Protective and Therapeutic Effect of Platelet-Rich Plasma on Experimental Cisplatin Ototoxicity

Original Investigation

Bahadır Gözaydın[1], Asude Ünal[2], Doğukan Özdemir[3], Ayşe Çeçen[3], Mustafa Bakırtaş[4]

[1]Clinic of Otorhinolaryngology, Ünye State Hospital, Ordu, Turkey
[2]Department of Otorhinolaryngology, University of Health Sciences, Samsun Training and Research Hospital, Samsun, Turkey
[3]Department of Otorhinolaryngology, Samsun University Faculty of Medicine, Samsun, Turkey
[4]Department of Pathology, University of Health Sciences, Samsun Training and Research Hospital, Samsun, Turkey

Abstract

Objective: Cisplatin is a chemotherapeutic agent with an ototoxic effect that is frequently used in head and neck cancers. There are studies in the literature conducted with various antioxidant substances to protect and/or prevent ototoxicity. This study aims to investigate whether platelet-rich plasma (PRP) has a protective and therapeutic effect on cisplatin ototoxicity.

Methods: A total of 40 Sprague Dawley albino rats were divided into six groups as control group (n=6), PRP-only group (n=6), cisplatin group (n=6), cisplatin + PRP group (n=6), PRP + cisplatin group (n=6), and donor group (n=10). At the beginning of the study and the 8th day, they were tested with distortion product otoacoustic emission (DPOAE). Assessment of DPOAE results was based on the signal-to-noise ratio in 2000, 3000, 4000, 6000, and 8000 Hz frequency bands. On the 8th day, the rats were sacrificed. For histological examinations, the temporal bones were dissected and fixed. After hematoxylin and eosin staining, the tissues were evaluated by light microscopy.

Results: In the DPOAE tests performed on the 0th and 8th days of the cisplatin group, it was observed that cisplatin caused hearing loss in the rat ears. It was determined that the cisplatin group at 2000 Hz, 3000 Hz and 4000 Hz had a significant decrease in hearing compared to all groups ($p<0.015$), while the cisplatin group at 6000 and 8000 Hz was characterized by hearing loss at a higher rate than all groups ($p<0.001$). At the end of the study, negative effects of cisplatin on both cellular dimensions (cytoplasmic vacuolization, cell degeneration, dilatation, apoptotic cells, nerve degeneration) and hearing function were observed. No protective or therapeutic effect of PRP on cisplatin ototoxicity was observed.

Conclusion: Our study showed that platelet-rich plasma did not have a significant effect in the treatment of hearing loss due to cisplatin ototoxicity and in preventing hearing loss in rats.

Keywords: Ototoxicity, hearing loss, cisplatin, otoacoustic emissions, platelet-rich plasma, animal experimentation

ORCID IDs of the authors:

B.G. 0000-0003-2497-5446;
A.Ü. 0000-0003-0282-8277;
D.Ö. 0000-0003-2008-163X;
A.Ç. 0000-0001-6255-6125;
M.B. 0000-0003-3185-6947.

Cite this article as: *Gözaydın B, Ünal A, Özdemir D, Çeçen A, Bakırtaş M. Protective and Therapeutic Effect of Platelet-Rich Plasma on Experimental Cisplatin Ototoxicity. Turk Arch Otorhinolaryngol 2023; 61(2): 75-82*

Corresponding Author:
Ayşe Çeçen;
aysebel55@hotmail.com

Received Date: 03.08.2022
Accepted Date: 02.03.2023

DOI: 10.4274/tao.2023.2022-7-9

Introduction

Ototoxicity refers to the occurrence of the symptoms of hearing loss and/or balance disorder via functional impairment or cellular degeneration in the inner ear caused by exposure to different therapeutic agents and chemicals. There should be the development of sensorineural hearing loss of 20 dB or more in at least two subsequent frequencies so that it is possible to talk about ototoxicity in the audiological evaluation (1-3). Numerous drugs and chemicals such as antibiotics of the aminoglycoside group, many antineoplastic agents including cisplatin, some diuretics, anti-inflammatory and antimalarial drugs and some antiseptic solutions, arsenic, and ethyl and methyl alcohol are known to have ototoxic effects (1, 2).

Cisplatin (cis-diamminedichloroplatinum-II) is a chemotherapeutic agent which is effectively, successfully, and commonly used to treat various malignant diseases such as testicular cancers, head and neck cancers, small cell lung cancer, ovarian cancers, central nervous system malignancies, gastric cancers, and bladder cancers (2, 3). Cisplatin frequently causes ototoxicity and nephrotoxicity and may have significant adverse effects such as bone marrow suppression, gastrointestinal toxicity, and peripheral neuropathy that limit its use in clinical practice (1, 3). In particular, nephrotoxicity and ototoxicity are major dose-limiting adverse effects. These effects are dose-dependent, cumulative and usually lasting. Its nephrotoxic effects can be overcome with hydration; however, there is still no treatment to avoid its ototoxic effects (1-3).

