COCHLEAR DYSFUNCTION AFTER KANAMYCIN INJECTION IN MULTIDRUG RESISTANT TUBERCULOSIS PATIENTS

Aditya Brahmono, Nyilo Purnami, Bakti Surarso
Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Long-term exposure to aminoglycoside such as kanamycin to cochlear cells is known to be associated with damage to outer hair cells in the organ Corti and type 1 sensory hair cells in the vestibular organs which ultimately causes permanent damage to hair cells. Hair cell damage occurs from the basal cochlea (high frequency area) to the apex cochlea (low frequency area) and followed by damage from the auditory nerve. Evaluation of cochlear dysfunction on multidrug resistant tuberculosis (MDR TB) patients have been rarely reported in the literature based on distortion product otoacoustic emission (DPOAE). Objectives: To prove cochlear dysfunction after kanamycin injection in MDR TB patient based on DPOAE examination of the overall frequencies and specific frequency. This was an observational longitudinal analytic with pre and post design without control group conducted in the infection division of MDR TB Outpatients Pulmonology Department and Otorhinolaryngology Community division of ORL-HNS Department, Dr. Soetomo General Hospital, Surabaya, within 3 months in 2018, 15 ear with the best baseline examination were taken by consecutive sampling and statistical analysis for cochlear dysfunction based on overall frequency and specific frequency DPOAE examination using Mc Nemar test. Based on DPOAE examination of overall frequencies there was no cochlear dysfunction (p>0.05) but a significant difference was found at frequency of 10,000 Hertz (Hz) (p=0.002). On ototoxicity monitoring there was no cochlear dysfunction after 4 weeks Kanamycin injection but cochlear dysfunction occurs at a specific frequency of 10,000 Hz.

***Keywords**: Cochlear dysfunction; DPOAE; kanamycin; multi drug resistant tuberculosis*

ABSTRAK

Paparan jangka panjang aminoglikosida seperti kanamisin hingga sel koklea diketahui terkait dengan kerusakan sel rambut luar di organ Corti dan sel rambut sensorik tipe 1 di organ vestibular yang pada akhirnya menyebabkan kerusakan permanen pada sel rambut. Kerusakan sel rambut terjadi dari koklea basal (area frekuensi tinggi) ke koklea apeks (area frekuensi rendah) dan diikuti oleh kerusakan saraf pendengaran. Evaluasi disfungsi koklea pada pasien TB yang resistan terhadap beberapa obat (MDR TB) jarang dilaporkan dalam literatur berdasarkan distorsi produk emisi otoakustik (DPOAE). Tujuan: Untuk membuktikan disfungsi koklea setelah injeksi kanamisin pada pasien TB MDR berdasarkan pemeriksaan DPOAE frekuensi keseluruhan dan frekuensi spesifik. Jenis penelitian ini adalah observasional longitudinal analitik dengan pre dan post design without control group yang dilakukan di bagian infeksi Bagian Infeksi pada Bagian Paru Pasien Rawat Jalan TB MDR dan Bagian Komunitas Otolaringologi Bagian ORL-HNS RSUP Dr. Soetomo Surabaya selama 3 bulan pada tahun 2018, 15 Pemeriksaan telinga dengan baseline terbaik diambil secara consecutive sampling dan analisis statistik disfungsi koklea berdasarkan frekuensi keseluruhan dan frekuensi spesifik pemeriksaan DPOAE menggunakan uji Mc Nemar. Berdasarkan pemeriksaan DPOAE frekuensi keseluruhan tidak terdapat disfungsi koklea (p> 0,05) tetapi terdapat perbedaan bermakna pada frekuensi 10.000 Hertz (Hz) (p = 0,002). Pada pemantauan ototoksisitas tidak ada disfungsi koklea setelah 4 minggu injeksi Kanamycin tetapi disfungsi koklea terjadi pada frekuensi tertentu 10.000 Hz.

