The Effect of Intratympanic Dexamethasone on Hearing Function in Cisplatin Chemotherapy, (Meta-Analysis)

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KEYWORDS
Cisplatin, ototoxicity, dexamethasone, intratympanic, hearing threshold

ABSTRACT
Background: Hearing loss due to cisplatin is still a major health problem. Cisplatin is an antineoplastic agent that is the first line treatment for various malignancies and can cause ototoxicity in the form of bilateral hearing loss. Dexamethasone has the potential to reduce the ototoxic effects of cisplatin. Intratympanic dexamethasone injection allows higher concentrations in the cochlea, and avoids systemic side effects. **Methods:** This study was a meta-analysis of randomized control trial articles with hearing threshold and intratympanic dexamethasone injection vs no treatment as variables. The population are subjects with malignancies receiving cisplatin chemotherapy. The mean difference and standard deviation (Δ Mean + SD) of hearing thresholds in the intervention and control groups was assessed. The hearing frequencies examined were at 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz. **Results:** The database search yielded four eligible articles. There was no significant difference between intratympanic dexamethasone and no treatment at 500 Hz (p = 0.93; MD 0.13; CI95% -2.65 to 2.91), at 1000 Hz (p = 0.19; MD 2.09; CI95% -1.02 to 5.20), at 2000 Hz (p = 0.56; MD 0.21; CI95% -0.49 to 0.90), at 4000 Hz (p = 0.36; MD -0.46; CI95% -1.45 to 0.53), and at 8000 Hz (p = 0.13; MD -4.97; CI95% -21.75 to 1.46). **Conclusion:** There is no effect of intratympanic dexamethasone on hearing function in malignant patients with cisplatin chemotherapy. However, further RCT research using high frequency audiometry are needed to confirm this finding.

Introduction

Cisplatin is a platinum-based antineoplastic agent which is the first line in the treatment of various malignancies.(1)(2) Cisplatin use carries risk of ototoxicity which will manifests as bilateral permanent hearing loss.(3) It accounts for around 500,000 cases of hearing loss per year, with a prevalence rate of 49.21%. Ten million people worldwide are estimated to be at risk of suffering from malignancies that are commonly treated using cisplatin, with an estimated number of malignancy cases receiving cisplatin therapy of one million cases per year.(4)

Cisplatin ototoxicity can be attributed to the increasing formation of Reactive Oxygen Species (ROS) inside the cochlea.(5) Cisplatin stimulates various enzymatic systems and inactivates endogenous antioxidant systems.(3) Excessive ROS production disrupts the antioxidant system and causes apoptosis in outer hair cells (OHC), spiral ganglion cells, supporting cells, and stria vascularis. Inflammation caused by cisplatin in the cochlea is also suspected as a mechanism for ototoxicity. This results in cochlear cell apoptosis which clinically manifests as bilateral and permanent high frequency sensorineural hearing loss and tinnitus.(6)

Intratympanic dexamethasone injection has been used on various inner ear disorders such as Meniere`s disease, sudden deafness, and tinnitus.(7) Dexamethasone protects against apoptosis induced by Tumor Necrosis Factor–alpha (TNF-α) through activation of the PI3K/Akt and NFκB pathways.(8) Dexamethasone also reduces ROS production and inflammation in the inner ear.(9)(10) Intratympanic route of administration allows for higher concentrations in cochlea and avoids systemic steroid effects.(11)

Clinical trials had been done on this subject. A clinical trial of intratympanic dexamethasone injection in 23 patients receiving cisplatin chemotherapy with the result that the difference in mean hearing threshold between the treated and control ears reached 10 db.(12) A different study comparing the effectiveness of intratympanic N-acestylcysteine and intratympanic dexamethasone on cisplatin ototoxicity gave results of a better otoprotective effect when administering N-acestylcysteine, while in the dexamethasone group there was a significant increase in hearing threshold at a frequency of 8 kHz.(13) In another study, intratympanic

dexamethasone given immediately before cisplatin administration only provided a minimal protective effect against cisplatin ototoxicity.(14)
The objective of this meta-analysis is to compare the degree of hearing loss of intratympanic dexamethasone vs no treatment in prevention of cisplatin ototoxicity.