Cisplatin-induced hearing loss is generally progressive, bilateral, symmetrical, irreversible and sensorineural in character. Hearing loss first starts at high frequencies and then gets into lower frequencies over time (4, 5). The ototoxic effects of cisplatin result from the fact that it gradually destroys outer hair cells from the basal to the apical parts of the cochlea. In the literature, several antioxidant substances were used to avoid and/or prevent this ototoxicity (1, 2, 4-7).

Platelet-rich plasma (PRP) was developed as a byproduct of multi-component blood products in the early 1970s. Autologous PRP is the plasma with a high platelet concentration, which is rich in growth factors and obtained from the person's own blood by centrifuging the whole blood. The density and activity of platelets in PRP are four times higher compared to those in whole blood (8). In addition to their role in hemostasis, platelets also play a significant role in the repair of tissues by releasing growth factors from α-granules in tissue damage (9). Alpha granules, platelet-derived growth factor (PDGF), transforming growth factors α and β, epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) also contain cytokines and chemokines. Growth factors, cytokines, chemokines and other secretory molecules known as integrins are abundant in young platelets and they continue to be secreted in small amounts throughout the 7–10-day life span of the platelets. PDGF increases the number of fibroblasts in the damaged area by stimulating the growth of endothelial cells and ensures the differentiation of neutrophils and monocytes. Thus, capillary vessel formation, increasing collagen production and granulation formation are supported. TGF-β is of vital importance in the restructuring of the skin: for example, in addition to stimulating collagen synthesis during the wound healing process, it also participates in the inflammatory response with PDGF and stimulates the synthesis of extracellular matrix. EGF takes part in chemotaxis and stimulates the proliferation of keratinocytes and fibroblasts. Proliferating fibroblasts increase collagen production. VEGF stimulates the proliferation of endothelial cells, thereby increasing new vessel formation, increasing existing capillary permeability, and contributing to the microenvironment necessary for cell growth and angiogenesis (8, 9).

While PRP is known to be used especially in orthopedics, periodontology, facial plastic surgery, chest and cardiovascular surgery and ophthalmology because of its positive effects on healing, its use in novel indications in ear, nose, and throat practice has drawn attention in recent years (8-11).

This study aimed to investigate the efficacy of PRP in the prevention and treatment of oxidative damage in experimentally induced cisplatin ototoxicity in rats.

Methods

This study was approved by the Experimental Animals Ethics Committee of Recep Tayyip Erdoğan University, Rize, Turkey (decision no: 2017/13, date: 29.03.2017). A total of 40 male adult (3–5 months old) Sprague-Dawley albino rats weighing 250–350 g were used in this study. The principles of the Declaration of Helsinki were followed for all procedures. The study was carried out in the animal experiments laboratory of the university.

All animals were cared for and fed in a sterile experimental animal unit environment with 12-hour light and 12-hour dark cycle at a moisture of 55–60% and at a room temperature of 22°. The external auditory canals and middle ears of the rats were examined by otoscopic examination. By cleaning the plugged ears, the rats with infection in the external auditory canal, opacification and perforation of the tympanic membrane and infection in the middle ear were excluded from the study and new rats were included in the study for completing the number of groups. The rats that died during follow-up and developed otitis were excluded from the study and new rats were included in the study. Before starting the study, distortion product otoacoustic emission (DPOAE) was performed on the rats in all groups and baseline signal-to-noise ratio (SNR) values at each frequency were calculated. SNR values were calculated by performing

DPOAE again on the 8th day of the study. Obtained SNR values were compared within and between groups. Since no significant difference was found between the two ears in the in-group evaluations, the measurements were evaluated on the right ear.

Platelet-Rich Plasma and Its Preparation

The rats from group 6, which were reserved as PRP donors for the intratympanic administration of PRP on days 1, 3, 5, and 7, were sacrificed and intracardiac blood was collected. Approximately 10 mL of blood taken for the intratympanic administration of PRP was added to anticoagulant tubes containing acid citrate dextrose for the preparation of PRP and shaken for 10 seconds to ensure mixing. When it was centrifuged at a low speed (3000 rpm, three minutes), three parts were differentiated in the tube. While erythrocytes were present in the lower part, a platelet-leukocyte mixture called buffy coat was present in the middle part and plasma was present at the top. When the buffy coat and the platelet-poor plasma at the top were recentrifuged at 4000 rpm for three minutes, PRP at a concentration of 10% was obtained.

