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THE EFFECTS OF CISPLATIN AND PACLITAXEL THERAPY WITH AND WITHOUT GINKGO BILOBA ON HEARING THRESHOLD AND FUNCTION OF COCHLEAR OUTER HAIR CELLS IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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ABSTRACT
Background: Cisplatin chemotherapy is one of the main modalities of therapy that is often given to patients with nasopharyngeal carcinoma which is often combined with Paclitaxel, one of the side effects of Cisplatin can cause damage to the outer hair cells of the cochlea which in turn causes hearing loss caused by the formation of free radicals that cause damage to the outer hair cells of the cochlea. Cochlear outer hair cell death. Ginkgo Biloba is an antioxidant that has an autoprotective effect against the ototoxicity effect of Cisplatin by inhibiting the formation of free radicals.

Objective: To determine the effect of cisplatin and paclitaxel therapy with and without ginkgo Biloba on hearing threshold and function of cochlear outer hair cells in patients with nasopharyngeal carcinoma.

Methods: This study is a double-blind randomized control trial with a pre-post test design, conducted on 18 nasopharyngeal carcinoma patients receiving Cisplatin and Paclitaxel chemotherapy. Subjects were divided into control groups (without giving 80 mg Ginkgo Biloba extract) and treatment groups (who received 80 mg Ginkgo Biloba extract). Pure tone audiometry, tympanometry, and Distortion Product Otoacoustic Emission were examined before chemotherapy, and after the first and second chemotherapy.

Results: There were significant results in the hearing threshold p value = 0.034 ($p < 0.05$) and DPOAE results with p value = 0.047 ($p < 0.05$) after the second chemotherapy. There were significant results for the DPOAE examination after the second chemotherapy with p value = 0.010 ($p <0.05$) in 16 patients (6 treatment patients and 10 control patients) with all type A tympanometry results.
Conclusion: Administration of Ginkgo Biloba 80 mg per day can affect the function of cochlear outer hair cells in nasopharyngeal carcinoma patients with Cisplatin and Paclitaxel therapy.

Keywords: DPOAE, Hearing Threshold, Cisplatin, Ginkgo Biloba, Carcinoma nasopharynx

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INTRODUCTION

The average incidence of NPC in Indonesia is 6.2 per 100,000 population or 12,000 new cases every year, with the ratio between men and women being 2-3:1.[1] In Indonesia, the incidence of NPC is almost evenly distributed in all regions, namely 3.9 per 100,000 events every year.[2] Incidence in Makassar, South Sulawesi province, reported at Dr. Wahidin Sudirohusodo Hospital for the period January 2004 to June 2007 found 33% of malignancies in the ear, nose and throat.[3] While for a period of 8 years (2011-2019) found 280 cases of NPC with a ratio between men and women is 2:1, were found 188 cases in men (67%) and 92 cases in women (33%).[4]

The most widely used chemotherapy drugs in NPC therapy are platinum groups and are more effective when used in combination. Platinum class chemotherapy drugs, such as Cisplatin and Carboplatin, are effective therapeutic regimens for NPC. However, with its ototoxic side effects, it can cause 60% of patients to experience hearing loss which results in difficulty in communicating with their environment and also isolation. [5]

Cisplatin (cis-diamminedichloroplatinum) is one of the most widely used chemotherapy drugs. Cisplatin has an ototoxic side effect. The ototoxic effect of Cisplatin is irreversible, progressive, bilateral sensorineural hearing loss starting at a frequency of 8000 Hz which will eventually hit a lower frequency if therapy is continued and is accompanied by tinnitus. Cisplatin damages the outer hair cells of the cochlea progressively from the base to the apex so that sensorineural hearing loss occurs starting at high frequencies. The ototoxic mechanism of Cisplatin occurs through an apoptotic process induced by an increase in free radicals in the inner ear induced by cisplatin.[6] Damage to outer hair cells results in disturbances in the otoacoustic emission process. Cisplatin-induced cochlear outer hair cell damage occurs from the third day at the base and continues to the apex. [7]