Material and methods

Data Sources and Search Strategy

The sample for this study is articles that have been selected in the form of randomized controlled trials. Article searches were carried out by searching electronic databases on the PubMed central and publisher website, Cochrane library, ScienceDirect, and SAGE journals with a search strategy using Boolean operators: ("cisplatin" OR CDDP) AND (intratympanic OR transtympanic) AND dexamethasone AND (ototoxic OR ototoxicity OR "hearing loss").

Inclusion and Exclusion Criteria

Outcome for this study were defined before research began. Hearing loss in the form of mean difference of hearing threshold before and after treatment is the primary outcome. The inclusion criteria were as follows: Randomized Controlled Trial (RCT) research design, evaluation by assessing the hearing threshold in dBHL units, and data is displayed as mean + standard deviation (SD) or mean, upper and lower limits of the confidence interval, and sample size. Trials in which patients with any malignancies receive cisplatin and intratympanic dexamethasone as the treatment and no treatment as control were included. Trials in which the research reports in languages other than English and Indonesian, data is incomplete, or full manuscripts cannot be downloaded were excluded.

Data Extraction and Statistical Analyses

The next step is to combine the results of research that has carried out critical appraisal. All research article data that passed the eligibility stage underwent meta-analysis. Data analysis used Review Manager 5.4 software issued by the Cochrane Collaboration. The meta-analysis process includes calculating the treatment effect and confidence interval for each study, calculating heterogeneity (I^2) to determine the discrepancy in the treatment effect in each article. If $I^2 < 50\%$, then heterogeneity is low so the fixed effect method is used. If the variation in article I^2 is > 50% then heterogeneity is high so the random effect method is used.

Critical Appraisal and Risk of Bias Assessment

Critical appraisal and risk of bias assessment was carried out independently by the authors and the consultant supervisor from the Neuro-otology division. The articles were screened and appropriate studies are included in this meta-analysis. The quality of the articles was assessed using a tool appropriate to the type of research, namely RCT studies using the Risk of Bias 2 (RoB2) algorithm developed by Cochrane. Assessment using RoB2 helps to identify and examine bias in RCTs. Biases that may arise in an RCT study are randomization process bias, bias related to changes of intervention, bias related to missing outcome data, bias in outcome measurement, and bias related to selection of results reporting. These biases are summarized in questions in five domains.

Results

Included studies

A search of electronic databases resulted in 204 articles being identified. Four articles were screened and their suitability was assessed. No articles were excluded due to risk of bias, resulting in a total of four articles included in the meta-analysis study. The PRISMA flow diagram is illustrated on figure 1.

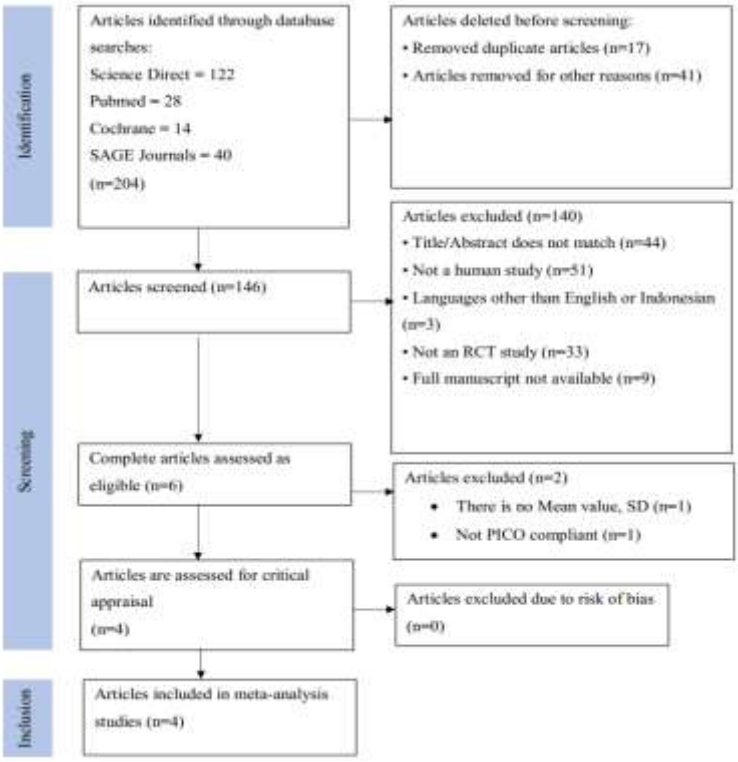

Figure 1. PRISMA flow diagram

Basic data and characteristics of the study population included in this meta-analysis are presented in Table 1 and Table 2. The four studies had a total of 158 research subjects, with the most in the study by Gupta et al being 100 research subjects. The populations of the four included studies were patients with malignancies ranging in age from 40 to 80 years. The types of malignancies suffered by research subjects in these four studies varied. The study by Gupta et al limited the type of malignancy to the head and neck, whereas in the three other studies the location of the malignancy in the research subjects was not limited. The similarities in the types of malignancies of the research subjects in these four studies were all types of malignancies that were treated using cisplatin.