Control and Experimental Groups

After adequate time passed for adaptation to laboratory conditions, 40 experimental animals were randomly allocated into six groups, six rats in each group and 10 rats in the donor group.

The rats were anesthetized, then distortion product otoacoustic emission (DPOAE) recordings were performed, and their hearing thresholds were identified. The evaluation of DPOAE results was based on the SNR in 2000, 3000, 4000, 6000, and 8000 Hz frequency bands. The SNR is more reliable for the evaluation of DPOAE responses than DPOAE amplitudes.

Group 1 (control group/n=6) was defined as the control group. No injection was administered to this group. DPOAE recordings were taken at the beginning of the study and on day 8.

Group 2 (PRP control group/n=6) was administered PRP (0.1–0.3 mL) intratympanically for four days every other day. DPOAE recordings were taken at the beginning of the study and on day 8.

Group 3 (cisplatin group/n=6) was defined as the cisplatin control group. This group was administered 16 mg/kg single dose cisplatin (cisplatin DBL 100 mg/100 mL vial, Orna İlaç, İstanbul, Turkey) intraperitoneally. DPOAE recordings were taken at the beginning of the study and on day 8.

Group 4 (cisplatin + PRP group/n=6) was intraperitoneally administered 16 mg/kg single dose cisplatin (cisplatin DBL 100 mg/100 mL vial, Orna İlaç, İstanbul, Turkey). Then, PRP (0.1–0.3 mL) was administered intratympanically every other day on days 1, 3, 5, and 7; four doses in total. DPOAE recordings were taken at the beginning of the study and on day 8. The therapeutic effect of PRP on ototoxicity was evaluated.

Group 5 (PRP + cisplatin group/n=6) was administered PRP (0.1–0.3 mL) intratympanically every other day on days 1, 3, 5 and 7; four doses in total. 16 mg/kg single dose cisplatin (cisplatin DBL 100 mg/100 mL vial, Orna İlaç, İstanbul, Turkey) was intraperitoneally administered on day 3. DPOAE recordings were taken at the beginning of the study and on day 8. The protective effect of PRP on ototoxicity was evaluated.

Group 6 (PRP donor group/n=10) was defined as the group to be used as a donor group for the supply of PRP.

Auditory Assessment

DPOAEs were measured in the DPOAE mode using an Echoport ILO292-II (Otodynamics, Hatfield, UK) device. The rat's head was placed in a horizontal position in a quiet room and then the measurement was performed using the neonatal probe suitable for the external auditory canal. The measurement was initiated after seeing that the device was in an appropriate measuring position with a suitable configuration of the probe indicator and stimulus waveform on the device. DPOAEs were measured with a microphone in the external auditory canal and recorded at frequencies of 2000, 3000, 4000, 6000 and 8000 Hz. The values of DPOAE amplitudes that were 3 dB above the noise threshold were considered significant. The evaluation of DPOAE results was based on the SNR that occurred in 2000, 3000, 4000, 6000 and 8000 Hz frequency bands. The SNR is more reliable for the evaluation of DPOAE responses than DPOAE amplitudes. The SNRs were evaluated specifically to frequency for each rat in our study. SNR frequency curves were drawn. All subjects underwent DPOAE testing at the beginning of the study and the baseline values were calculated. DPOAE measurements were performed again eight days after the administration of cisplatin.

Histopathological Evaluation

After the final DPOAE test was performed, all rats were sacrificed for the histopathological evaluation of our study. The bulla was opened after dissecting the temporal bones. After removing the lateral wall of the cochlea and slowly injecting the 2.5% solution of glutaraldehyde, fixation was performed. The temporal bones were kept in the same solution at +4 °C overnight. After fixation, the temporal bones were kept in a 10% solution of EDTA at +4 °C for 10 days for decalcification. The cochlea specimens were dehydrated with ethanol and then embedded in paraffin blocks. The paraffin blocks were prepared in 5-micron-thick sections and then stained with hematoxylin and eosin (H&E). At least 15 sections were evaluated for

each rat cochlea. In the histopathological evaluation, cell degeneration was evaluated using a light microscope by performing a blind rating between 0–4 based on the area of degeneration at x100 magnification as 0: normal (no degenerate cells), 1: mild (1–5 cells degenerate), 2: medium (5–10 cells degenerate), 3: intermediate-advanced (10–15 cells degenerate), 4: advanced degree (15 or more cells degenerated). The median values of the histopathological blind grading of cytoplasmic vacuolization, dilatation, apoptotic cells and nerve degenerations in the groups are summarized in Table 1.