***Kata kunci:** Disfungsi koklea; DPOAE; kanamisin; TB yang resistan terhadap obat*

Correspondence: Nyilo Purnami, Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Teaching Hospital, Surabaya, Indonesia. E-mail: nyilo.dr@gmail.com

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INTRODUCTION

Aminoglycoside, such as kanamycin, is known arouse the permanent damage and keep giving the ototoxic effect even after several weeks and months administration (Ribeiro et al 2015). Hearing loss in patient with multidrug resistant tuberculosis (MDR TB) is suspected due to the effects of long-term kanamycin

injection, for that hearing examination needs to be done routinely. The hearing damage can be known by pure tone audiometry and high frequency audiometry examination, meanwhile the damage of cochlear outer hair cell function is evaluated using otoacoustic emission (OAE) (Petersen & Rogers 2015).

Generally, amynoglicoside ototoxic effect that occurred on hearing organs is symmetrically bilateral but could be asymmetric, drug ototoxic effects start from the basis of cochlear and raise progressively to the apex of cochlear. This leads to appearance of sensorineural hearing loss (SNHL) with high frequency for the first time and gradually affects lower frequency (Rachana & Shabnam 2017, Schlauch & Nelson 2015). Ototoxicity onset frequently is unpredictable, significat hearing loss can be happened even after single dose administration. Furthermore, ototoxicity might be without any clinical manifestations on weeks, months, or years after stop or finish the therapy (Kumar et al 2017).

Pure tone audiometry is recognized as simple method on monitoring decreased hearing after amynoglicoside administration but inadequate on monitoring the amynoglicoside ototoxicity effects. Several studies showed that distortion product otoacoustic emission (DPOAE) is a monitoring tool that detects early amynoglicoside ototoxicity more sensitively. Stavroulaki and Katbamna showed the result of normal audiometry before and after aminoglycoside administration that statistically showed significant marks towards outer hair cell/OHC decrease (Reavis et al 2011).

Bloss reported 19% of 1.027 MDR TB patients experience hearing loss after aminoglycoside administration. Harris showed that 87 (58%) of 151 MDR TB patients in Brooklyn hospital, Shouth Africa was detected having high frequency hearing disfunction. Peloquin reported 32 of 87 MDR TB patients experience hearing dysfunction after 5 weeks and 9 weeks aminoglycoside administration, pure tone audiometry examination showed that most of patient are having hearing loss on = 2,000 Hz frequency with a hearing threshold of = 20 decibels (dB) (Reavis et al 2011).

The study result of Rakhmawati showed cochlear dysfunction in bilteral ears starting frequency of 10,000 Hz on days 19 to 21, then concerning the frequency of 8,000 Hz on days 25 to 27. The ototoxicity event opportunity of TB MDR patients that receive kanamicyn injection occurs in the end of second week after affecting high frequency in the beginning followed by lower frequency (Rakhmawati et al 2015).

Ototoxicity effects had been identified generally but there is still but there are still many questions that cannot be answered as to why there are significant variations in reported ototoxic effects of aminoglycosides and what is the most appropriate method of auditory examination that should be used to detect ototoxic effects (Reavis et al 2011).

Based on description above, the researchers intend to identify the occurrence of cochlear dysfunction after kanamycin injection on MDR TB patients using DPOAE baseline and DPOAE assessment after kanamycin injection in the MDR TB outpatient unit at Dr. Soetomo Hospital Surabaya. Knowing the ototoxic effect will be used as a basis for monitoring cochlear function. Furthermore, the prevention of side effects of hearing loss is more effective and expected to improve the quality of life for patients.

MATERIALS AND METHODS

This was an observational analytical-longitudinal study using pre and post-test approach without comparison or control. The measurement using DPOAE baseline and DPOAE values after 4 weeks of kanamycin injection administration on every subjects.