Table 1. Included studies

Researcher	Year	Journal	Country of Origin	Article title
Gupta *et al.,*	2023	Cureus	India	*Intratympanic Dexamethasone Role in Hearing Protection in Cancer Patients*
Marshak *et al.,*	2014	Otolaryngology - Head and Neck Surgery	Israel	*Prevention of Cisplatin-Induced Hearing Loss by Intratympanic Dexamethasone: A Randomized Controlled Study*
Moreno *et al.,*	2022	Ear & Hearing	Spain	*Evaluating the Efficacy of Intratympanic Dexamethasone in Protecting Against Irreversible Hearing Loss in Patients on Cisplatin-Based Cancer Treatment: A Randomized Controlled Phase IIIB Clinical Trial*
Nasr *et al.,*	2018	Indian Journal of Otology	Egypt	*Treatment of Cisplatin-induced Ototoxicity by Intra-tympanic Corticosteroid Injection*

The risk of bias of these studies are shown on figure 2 and figure 3. Risk of bias assessment with the RoB2

tool produced three articles with low risk of bias and one article with some concerns. The results of some concerns were obtained in an article by Gupta in 2023 which was obtained in domain 1 (randomization process). The article by Gupta was found to be concerned with the randomization process, where the side of the ear that received intervention was determined by the side of the malignant lesion in the research subject.

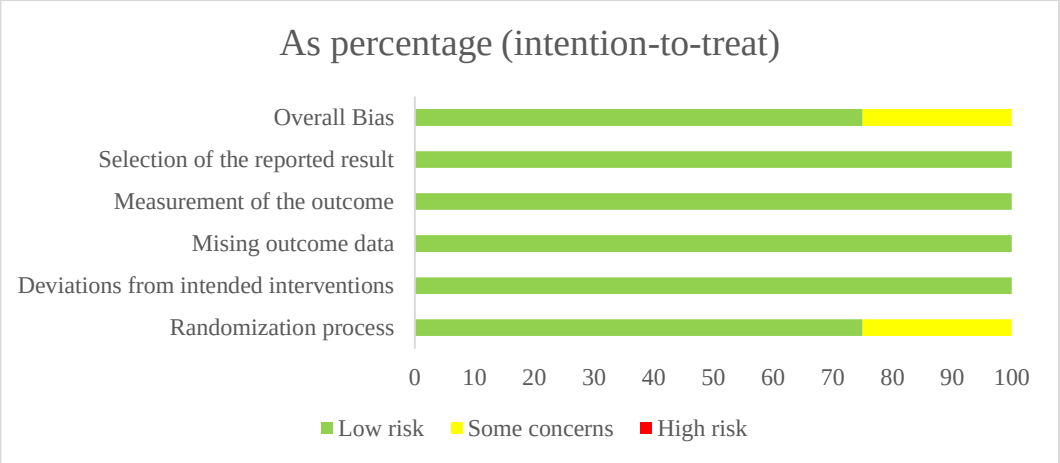

Figure 2. Risk of bias graph for all included studies

Figure 3. Risk of bias for all included studies

Effects of intervention

Meta-analysis of the effect of intratympanic dexamethasone on hearing thresholds in malignant patients with cisplatin chemotherapy measured the mean difference in outcomes before and after treatment in each group. The difference in the mean and standard deviation of the differential (Δ Mean + SD) hearing thresholds in the intervention and control groups in this meta-analysis is attached in the Table 2.