However, to reduce the side effects of using Cisplatin chemotherapy, antioxidant drugs can also be used. In this study, the antioxidant used was Ginkgo Biloba Extract because Ginkgo Biloba leaf extract has the advantage of containing flavonoids and terpenoids, two important chemical compounds that act as antioxidants. Several animal experiments have proven this, but human studies are still needed to confirm the autoprotective role of Ginkgo Biloba against the ototoxic effects of Cisplatin in humans. [8,9] Ginkgo biloba inhibits the increase of Cisplatin-induced Reactive Oxygen Species (ROS) by inhibiting the formation oxidative nicotinamide adenine dinucleotide phosphate (NADPH). In addition, ginkgo biloba also prevents endoplasmic reticulum stress and DNA damage, resulting in decreased caspase-12 and P53. By inhibiting endoplasmic reticulum stress, DNA damage and increased ROS, Ginkgo Biloba reduces the apoptotic process of outer hair cells, so that hearing loss will not occur. [10]

Audiological monitoring to prevent hearing loss due to ototoxic drugs is very important, because based on this we can change drug doses, change drugs or give antioxidant drugs, and provide explanations to patients, so that more severe sensorineural hearing

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loss can be avoided and the patient is mentally prepared with risks that will occur.[11] The electrophysiological tool used to quickly and objectively determine the condition and function of the outer cochlear hair cells is the otoacoustic emission (OAE). Cochlear outer hair cells emit emissions that are captured by the OAE. Distortion product otoacoustic emission (DPOAE) can detect responses at high frequencies which are sensitive frequencies for detecting ototoxicity. [6]

The best way to reduce the effect of ototoxicity is by early detection, because there is no clinically proven prevention without reducing the anti-neoplastic effect. Pure tone audiometry examination can be one of the means for early detection of ototoxic hearing loss. [5]

METHOD

Study this is quasi-experimental clinical trial. Participants were obtained from the units ENT outpatient clinic. Request permission from patients who meet the criteria using an informed consent form . This research has met the requirements of the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University with the recommendation of ethical approval number 414/UN4.6.4.5.31/PP36/2021

Research subjects are NPC patients who will treat Cisplatin and Paclitaxel chemotherapy regimen, subject study shared Becomes two groups that is group treatment that gets Extract Ginkgo B iloba (EGB) 80 mg/day for 1 month and gets chemotherapy Cisplatin and paclitaxel and group control is NPC patients receiving Cisplatin and Paclitaxel. Treatment without therapy EGB 80 mg/day. EGB 80 mg given once per day started since 3 days before chemotherapy cycle first until with 3 days after cycle chemotherapy second. Done inspection pure tone audiometry, tympanometry and Distortion Product Otoacoustic Emission (DPOAE) examination on all research subjects before chemotherapy, audiometry and DPOAE were repeated 3 days after the first and second cycles of administration.

Criteria inclusion among others, NPC patients who first received chemotherapy combination regimen of Cisplatin and Paclitaxel cycle first and second, aged 20-60 years and sufferers could follow as well as understand instructions in inspection pure tone audiometry. Criteria exclusion in research this is patients who have history or currently suffer disease infection ear middle and deep or abnormality congenital ear outside and sufferer with history or temporary get drugs that are ototoxic . Taking sample done by random with double-blind

During the period 3 months time that is from June 2021 to with In August 2021, 18 NPC patients were found and all of them could complete inspection until end study , 18 patients divided into 2 groups, namely the treatment and control groups. The hearing threshold and function of the cochlear outer hair cells were analyzed separately to obtain 36 ear

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data from 18 patients. Prior to performing the DPOAE examination, all ear samples were examined for a tympanogram.

Data analyzed with SPSS version 23**.** The statistical test procedure used the chi-square test with the significance of the test determined based on the P-value <0.05 for a threshold analysis listen and fisher's exact test if there is a value of a/b/c/d < 5 for analysis function cell hair outside cochlea .

RESULTS

The general characteristics of patients with malignant tumors who were the subject of the study included age, gender, and diagnosis.

Table 1. Distribution Sample Based On Characteristics Age, Type Gender And Stage Of Carcinoma Nasopharynx

Variable	Group				p
	Treatment		Control		
	n	%	n	%	
Age :					
<30 years old	0	0.0	3	33.3	0.121*
30-39 years old	3	33.3	4	44.4	
40-49 years old	4	44.4	2	22.2	
50-59 years old	2	22.2	0	0.0	
Gender :					
Male	6	66.7	7	77.8	1,000**
Woman	3	33.3	2	22.2	
NPC Stage:					
Stage II	1	11.1	1	11.1	0.138*
Stage III	5	55.6	1	11.1	
Stage IV A	2	22.2	5	55.6	
Stage IVB	1	11.1	2	22.2	
Amount	9	100	9	100	

Description : * Chi square test
** Fisher's exact test

Most NPC patients in the group treatment is on group 40-49 years old that is as much as 33.3%, and in the group control is in the group 30-39 years old that is a total of 44.4. Not found meaningful relationship between the two group for difference average age patient with mark p = 0.121 (p > 0.05) .