This study was conducted in July 2018 until October 2018 to 15 MDR TB patients in infection division of MDR TB Outpatients Pulmonology Department and Otorhinolaryngology Community division of ORL-HNS Department Dr. Soetomo general hospital Surabaya. The inclusion criteria are the MDR TB patients that received 750 miligram (mg) kanamycin injection (intramuscular) every day for 4 weeks and had age range between 17 until 60 years old. Exclusion criteria are patients who having symptoms that lead to hearing dysfunction (acute airway infection, allergic rhinitis, nasal polyps), working in noisy environments, pure tone audiometry results in conduction type or mixed type abnormalities, consuming ototoxic drugs and receiving streptomycin injections (OAT category 2). The DPOAE tool (1,000 Hz, 2,000 Hz, 4,000 Hz, 6,000 Hz, 8,000 Hz and 10,000 Hz) used is Audx Pro with criteria 4/6 pass, pure tone audiometry and otoscope.

DPOAE baseline and pure tone audiometry examination were performed on all study subjects, of which 30 ears were examined, 15 ears were taken as the best baseline results for statistical tests. This study was determined by the level of significance (?) of 0.05 or 5%. Statistic analysis to determine the occurrence of cochlear dysfunction based on DPOAE examination overall frequency and specific frequency in MDR TB patients

who received kanamycin injections using the Mc Nemar test.

RESULTS

In this study, the youngest age was 26 years and the oldest was 56 years with an average age of 39 years. The most age group who received kanamycin injections 41 to 50 years as many as 6 patients (40%), followed by 21-30 years age groups as many as 4 patients (26.66%) and 31 to 40 years age groups as well as 4 patients (26, 66%). Distribution based on gender obtained more male samples than women with a ratio of 1: 1,14. The number of male samples are 8 patients (53.33%) and 7 women (46.67%). Before receiving kanamycin injection, all MDR TB patients have no complaints on their ears such as decreased hearing, tinnitus or vertigo, there are 7 patients (46.67%) who complain about tinnitus after administration of kanamycin injections.

The results of pure tone baseline audiometry examination showed a hearing threshold of 30 ears still within normal limits. The results distribution of the baseline DPOAE examination and after kanamycin injection of 15 MDR TB patients based on the overall frequencies is shown in Table 1. The results distribution of baseline DPOAE examination and after kanamycin injection in both ears of 15 MDR TB patients based on the results of each frequency are shown in Tables 2a and 2b.

Distribution of baseline DPOAE examination and after kanamycin injection based on the overall frequencies of 30 ears showed the largest change to refer in the right ear as much as 4 ears (26.67%) while in the left ear only 1 ear (6.67%) (Table 1). The distribution of baseline DPOAE examination and after kanamycin injection each frequency showed the largest change to refer to be seen at a specific frequency of 10,000 Hz as many as 7 right ears (46.67%) and 6 for the left ears (40%) (Tables 2a and 2b).

Statistical analysis of baseline DPOAE examination and after kanamycin injections was conducted on the ears of MDR TB patients which had the best baseline values. The analysis was examined based on the DPOAE results overall frequencies and each frequency. The distribution of DPOAE data measured by statistical analysis can be seen in tables 3 and 4. Changes to refer in 15 ears after kanamycin injection were 4 ears (26.73%), based on DPOAE correlation overall frequencies. The calculation of the correlation test for the overall frequencies is done by the Mc Nemar statistical test, the results of the statistical correlation test for the overall frequencies showed a non-significant result ($p > 0.05$) with a p value=0.12 (Table 3).

Based on the results of DPOAE at each frequency, the biggest changes to refer after administrating kanamycin injections at a specific frequency of 10,000 Hz in 9 ears (60%) followed by a frequency of 8,000 Hz as much as 4 ears (26.67%) and at a frequency of 6,000 Hz (3 ears) 20%) (table 4). Statistical calculations were performed by Mc Nemar test at each baseline frequency and after kanamycin injection, the results of statistical tests at a frequency of 1,000 Hz to 8000 Hz found no significant difference ($p > 0.05$), while the difference was significant ($p < 0.05$) with the value of p=0.002 is obtained at a specific frequency of 10,000Hz.