Table 2. Baseline characteristics and data of all included studies

No.	Study, country of origin	Outcome	Sample size		Average age	Sex ratio (M:F)	Frequency (Hz)	Δ Mean + SD*		Concentration, dose (dexamethasone)	Mean cumulative dose (cisplatin) ± SD
			I	C				I	C		
1	Gupta *et al.*, 2023	Hearing threshold (dBHL)	100	100	58.2±6.3	17:8	500	6.45 + 3.76	5.95 + 3.17	Dexamethasone 4mg/mL, 0.5-0.7 mL	NA
							1000	1 ± 2.05	0.95 ± 2.55		
							2000	-3.35 ± 2.6	-3.55 ± 2.52		
							4000	8.45 ± 3.46	8.9 ± 3.78		
							8000	10.45 ± 4.05	14.2 ± 3.38		
2	Marshak *et al.*, 2014	Hearing threshold (dbHL)	15	15	61.5± 9.8	2:3	500	-0.4 ± 8.22	0 ± 7.3	Dexamethasone phospate 10 mg/ml, 0.7 – 1.0 ml	517 ± 184 mg
							1000	0 ± 9	0.8 ± 9.13		
							2000	0.4 ± 14.8	-0.4 ± 9.46		
							4000	0.7 ± 17.5	2 ± 17.65		
							8000	7.4 ± 22.95	11.3 ± 23.43		
3	Moreno *et al.*, 2022	Hearing threshold (dBHL)	23	23	60 ± 7.5	18:5	500	2.7 ± 6.8	-1.8 ± 7.7	Dexamethasone (Fortecortin) 40 mg/5 mL, 1 mL	444.87 ± 235.2 mg
							1000	2.8 ± 8.76	-4 ± 9.96		
							2000	2.3 ± 13.72	-3.2 ± 11.14		
							4000	6.3 ± 35.5	0.2 ± 17.03		
							8000	20.5 ± 22.46	15.3 ± 23.45		
4	Nasr *et al.*, 2018	Hearing threshold (dbHL)	20	20	57.9±6.797	13:7	500	-0.85 ± 3.99	2.6 ± 5.59	Dexamethasone phospate, 4 mg/ ml, 0.3–0.5 ml	546.3 ± 111.58 mg
							1000	3.95 ± 5.8	0.45 ± 5.325		
							2000	0.69 ± 7.39	1.998 ± 5.23		
							4000	13.15 ± 10.2	15 ± 11.78		
							8000	17.45 ± 14.54	31 ± 11.77		

Table 2 shows the difference in mean hearing thresholds at frequencies of 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz in the four studies summarized in this meta-analysis. The mean difference value of hearing threshold was obtained by subtracting the hearing threshold after intervention (cisplatin chemotherapy + intratympanic dexamethasone in treatment group, and cisplatin only in control group) from the baseline hearing threshold (before treatment). A negative value indicates the hearing threshold after intervention is lower than the baseline hearing threshold. The data obtained is continuous data (hearing threshold values in dBHL units) which are measured with the same measuring units, so the analysis used is unstandardized mean difference (MD). The SD value of the mean difference is calculated using the differential standard deviation formula. Data processing and analysis in this research was carried out using Microsoft Excel 365 and Review Manager 5.4 software.

Effects of intervention

Meta-analysis of the effect of intratympanic dexamethasone on hearing thresholds measured by the average hearing threshold before and after administration of intratympanic dexamethasone. The hearing frequencies examined in the articles included in the meta-analysis were 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz.

Forest plot results of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 500 Hz are presented in Figure 4. Meta-analysis plot of the effect of intratympanic dexamethasone on hearing threshold at 500 Hz showed a combined effect size of 0.09. The results of the analysis above show high heterogeneity between research articles (I^2=70%), so the random effect method was used to combine the results. These results show that in the studies included in this meta-analysis, the difference in hearing thresholds in the intratympanic dexamethasone treatment group was lower than that of controls at a frequency of 500 Hz. The results obtained were not statistically significant (p = 0.93; MD 0.13; CI95% -2.65 to 2.91).

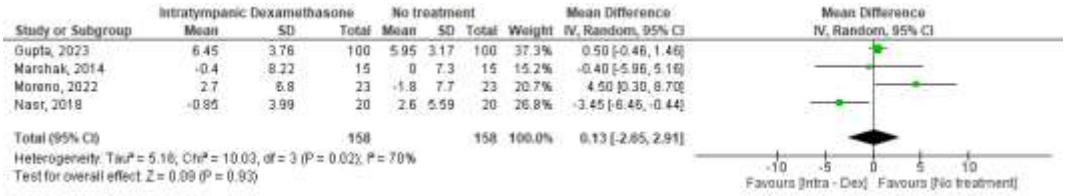

Figure 4. Forest plot of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 500 Hz

Forest plot results of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 1000 Hz are presented in Figure 5. Meta-analysis plot of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 1000 Hz showed a combined effect size of 1.32. The results of the heterogeneity analysis showed high heterogeneity between research articles (I^2=68%), so the random effect method was used to combine the results. These results show that in the studies included in this meta-analysis, the difference in hearing thresholds in the intratympanic dexamethasone treatment group was lower than that of controls at a frequency of 1000 Hz. The results obtained were not statistically significant (p = 0.19; MD 2.09; CI95% -1.02 to 5.20).