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Based on type sex showed that most NPC patients is male gender, namely 13 samples (72.2%) and female as many as 5 samples (27.8%) and the fisher extract test was carried out with the results of p = 1,000 (p > 0.05) which means that there is no significant relationship between the two variables, which means that the subject is homogeneous.

According to the most NPC stage from study this was stage IV A as many as 7 patients (38.9%) and the least is stage II as many as 2 patients (11.1%), chi squared test was performed with the results of p = 0.138 (p > 0.05) which means that there is no significant difference which means that the subject is homogeneous.

Table 2. Characteristics Research data by Tympanometry examination Before Chemotherapy

Tympanometry	treatment	Control	Amount
Type A	6 (3 3.3 %)	10 (55.6%)	1 6 (4 4.4 %)
Type As	5 (2 7.8 %)	4 (2 2.2 %)	9 (25.0%)
Type B	5 (27.8%)	2 (11.1%)	7 (19.4%)
Type C	2 (11.1%)	2 (11.1 %)	4 (11.1 %)
Amount	18 (100%)	18 (100%)	36 (100%)

Table 2 shows the results of different tympanometry examinations before being given Cisplatin chemotherapy. In fact, only part of the data (44.2 %) showed tympanometry results of type A which described normal middle ear conditions, and most of the data (55.8 %) showed tympanometry results other than type A which described abnormalities in the middle ear.

Table 3. Hearing Threshold before chemotherapy, after chemotherapy first and after chemotherapy second

Diagnosis threshold of hearing	**Before chemotherapy**		**p**
	Treatment	**C control**	
NH	5 (27.8%)	8 (44.4%)	0.395
Mild CHL	6 (3 3.3%)	8 (44.4 %)	
Moderate CHL	3 (16.7%)	2 (11.1%)	
Moderate MHL	1 (5.6%)	0 (0.0%)	
Moderate Severe MHL	1 (5.6%)	0 (0.0%)	
Severe MHL	2 (11.1 %)	0 (0.0 %)	
Diagnosis threshold of hearing	**After chemotherapy _ first**		**p**
	Treatment	**Control**	
NH	7 (38.9 %)	8 (44.4%)	

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Mild CHL	6 (3 3.3%)	6 (33.3 %)	0.216
Moderate CHL	1 (5.6 %)	1 (5.6 %)	
Mild MHL	0 (0.0 %)	3 (16.7 %)	
Severe MHL	2 (11.1 %)	0 (0.0%)	
Profound MHL	2 (11.1 %)	0 (0.0 %)	
Diagnosis threshold of hearing	**After second chemotherapy**		**p**
	Treatment	**C control**	
NH	10 (55.6 %)	5 (27.8 %)	
Mild CHL	3 (16.7%)	3 (16.7%)	
Moderate CHL	1 (5.6%)	0 (0.0%)	
Mild SNHL	0 (0.0%)	2 (11.1 %)	
Moderate Severe SNHL	1 (5.6%)	0 (0.0%)	0.034
Mild MHL	0 (0.0%)	7 (38.9%)	
Moderate Severe MHL	3 (16.7%)	1 (5.6%)	

Description: NH = Normal Hearing
CHL = Conductive Hearing Loss
SNHL = Sensorineural Hearing Loss
MHL = Mixed Hearing Loss

From table 3, it is found that the distribution of the highest hearing threshold before chemotherapy in the treatment group was mild CHL with 6 ears (33.3%) and in the control group, the highest hearing threshold was NH and CHL, namely 8 ears (44.4%). The Chi Square statistical test was performed, obtained a p-value = 0.395 (p>0.05), which means that there is no statistically significant difference between the treatment group and the control group. After chemotherapy first obtained threshold hear most in the group treatment were NH in 7 ears (38.9%) and in the group, control is NH as much as 8 ears (44.4%). The Chi Square statistical test was carried out, it was obtained a p-value = 0.034 (p>0.05) which means there is a meaningful difference statistically between-group treatment and group control.