Table 1. The distribution of DPOAE overall frequencies baseline and after kanamycin injection towards 30 ears

DPOAE Results	Baseline		After kanamycin injection	
	Right Ear	Left Ear	Right Ear	Left Ear
Pass	14 (93.33%)	13 (86.67%)	10 (66.67%)	12 (80%)
Refer	1 (6.67%)	2 (13.33%)	5 (33.33%)	3 (20%)
Total	15 (100.00%)	15 (100.00%)	15 (100.00%)	15 (100.00%)

Table 2a. The Distribution of DPOAE baseline each frequency in 30 ears

Frequency (Hz)	Right Ear			Left Ear		
	Pass	Refer	Total	Pass	Refer	Total
1000	12 (80%)	3 (20%)	15	12 (80%)	3 (20%)	15
2000	13 (86.67%)	2 (13.33%)	15	13 (86.67%)	2 (13.33%)	15
4000	13 (86.67%)	2 (13.33%)	15	14 (93.33%)	1 (6.67%)	15
6000	9 (60%)	6 (40%)	15	14 (93.33%)	1 (6.67%)	15
8000	14 (93.33%)	1 (6.67%)	15	13 (86.67%)	2 (13.33%)	15
10000	13 (86.67%)	2 (13.33%)	15	14 (93.33%)	1 (6.67%)	15

Table 2b. The Distribution of DPOAE after kanamycin injection in each frequency on 30 ears

Frequency (Hz)	Right Ear			Left Ear		
	Pass	Refer	Total	Pass	Refer	Total
1000	11 (73.33%)	4 (26.67%)	15	11 (73.33%)	4 (26.67%)	15
2000	14 (93.33%)	1 (6.67%)	15	12 (80%)	3 (20%)	15
4000	12 (80%)	3 (20%)	15	13 (86.67%)	2 (13.33%)	15
6000	7 (46.67%)	8 (53.33%)	15	10 (66.67%)	5 (33.33%)	15
8000	8 (53.33%)	7 (46.67%)	15	14 (93.33%)	1 (6.67%)	15
10000	8 (40%)	9 (60%)	15	8 (53.33%)	7 (46.67%)	15

Table 3. Statistical analysis of DPOAE overall frequencies on 15 ears

DPOAE Result	Baseline		After Kanamycin Injection		Mc Nemar Test
Pass	15	(100%)	11	(73.33%)	0.12
Refer	0	(0 %)	4	(26.67%)	
Total	15	(100%)	15	(100%)	

Note: There is no significant difference in statistical test (p>0.05)

Table 4. Statistical analysis of DPOAE each frequency on 15 ears

Frequency (Hz)	Baseline			After Kanamycin Injection			Mc Nemar Test
	Pass	Refer	Total	Pass	Refer	Total	
1000	13 (86.67%)	2 (13.33%)	15	12 (80%)	3 (20%)	15	1.00
2000	14 (93.33%)	1 (6.67%)	15	14 (93.63%)	1 (6.67%)	15	1.00
4000	14 (93.33%)	0 (0%)	15	12 (80%)	3 (20%)	15	0.25
6000	15 (100%)	3 (20%)	15	9 (60%)	6 (40%)	15	0.37
8000	12 (80%)	2 (13.33%)	15	9 (60%)	6 (40%)	15	0.21
10000	13 (86.67%)	1 (6.67%)	15	5 (33.33%)	10 (66.67%)	15	0.002*

Note: There is a significant difference in statistical test (p>0.05)

DISCUSSION

The age distribution of MDR TB patients who received kanamycin injections in this study was mostly in the age group 41 to 50 years as many as 6 patients, the results of this study in line with the research conducted by Magdalena, MDR TB patients age were less than 50 years with 65 people (80.2%). Munir's study showed that MDR TB patients were at a productive age between the ages of 25 and 34 years (Magdalena et al 2013).