Statistical Analysis

The variables measured by the DPOAE test and histopathological variables of the subjects in the six groups were compared both within and between the groups. The median value was used because the distribution of the data did not fit the normal distribution. All statistical comparisons were performed in a computer environment using the SPSS 16.0 package program (Chicago, IL, USA). In intra- and inter-group comparisons, the t-test and the Mann-Whitney U test were used for normally distributed data and non-normally distributed data, respectively. In all measurements, a p-value <0.05 was considered significant.

Results

Regarding the DPOAE results, DPOAE was performed on rats in all groups before starting the study and then the baseline SNR values at each frequency were calculated (first measurement). On day 8 of the study, the SNR values were calculated by once more performing the DPOAE (last measurement). The SNR values obtained were compared within and between the groups. The measurements were evaluated over the right ear since there was no significant difference between the two ears in the evaluations made within the groups. The SNR values at 2000, 3000, 4000, 6000 and 8000 Hz were compared between the groups before and after the study. It was observed that there were no significant differences between the groups before the procedure (p>0.05) (respectively; p=0.722, p=0.195, p=0.224, p=0.676, p=0.321).

No significant differences were identified in terms of hearing in the DPOAE tests of the group 1 performed on days 0 and 8 (p>0.05) (respectively; p=0.523, p=0.082, p=0.112, p=0.486, p=0.735) (Figure 1, Chart 1).

No significant differences were observed in terms of hearing in the DPOAE tests of the group 2 performed on days 0 and 8 (p>0.05) (respectively; p=0.292, p=0.782, p=0.248, p=0.116, p=0.935) (Figure 1, Chart 2). The PRP extract was found to have no effect on hearing in the normal ear.

In the DPOAE tests of the group 3 performed on days 0 and 8, it was observed that cisplatin caused a significant hearing loss at all frequencies (2000 Hz; p=0.013, 3000 Hz; p=0.003, 4000 Hz; p=0.001), which was more significant at 6000 and 8000 Hz (p<0.001), compared to the other groups (Figure 1, Chart 3).

There was a significant difference in terms of hearing in the DPOAE tests of the group 4 performed on days 0 and 8 (p<0.05) (2000 Hz; p=0.011, 3000 Hz; p=0.003, 4000 Hz; p=0.001, 6000 Hz; p<0.001, 8000 Hz; p<0.001). It was found that the hearing loss caused by cisplatin in the rats' ears was not treatable with PRP plasma (Figure 1, Chart 4).

There was a significant difference in terms of hearing in the DPOAE tests of the group 5 performed on days 0 and 8 (p<0.05) (2000 Hz; p=0.010, 3000 Hz; p=0.006, 4000 Hz; p=0.001, 6000 Hz; p<0.001, 8000 Hz; p<0.001). It was observed that the hearing loss caused by cisplatin in the rats' ears could not be prevented by PRP (Figure 1, Chart 5).

In the histopathological light microscopic examination group 1 showed that the general structure of the tissue was observed to have a normal histological appearance, group 2 revealed that the tissue had a normal histological structure and that PRP had no positive or negative effect on either the morphology or the cellular structures of the tissues and was observed to have normal histological structures, group 3 it was found that the general structure of the tissue deteriorated, cytoplasmic vacuolization increased in the cells, and degeneration-related cell shedding was observed, it was observed that the general structure of group 4 and group 5 tissue was affected by cisplatin and morphologically deteriorated, cytoplasmic vacuolization and degeneration in

Table 1. Grading of histological parameters in groups

Group	Cytoplasmic vacuolization	Cell degeneration	Dilatation	Apoptotic cells	Nerve degeneration
Control group	0,0,0,0,1,0	0,0,0,0,0,1	0,0,1,0,0,0	0,0,0,1,1,1	0,0,0,0,1,1
PRP control group	0,0,0,0,1,1	0,0,0,0,0,0	0,0,0,1,0,1	0,0,0,1,1,1	0,0,0,0,1,1
Cisplatin group	3,3,4,4,4,4	3,3,3,3,3,4	2,2,3,4,3,3	3,3,3,3,3,3	2,2,2,2,3,3
Cisplatin + PRP group	3,3,3,3,3,3	4,3,4,4,4,4	3,3,3,3,3,3	2,2,3,4,3,3	2,2,2,3,3,3
PRP + cisplatin group	3,3,3,3,3,3	2,2,3,3,3,3	4,3,4,4,4,4	3,3,3,3,3,4	2,2,3,4,3,3

PRP: Platelet-rich plasma

cells were more frequent than in the control group, although there was a minimal difference with the cisplatin group, there was no pathologically significant difference (Figure 2).

There were no statistically significant differences between the control group and the PRP control groups, cisplatin group and the cisplatin + PRP therapeutic and PRP + cisplatin protective groups, PRP control group and the cisplatin + PRP therapeutic and PRP + cisplatin protective groups in terms of all evaluation criteria ($p>0.05$).