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Table 4. DPOAE results before chemotherapy , after chemotherapy first and after chemotherapy second

Group	DPOAE		p
	Pass	Refer	
Before Chemotherapy			
With EGB80	12 (66.7%)	6 (33.3%)	0.471
Without EGB80	14 (77.8%)	4 (22.2%)	
After First Chemotherapy			
With EGB80	11 (61.1%)	7 (38.9%)	1,000
Without EGB80	10 (55.6%)	8 (44.4%)	
After Second Chemotherapy			
With EGB80	12 (66.7%)	6 (33.3%)	0.047
Without EGB80	6 (33.3%)	12 (66.7%)	

From table 4 we get DPOAE results before chemotherapy the highest DPOAE results in the group treatment (with EGB80) is PASS results were 12 ears (66.7%) and in the group control (without EGB80) result the highest number was PASS with 14 ears (77.8%) . The Independent Sample Test statistical test was carried out and it was obtained p value = 0.471 (p> 0.05) which means not statistically there is difference mean among second group.

After chemotherapy first the highest DPOAE results in the group treatment is PASS results were 11 ears (61.1%) and in the group control results The highest number was PASS with 10 ears (55.6%). The Independent Sample Test statistical test was carried out and it was obtained p value = 1,000 (p> 0.05) which means no there is meaningful difference between second group by statistics.

After chemotherapy second the highest DPOAE results in the group treatment is PASS results were 12 ears (66.7%) and in the group control results the highest number is REFER as many as 6 ears (33.3%). The Independent Sample Test statistical test was carried out and it was obtained p value = 0.047 (p < 0.05) which means there is meaningful difference between second group by statistics.

From initial data tympanometry (Table 2) obtained 16 ears (44.4%) with results tympanometry type A which consists of of 6 ears in the group treatment and 10 ears in the group control. From result this we process back to statistical test special for ear with results Tympanometry type A and obtained DPOAE results before chemotherapy all Pass on group treatment and group control. After chemotherapy first found in the group treatment all ear result keep pass and on group control of 10 ears that pass down into 6 ears , and carried out the Fisher Exact Test, it was obtained p value = 0.234 (p> 0.05), which means not statistically there is meaningful relationship between the two group.

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DPOAE results after chemotherapy second found in the group treatment result keep pass on all ear and on the group control pass results as much as 3 ears. Statistical test performed with the Fisher Exact Test and obtained result p= 0.010 (p<0.05) which means statistically there significant difference among second group (table 5).

Table 5. DPOAE results with tympanometry type A

Group	DPOAE		p
	Pass	Refer	
Before Chemotherapy			
Treatment	6 (50.0%)	0 (0.0%)	-
Control	10 (50.0%)	0 (0.0%)	
After First Chemotherapy			
Treatment	6 (50.0%)	0 (0.0%)	0.234*
Control	6 (50.0%)	4 (100%)	
After Second Chemotherapy			
Treatment	6 (66.7%)	0 (0.0%)	0.010*
Control	3 (33.3%)	7 (100%)	

*Fisher Exact Test

Table 6. Threshold results hear with tympanometry type A

Group	Threshold Diagnosis Hear					p
	NH	Mild CHL	Mild MHL	Mild SNHL	Profound MHL	
Before Chemotherapy						
Treatment	3 (33.3%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,000*
Control	6 (66.7%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
After First Chemotherapy						
Treatment	3 (33.3%)	3 (60.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Control	6 (66.7%)	2 (40.0%)	2 (100%)	0 (0.0%)	0 (0.0%)	0.309**
After Second Chemotherapy						
Treatment	4 (50.0%)	2 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Control	4 (50.0%)	0 (0.0%)	3 (100%)	2 (100%)	1 (100%)	0.113**

*Fisher Exact Test
** Chi Square

From table 6, the diagnosis of hearing threshold before chemotherapy was obtained in the treatment group from 6 ears consisting of 3 ears with NH hearing threshold (50%) and 3 ears with mild CHL hearing threshold (50%) and in that group, the most hearing control

Xi'an ShiyouDaxueXuebao (ZiranKexue Ban)/
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threshold was NH (60%). There is no statistically significant difference between the two groups (p=1,000). After the first chemotherapy, the distribution of hearing threshold was still the same in the treatment group, namely 3 ears with NH (50%) and 3 ears with mild CHL (50%) and in the control group, the highest hearing threshold was NH (60%). The Chi-Square test was performed and the results were p=0.309 (p>0.05), which means that there was no statistically significant difference between the two groups. After the second chemotherapy, the highest hearing threshold in the treatment group was NH (66.7%) and in the control group was NH (60%). The Chi-Square test was performed and the results were p=0.113 (p>0.05), which means that there was no statistically significant difference between the two groups.