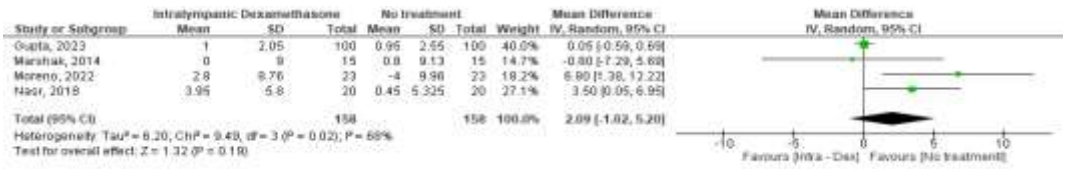

Figure 5. Forest plot of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 1000 Hz

Forest plot results of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 2000 Hz are presented in Figure 6. Meta-analysis plot of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 2000 Hz showed a combined effect size of 0.58. The results of the analysis above show that there is no heterogeneity between research articles (I^2=0%), so the fixed effect method is used to combine the results, so the random effect method is used to combine the results. These results show that in the

studies included in this meta-analysis, the difference in hearing thresholds in the intratympanic dexamethasone treatment group was lower than that of controls at a frequency of 1000 Hz. The results obtained were not statistically significant (p = 0.56; MD 0.21; CI95% -0.49 to 0.90).

Figure 6. Forest plot of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 2000 Hz

Forest plot results of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 4000 Hz are presented in Figure 7. Meta-analysis plot of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 4000 Hz showed a combined effect size of 0.36. The results of the analysis above show that there is no heterogeneity between research articles (I^2=0%), so the fixed effect method is used to combine the results. These results show that in the studies included in this meta-analysis, the hearing threshold with intratympanic dexamethasone treatment was lower than that of controls at a frequency of 4000 Hz. The results obtained were not statistically significant (p = 0.36; MD -0.46; CI95% -1.45 to 0.53).

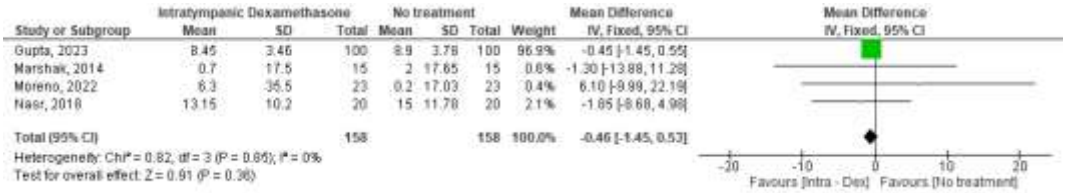

Figure 7. Forest plot of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 4000 Hz

Forest plot results of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 8000 Hz are presented in Figure 8. Meta-analysis plot of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 8000 Hz showed a combined effect size of 1.51. The results of the analysis above show high heterogeneity between research articles (I^2=58%), so the random effect method was used to combine the results. These results show that in the studies included in this meta-analysis, the difference in hearing thresholds in the group treated with intratympanic dexamethasone was higher than in controls at a frequency of 8000 Hz. The results obtained were not statistically significant (p = 0.13; MD -4.97; CI95% -21.75 to 1.46).

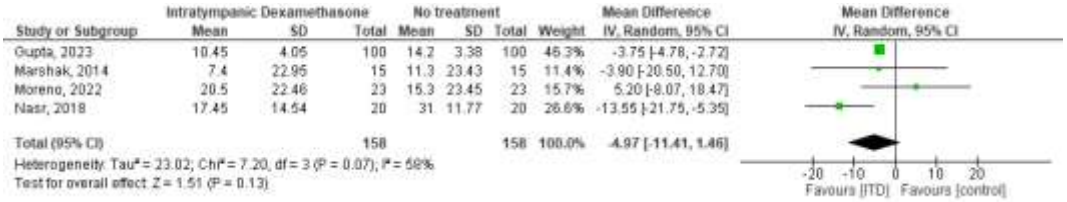

Figure 8. Forest plot of the effect of intratympanic dexamethasone on hearing threshold at a frequency of 8000 Hz