There was a statistically significant difference between the control group and the cisplatin group in terms of all evaluation criteria ($p<0.005$) (Table 1).

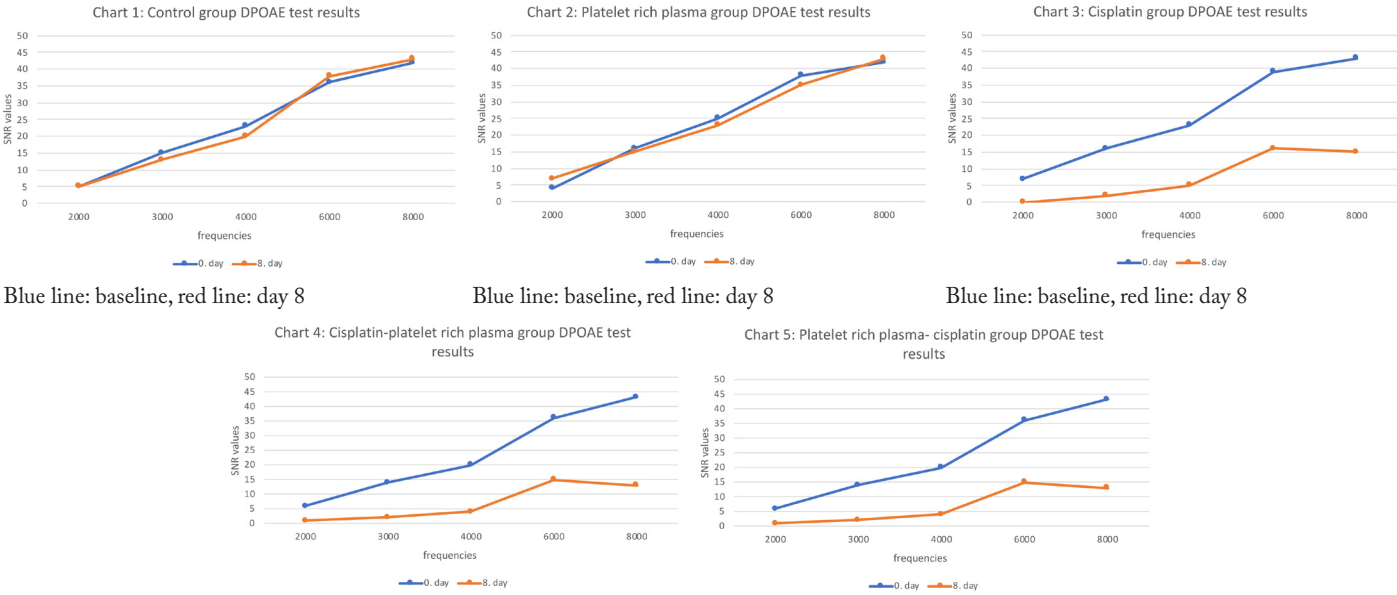

Figure 1. Days 0 and 8 SNR values of the groups at all frequencies

SNR: Signal-to-noise ratio, DPOAE: Distortion product otoacoustic emission

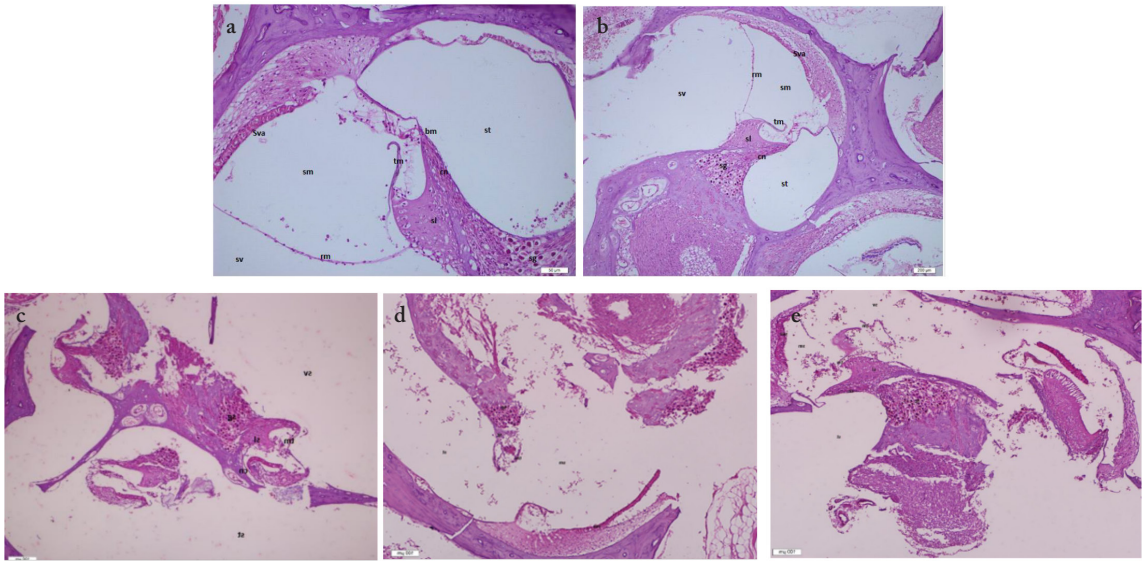

Figure 2. Image of inner ear structures examined with light microscopy in groups. **a)** Control group, normal histological appearance inner ear structures (Hematoxylin and eosin stain, x200). **b)** Platelet-rich plasma group, normal histological appearance inner ear structures (Hematoxylin and eosin stain, x200). **c)** Cisplatin group, increased cytoplasmic vacuolization and degeneration of inner and outer hair cells (Hematoxylin and eosin stain, x40). **d)** Cisplatin + PRP group, cytoplasmic vacuolization and degeneration in cells (Hematoxylin and eosin stain, x40). **e)** PRP + Cisplatin group, cytoplasmic vacuolization and degeneration in cells (Hematoxylin and eosin stain, x40)

SL: Spiral limbus, Rm: Reissner membrane, Sv: Scala vestibuli, Sm: Scala media, St: Scala tympani, bm: Basilar membrane, tm: Tectorial membrane, Cn: Cochlear nerve, Sva: Stria vascularis, Sg: Spiral ganglion and spiral ganglion cells, Sl: Spiral ligament

Discussion

One of the important causes of hearing and balance impairment is ototoxicity. Hearing loss, tinnitus, imbalance and vertigo are the major complaints caused by ototoxic substances. Tinnitus is the most common and often the first symptom among these complaints (12). The route of administration, cumulative dose, age, dietary factors, serum protein levels, genetic factors, use of additional ototoxic drugs, presence of nephropathy, exposure to noise and history of cranial radiotherapy are among the factors that affect the incidence of ototoxicity (3).

Cisplatin-induced ototoxicity is generally manifested with tinnitus starting at high frequencies and hearing loss. However, it ultimately extends to lower frequencies and affects speech perception. These effects are dose-dependent, cumulative and usually lasting. Histopathological examinations revealed that outer hair cells in the basal and middle parts of the cochlea were areas that were mostly affected by cisplatin ototoxicity (2, 4).