DISCUSSION

Characteristics of Research Sample

Most of our research subjects were men with the highest age range from 30 to 39 years, namely 38.89%. This finding is similar to a study conducted by Jayalie et al in 2016 at Cipto Mangunkusumo Hospital Jakarta.[12] They reported that 68.3% of NPC patients were male and 80.2% were over 30 years old. Characteristics of patients according to gender (table 1), show that patients with malignant tumors are more experienced by men than women. This is because men are more often exposed to carcinogenic substances, including alcohol and cigarette smoke. This is in accordance with what was reported by Kristianti et al (2010) who was conducted at Hasan Sadikin Hospital, Bandung, of 30 NPC patients studied, 83.3% of the patients were male and 70% were over 30 years old.[6]

In this study, the highest NPC stage in this study was stage IVA, which was 38.9%. Stage NPC patients generally (60–90%) come for treatment at an advanced stage clinic with symptoms of spread outside the nasopharynx. Primary tumors in the nasopharynx obtained are T3 or T4, rarely with T1 or T2. In Romania, 50% of patients with NPC were diagnosed at an advanced stage, namely 33.33% at stage IV (27.78%: IVA, 5.57% IVB) and 16.66% at stage III. conducted by Wildeman et al (2013) at RSUP Dr. Sardjito Yogyakarta who conducted a study on 78 patients with nasopharyngeal carcinoma and found that 90% of patients came with an advanced stage consisting of stage III (36%), stage IV (54%).[13]

Tympanometry Results, PTA and DPOAE Results

The data from the tympanometry examination in this study (Table 2) showed mixed tympanometry results, where only 44.4% showed type A, which means there was no abnormality in the middle ear, while 55.6% of the remaining data would produce inaccurate data because the results of the DPOAE examination are influenced by conditions in the middle ear. The results of this study are different when compared to the results of previous studies reported by Kristianti et al (2010), where 56 of the 60 research

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data showed type A tympanometry results, and the remaining 4 were type As, so that in this study the determination of ototoxic events could use the results of the examination. DPOAE. Most of these abnormal tympanometry results can be caused by the pathophysiology of nasopharyngeal carcinoma, where the initial location of the onset of nasopharyngeal carcinoma is the Rosenmuller fossa area on the lateral wall of the nasopharynx which can spread and cause obstruction of the eustachian tube causing conductive deafness due to otitis media. [14]

However, in this study, we still present the results of the hearing threshold and DPOAE for all patients (36 ears) and we also perform separate statistical tests for 16 ears with type A tympanometry results consisting of 6 ears in the treatment group and 10 ears in the control group.

The hearing threshold after the first chemotherapy showed a better picture of the results in the treatment group where the NH hearing threshold increased from 27.78% to 38.89%, while in the control group the NH hearing threshold was the same as before chemotherapy, namely 44.44% and the hearing threshold was 44.44%. Mild CHL decreased from 44.44% to 33.33%, no significant results were found between the control and treatment groups with p value = 0.395 (p>0.05). Similarly, the hearing threshold after the second chemotherapy showed better results in the treatment group where the NH hearing threshold was 55.56%, which increased from 38.89% after the first chemotherapy while in the control group the NH hearing threshold tended to decrease from after chemotherapy. the first, which decreased from 44.44% to 27.78%, and after the Chi Square statistical test for the hearing threshold after the second chemotherapy obtained significant results where the p value = 0.034 (p <0.05) between the treatment group and the control group. This is similar to the study conducted by Barata et al (2014) who conducted a study on 20 malignant tumor patients who received Cisplatin therapy, which were divided into 2 groups, namely the treatment group who received EGB 80 mg per day for 1 month and audiometric results were obtained after The first chemotherapy which was also not significant with the Chi-Square test results showed p = 0.058 (p>0.05) but significant results were obtained after the second chemotherapy with p value = 0.007 (p<0.05). The same results were also obtained by Hendriyanto et al (2020) who also conducted a study on 22 patients with advanced nasopharyngeal carcinoma who received Cisplatin and received Gingko Biloba capsules 80 mg per day for 45 days, the results were not significant with a p value of 0.214 (p>0.05) in the audiometric examination after the first chemotherapy cycle in the control and treatment groups but significant results were obtained for the audiometric examination after the second chemotherapy cycle with p value = 0.043 (p <0.05) and p value = 0.033 (p <0.05) after the third chemotherapy. [10,15]