Discussion

The total sample size in this study was 158 research subjects. There are differences in sample size for each study included in this meta-analysis, with the largest sample size in the study by Gupta et al, namely 100 research subjects, while the other three studies ranged from 15 – 23 research subjects. This difference can be caused by the recruitment process of research subjects in each study. The difference in sample size was also caused by dropouts during the study. Causes of drop out include loss to follow up, subjects withdrawing consent to research, subjects die, and subjects experience other illnesses so they cannot continue therapy.(9,12,14) The average age of the subjects in this study was around 60 years. The aging process can interact with ototoxic drugs and produce hearing loss that is more severe than that resulting from the aging

process alone.(15)
An increase in the difference in hearing threshold along with this frequency occurred in the intervention group and control group which can be seen in Table 5.3. It is known that cisplatin administration increases inflammation in the cochlea, one of which is mediated by TNF-α.(5) This TNF-α-mediated ototoxic effect is greater in the basal cochlea which may explain the characteristic cisplatin-induced ototoxicity that appears earlier at high frequencies.(8)
Intratympanic dexamethasone reduce the difference in hearing thresholds at frequencies of 4000 Hz and 8000 Hz with a combined effect size of 0.36 and 1.51. These results are not statistically significant (p=0. 36 and p=0.13, respectively). This result is shown in the forest plot in Figure 7 and Figure 8, where the combined effect diamond is located in the favor Intra-Dex area with the diamond part intersecting with the line of no effect. Interesting results were obtained in several articles where there were several frequencies where the control group experienced smaller changes in hearing thresholds than the intervention group. For each frequency examined, there was at least one article that reported these results. This is obtained up to a frequency of 8000 Hz.(12) These results might indicate that intratympanic dexamethasone has more beneficial otoprotective effects at high frequencies than at low frequencies.
It is known that the basal cochlea is a high frequency area while the apex of the cochlea is a low frequency area.(10) Dexamethasone enters the perilymph fluid by crossing the round window membrane.(16) The basal location of the cochlea directly adjacent to the round window may explain the better otoprotective potential of dexamethasone at high frequencies. In addition, the basal cochlea has lower levels of glutathione, which is an endogenous antioxidant, than the cochlear apex, which can explain the vulnerability of OHCs in the basal cochlea to ROS toxicity.(17) Dexamethasone also protects the cochlea from inflammation mediated by the proinflammatory cytokine TNF-α, with effects more pronounced at the basal cochlea than at the apex.(8)
The cumulative dose of cisplatin in these four articles ranged from 444.87 – 546.3 mg. There is an increase in the incidence of sensorineural hearing loss with the use of a cumulative dose of cisplatin > 200 mg/m2 in nasopharyngeal carcinoma patients receiving chemotherapy and radiotherapy.(18) Different results were reported in a regression meta-analysis study which stated that there was no correlation between the dose of cisplatin and/or carboplatin and the prevalence of hearing loss, although in this study there were research limitations where the definition of hearing loss was used in a binary manner.(4)
High-frequency audiometry examination was not carried out in the four articles included in this meta-analysis, where the lowest frequency range was examined starting from 125 Hz and the highest up to 8000 Hz. Hearing threshold examinations using audiometry are conventionally carried out up to a frequency of 8000 Hz, while high frequency audiometry is examined at frequencies of more than 8000 Hz.(4) High frequency audiometry examination increases the likelihood of ototoxicity detection compared with audiometry at conventional frequencies.(19) This may result in a lower number of ototoxicity detections than is actually the case. Studies that include high frequency audiometry are more likely to detect a higher prevalence of cisplatin ototoxicity.(4) ANM examination carried out from a frequency of 0.25 kHz to 20 kHz is the ideal range to detect cisplatin ototoxicity maximally.(19) The weakness of high frequency ANM examination is the long duration of the examination which may be difficult to apply to patients with malignancies who often present with poor general conditions.(9)

Conclusion

In conclusion, this meta-analysis suggests that there is no effect of intratympanic dexamethasone on hearing function in malignant patients with cisplatin chemotherapy. These results indicate the need to conduct further RCTs regarding the use of intratympanic dexamethasone where hearing threshold examination is carried out using high frequency audiometry.

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