The molecular and cellular mechanisms of cisplatin ototoxicity have not been fully understood. Nevertheless, it is known that oxidative stress may be very important for the pathogenesis of ototoxicity. Cisplatin leads to oxidative damage and apoptosis in the cochlea and outer hair cells by increasing the production of free oxygen radicals. Furthermore, it decreases antioxidant enzyme levels through the excessive production of free oxygen radicals. Along with the consumption of antioxidant enzymes, superoxide, hydrogen peroxide and toxic lipids result in the penetration of calcium into cochlear cells by triggering apoptosis (3). In case of the disruption of stability between the production of free oxygen radicals and the antioxidant defense mechanisms, oxidative stress may lead to cochlear cell damage or death (3, 4).

For the prevention of ototoxicity occurring with the use of cisplatin due to the widespread use of this drug as an antineoplastic drug, experimental studies have been conducted with many antioxidant drugs such as ginkgo biloba (gb), sodium thiosulphate, diethyldithiocarbamate, 4-methylthiobenzoic acid, ebselen and lipoic acid, thymol, vitamin E and steroids (1, 2, 4-7).

In their experimental study, Huang et al. (6) evaluated the effects of gb extract, an anthocyanin, on cisplatin ototoxicity through hearing and histopathological examinations. In the study, both a smaller decrease in hearing thresholds and a lower level of outer hair cell destruction were found in the group receiving gb + cisplatin compared to the group receiving only cisplatin and this difference was statistically significant.

Wang et al. (7) administered sodium thiosulphate, whose autoprotective effect has been known for a long time, during the administration of cisplatin in rats, in the form of intracochlear perfusion at a clinically high therapeutic dose. This strategy was highly successful and it was reported that no signs of hearing loss were observed. In histological analyses, nearly full protection of outer hair cells was observed in the organ of Corti; however, there was a significant loss in hearing and outer hair cells in the cisplatin-treated group.

Rybak (13) found that the use of antioxidants or preservatives such as diethyldithiocarbamate, 4-methylthiobenzoic acid, ebselen, and lipoic acid protected the cochlea against cisplatin damage and prevented hearing loss.