The results of DPOAE after the first chemotherapy were obtained from the distribution description in the treatment group with the results of Pass as much as 61.1% which decreased from 66.7% before chemotherapy while in the control group the results of Pass were 55.6% which decreased from 77.8% before chemotherapy. Independent Sample

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Test statistical test was performed and obtained p value = 1,000 (p> 0.05) which means there is no significant relationship between the two groups. This is different from the research conducted by Cakil et al (2012) who conducted research on 20 albino wistar rats which were divided into two groups consisting of the Cisplatin therapy group and the Cisplatin therapy group accompanied by Ginkgo Biloba therapy for 10 days and 17 days. Then the results of DPOAE were obtained with p value <0.05 after 10 days and 17 days of administration which showed significant results between the two groups.[16]

The results of DPOAE after the second chemotherapy showed a better picture of the DPOAE results in the treatment group where the Pass results were 66.7% which increased from the previous amount of 61.1% compared to after the first chemotherapy, while in the control group the pass results were 33.3 % which decreased from 66.6% after the first chemotherapy. Independent Sample Test statistical test was performed on the results of DPOAE after the second chemotherapy and obtained p value = 0.047 (p <0.05), which means that there is a significant difference between the control and treatment groups. This is in accordance with the research conducted by Hendriyanto et al (2020) who obtained insignificant DPOAE results after the first chemotherapy, but significant results after the second chemotherapy. The same results were also obtained in a study conducted by Dias et al (2015) who conducted a study on 15 malignant tumor patients who received Cisplatin chemotherapy at the Brasilia University Hospital which was divided into 8 treated patients who received Ginkgo Biloba and 7 control group patients without therapy. In addition to Ginkgo Biloba, significant results were obtained on DPOAE examination between the two groups with p value = 0.03 (p = <0.05) [10,17]

The data on the DPOAE examination did not match previous estimates (Table 4). Pre-chemotherapy DPOAE data should be mostly PASS in both the treatment and control groups, then the first and second post-chemotherapy DPOAE examinations only obtained REFER data. This is in accordance with the working principle of DPOAE examination and the pathophysiology of nasopharyngeal carcinoma as previously described.[18] However, of the 36 ears examined, there were 16 (44.4%) ears with type A tympanometry, consisting of 6 (37.5) %) ears in the treatment group and 10 (62.5%) ears in the control group. Then, the OAE and PTA data were redistributed from the 16 ears and statistical tests were carried out.

The results of DPOAE before chemotherapy in the ear with tympanometry A obtained all passed in the treatment group or the control group. After the first chemotherapy was obtained in the treatment group all ears (100%) the results still passed and in the control group from 10 ears (100%) which passed to 6 (60%) ears, and the Fisher Exact Test was carried out, the p value = 0.234 (p > 0.05), which means that it is not significant in both groups. The results of DPOAE after the second chemotherapy were obtained in the treatment group the results were still pass in all ears (100%) and in the control group the results were passed in 3 (30%) ears. Statistical tests were carried out using the Fisher Exact Test and the results were p = 0.010 (p <0.05), which means there was a significant difference between the two groups. This is not in accordance with the research conducted

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by Barata et al (2014) which obtained significant results after the first and second chemotherapy with a p value <0.05.[21] Wistar albino rats for 10 days and 17 days after administration of Ginkgo Biloba and obtained significant DPOAE results between the treatment group and the control group with p value <0.05.[19]

The results of the ear hearing threshold with type A tympanometry before chemotherapy, after the first chemotherapy and after the second chemotherapy obtained p>0.05, which means that there is no significant relationship between the two treatment and control groups. This result is different from the research conducted by Barata et al (2014) and Hendriyanto et al (2020) which obtained insignificant results after the first chemotherapy but significant results after the second chemotherapy with p value <0.05.[10.15]

CONCLUSION

Administration of Ginkgo biloba 80 mg per day can affect the function of cochlear outer hair cells in Nasopharyngeal Carcinoma patients with Cisplatin and Paclitaxel therapy. DPOAE examination can be used periodically for patients undergoing chemotherapy with Cisplatin and Paclitaxel regimens for early monitoring of cochlear outer hair cell damage due to ototoxicity.

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