Studies can be detailed in larger series and with histopathological examinations.

Conclusion

In the literature, no study was found in which oxytocin, dexamethasone and atosiban were evaluated together in cisplatin ototoxicity and both ABR and DPOAE were used. When the dexamethasone and oxytocin groups were compared with the other groups, a significant increase was found in the ABR threshold values, but the increase in the dexamethasone group was less. However, no difference was found between the two groups. A similar situation was observed at 2832 and 4004 frequencies in DPOAE. As a result, it has been shown that intratympanic oxytocin may be an option that can be used in the treatment, although it is not as effective as dexamethasone in preventing cisplatin ototoxicity.

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Author Contribution BMT: Planning, designing, data collection, literature survey, statistical analysis, interpretation of the results, writing. GŞ: planning, designing, data collection, literature survey, interpretation of the results. IÇK: planning, designing, literature survey, interpretation of the results. RK: planning, designing, literature survey, interpretation of the results. MA: planning, designing, literature survey, interpretation of the results, active intellectual support. All authors have contributed signifcantly, and that all authors are in agreement with the manuscript.

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Data Availability The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Patient images are stored in the private archive of our faculty and can be shared by the corresponding author upon reasonable request.

Declarations

Ethical Approval This study was carried out with the ethics committee approval of Experimental Animal Research Center of … (No: 14/20).

Conflict of Interest The authors declared no potential conflicts of interest concerning the research, authorship and/or publication of this article.

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