Koçak et al. (5) suggested that thymol, a natural monoterpene phenolic compound, could prevent cisplatin ototoxicity by increasing the antioxidant enzymes and reducing oxidant parameters. Until today, no agent has been widely accepted for use in clinical practice. Thus, alternative effective and protective treatments are still being investigated. In the presented study, we aimed to evaluate audiologically and histopathologically the protective and therapeutic effects of PRP on cisplatin ototoxicity in rats, as it is being used in many areas, especially in recent years, for its antioxidant activity in the prevention of cisplatin ototoxicity. PRP is obtained from autologous whole blood and has crucial roles in bone and soft tissue healing since it includes a high concentration of growth factors and cytokines.

In the literature, there is one study in which Yurtsever et al. (2) investigated whether PRP provided protection against cisplatin ototoxicity. In their study, they compared the study group, in which cisplatin was administered and PRP was used for preventive effect, with the control group, which received intratympanic saline and demonstrated that the number of outer hair cells in the organ of Corti decreased significantly in the PRP-treated group compared to the control group. They reported that PRP could prevent cisplatin-induced ototoxicity. The researchers indicated that the small number of animals used and the fact that the study was conducted with light microscopy were the weaknesses of the study. Compared to our study, it was considered that the difference between the results could be due to the small number of animals used, differences in forming the groups, and the evaluation of hearing at different times after PRP.

Terzi et al. (4), examining the efficacy of astaxanthin as a protective agent against cisplatin-induced ototoxicity, concluded that astaxanthin could protect hearing from cisplatin-induced ototoxicity, prevent cellular degeneration and significantly reduce oxidative stress. The authors reported the limitation of the study as the lack of DPOAE measurement at frequencies higher than 8 kHz, the H&E staining of the cochlea only, and the lack of immunohistochemistry staining to show apoptosis.

Among the studies in the literature conducted in the field of otolaryngology, there are various studies demonstrating the positive effects of PRP on tissue regeneration in tympanic membrane perforations, after rhinoplasty operations, after septoplasty and endoscopic sinus surgery by being absorbed into nasal packings, in vocal cord injuries and acute facial nerve injuries (14-18).

In the data we obtained at the end of the study, it could not be determined by DPOAE that PRP had a protective or therapeutic effect against hearing loss due to cisplatin ototoxicity at frequencies of 2000 Hz and above. In the histopathological evaluation, cisplatin's ototoxic effects were observed at the cellular level and no significant difference was found in terms of the protective or therapeutic efficacy of PRP. No significant antioxidant activity of PRP against cisplatin-induced ototoxicity was found in histopathological evaluation.

According to the histological results of our study, no statistical significance was observed in terms of the cytoplasmic vacuole, cell degeneration and dilatation, nerve degeneration and apoptosis when the cisplatin group and cisplatin + PRP groups were compared.

In the literature, there are various studies on tissue regeneration of PRP; however, limited studies on its effect on ototoxicity are available. As a result of otoacoustic emission and histopathological examinations in our study, it was observed that PRP did not have a significant effect on the protection of hearing and treatment of hearing loss in cisplatin ototoxicity.

Conclusion

For many years, numerous studies have been conducted to find ways to protect against cisplatin ototoxicity. However, no specific agent has been reported that can be transferred to routine clinical practice based on the results obtained from these studies.

We investigated the therapeutic and protective efficacy of PRP against cisplatin ototoxicity in our study. Although the therapeutic and protective efficacy of PRP against cisplatin ototoxicity is found in the literature, we could not obtain statistically significant results in our study. Nevertheless, there is a need for further studies to investigate the effects of PRP on different species at different doses with different routes of administration and duration of treatment.

Ethics Committee Approval: This study was approved by the Experimental Animals Ethics Committee of Recep Tayyip Erdoğan University, Rize, Turkey (decision no: 2017/13, date: 29.03.2017).

Informed Consent: The study does not require patient consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.G., A.Ü., D.Ö., Concept: B.G., A.Ü., Design: B.G., A.Ü., Data Collection and/or Processing: B.G., D.Ö., Analysis and/or Interpretation: B.G., A.Ü., D.Ö., M.B., Literature Search: B.G., A.Ç., Writing: B.G., A.Ü., A.Ç.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Main Points

- Cisplatin-induced ototoxicity is generally manifested with tinnitus starting at high frequencies and hearing loss.
- In the literature, several antioxidant substances were used to avoid and/or prevent this ototoxicity.
- Platelet-rich plasma (PRP) is obtained from autologous whole blood and has crucial roles in bone and soft tissue healing since it includes a high concentration of growth factors and cytokines.
- In the literature reported in the field of otolaryngology, there are various studies demonstrating that PRP has positive effects on tissue regeneration.
- We investigated the therapeutic and protective efficacy of PRP against cisplatin ototoxicity in our study.
- Although the therapeutic and protective efficacy of PRP against cisplatin ototoxicity is found in the literature, we could not obtain statistically significant results in our study.
- Nevertheless, there is a need for further studies to investigate the effects of PRP on different species at different doses with different routes of administration and duration of treatment.

References

1. Ravi R, Somani SM, Rybak LP. Mechanism of cisplatin ototoxicity: antioxidant system. Pharmacol Toxicol 1995; 76: 386-94. [Crossref]
2. Yurtsever KN, Baklaci D, Guler I, Kuzucu I, Kum RO, Ozhamam EU, et al. The protective effect of platelet rich plasma against cisplatin-induced ototoxicity. J Craniofac Surg 2020; 31: 506-9. [Crossref]
3. Taş A, Bulut E, Taş M, Yagız R, Turan P, Huseyinoglu A, et al. Effects of intratympanic steroid on cisplatin ototoxicity: an electrophysiological and ultrastructural study. Int J Hematol Oncol 2018; 28: 104-11. [Crossref]
4. Terzi S, Özgür A, Çeliker M, Mercantepe T, Yilmaz A, Tümkaya L, et al. The protective effect of astaxanthin on cisplatin-induced ototoxicity. Adv Clin Exp Med 2021; 30: 315-21. [Crossref]
5. Koçak İ, Ünal ÖF, Aydoğan E, Doğan R, Akakın D, Köroğlu K, et al. The protective effect of thymol against cisplatin-induced ototoxicity: an experimental animal study. Kbb-Forum 2017; 16: 43-52. [Crossref]

6. Huang X, Whitworth CA, Rybak LP. Ginko biloba extract (Egb 761) protects against cisplatin-induced ototoxicity in rats. Otol Nuerotol 2007; 28: 828-33. [Crossref]
7. Wang J, Lloyd Faulconbridge RV, Fetoni A, Guitton MJ, Pujol R, Puel JL. Local application of sodium thiosulfate prevents cisplatin-induced hearing loss in the guinea pig. Neuropharmacology 2003; 45: 380-93. [Crossref]
8. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; 85: 638-46. [Crossref]
9. Eppley BL, Pietrzak WS, Blanton M. Platelet-rich plasma: a review of biology and applications in plastic surgery. Plast Reconstr Surg 2006; 118: 147-59. [Crossref]
10. Savarino L, Cenni E, Tarabusi C, Dallari D, Stagni C, Cenacchi A, et al. Evaluation of bone healing enhancement by lyophilized bone grafts supplemented with platelet gel: a standardized methodology in patients with tibial osteotomy for genu varus. J Biomed Mater Res B Appl Biomater 2006; 76: 364-72. [Crossref]
11. Hanna R, Trejo PM, Weltman RL. Treatment of intrabony defects with bovine-derived xenograft alone and in combination with platelet-rich plasma: a randomized clinical trial. J Periodontol 2004; 75: 1668-77. [Crossref]
12. Yumusakhuylu AC, Yazici M, Sari M, Binnetoglu A, Kosemihal E, Akdas F, et al. Protective role of resveratrol against cisplatin induced ototoxicity in guinea pigs. Int J Pediatr Otorhinolaryngol 2012; 76: 404-8. [Crossref]
13. Rybak LP. Mechanisms of cisplatin ototoxicity and progress in otoprotection. Curr Opin Otolaryngol Head Neck Surg 2007; 15: 364-9. [Crossref]
14. El-Anwar MW, Elnashar I, Foad YA. Platelet-rich plasma myringoplasty: a new office procedure for the repair of small tympanic membrane perforations. Ear Nose Throat J 2017; 96: 312-26. [Crossref]
15. Sand JP, Nabili V, Kochhar A, Rawnsley J, Keller G. Platelet-rich plasma for the aesthetic surgeon. Facial Plast Surg 2017; 33: 437-43. [Crossref]
16. Kuzucu I, Beriat GK, Ezerarslan H, Ozdemir S, Kocaturk S. Effects of the autologous platelet-rich plasma in nasal pack on postoperative quality of life. J Craniofac Surg 2017; 28: 299-302. [Crossref]
17. Cobden SB, Oztürk K, Duman S, Esen H, Aktan TM, Avunduk MC, et al. Treatment of acute vocal fold injury with platelet-rich plasma. J Voice 2016; 30: 731-5. [Crossref]
18. Cho HH, Jang S, Lee SC, Jeong HS, Park JS, Han JY, et al. Effect of neural-induced mesenchymal stem cells and platelet-rich plasma on facial nerve regeneration in an acute nerve injury model. Laryngoscope 2010; 120: 907-13. [Crossref]