The results of a study by Sinaga in 2013 at the H. Adam Malik Hospital, Medan found that the majority of MDR TB patients aged 35-44 years. In accordance, the results of research by Munir in 2010 at the Persahabatan Hospital Jakarta showed that the majority of MDR TB patients were at the age of 25-34 years. The research results above are in accordance with WHO 2012 data in developing countries TB cases that TB cases occur mostly in productive age of 15 to 54 years. Productive age is quite dangerous to the media of transmission because they have high mobility, easy to interact with other people, and allow to spread their disease to other people and the environment around the place of residence (Yulianti & Mahdiani 2015).

Based on gender distribution, the samples number of MDR TB patients who received kanamycin injections was higher in 8 patients and 7 female patients. The results of this study are consistent with Munir's research in 2010 at the Persahabatan Hospital in Jakarta and the Sinaga study in 2013 at the Adam Malik Hospital in Medan. The results of Munir's research showed that male MDR TB who suffered were 53 people (52.5%) and women as many as 48 people (47.5%), while the results of the Sinaga study showed that there were 9 male MDR TB (64.3%) and 5 women (35.7%) sufferred. The WHO study in 2015 reports that the prevalence of pulmonary TB in men was 1.7 times than women because the nature of men of being more active and contact with others outside home frequently than women in addition to biological, socio-cultural factors. Women are often late and less interested in visiting health care centers than men, according to research conducted by Nakagawa (Azwar et al 2017).

Gender distribution in MDR TB patients correlated with cochlear dysfunction or hearing loss is statistically insignificant with research conducted by Kavalieratos in 2012 and Rakhmawati in 2015, therefore it can be concluded that cochlear function disorders associated with hearing loss in MDR TB patients is not influenced by gender.

Tinnitus after getting a 4-week kanamycin injection was experienced in 7 MDR TB patients, but this symptom did not disturb patient's activity because its temporarily and non-permanent. Other symptoms such as hearing loss and vertigo after kanamycin injections were not found in all patient samples.

The study by Mokrian in 2013 showed a low change in DPOAE amplitude in patients with Tinnitus symptom, in accordance with Ami in 2008 and Hesse in 2005 mentioning cochlear function disorders that leads into tinnitus symptoms are characterized by a decrease in DPOAE amplitude at high frequencies above 4,000 Hz. This finding is different from the research conducted by Szutka in 2010, mentioning symptom of tinnitus in patients with high DPOAE amplitude without symptom of hearing loss and audiometry examination results within normal limits can be caused due to increased motility of OHC by decreased activity efferent fibers from OHC and it eliminate the reason of cochlear dysfunction. Gouveris in 2005 reported patients with tinnitus showed an increase in DPOAE amplitude at high frequencies of 4,000 Hz and 6,000 Hz and decreased amplitude at lower frequencies (1,650-2,400 Hz) (Mokrian et al 2014).

The dose distribution of kanamycin administration in this study showed that 15 MDR TB patients received the same dose of kanamycin injection of 750 mg. The study by Magdalena showed that MDR TB patients who received kanamycin injections with a dose of 750 mg were 20 people (62.5%) and more dose of 750 mg were 33 people (67.3%), while the group of patients with hearing loss is 12 people (37.5%) were using injection doses of kanamycin 750 mg and 33 people were (67.3%) using doses of more than 750 mg (Magdalena et al 2013). The duration and dose of kanamycin injection increased the risk of hearing loss significantly (Peloquin et al 2004, Urbancic et al 2017). The study of Javadi showed that the dose and duration of therapy play a role in hearing loss, as well as Peloquin states that the cumulative total dose is associated with decreased hearing (Magdalena et al 2013).

Audiological monitoring of ototoxic events has two main objectives, early detection of hearing loss and audiological intervention whether hearing loss has occurred. The purpose of audiological monitoring in this study was to detect early cochlear disorders based on DPOAE examination , therefore early intervention can be obtained. If the main purpose of audiological monitoring has been achieved, the next goal will be attained especially the management of hearing disorders that difficult be treated medically such as counseling, communication strategies, and amplification or hearing tools (Petersen & Rogers 2015).

Distortion product otoacoustic emission examination is believed to be very useful in monitoring specific ototoxic effects on cochlear dysfunction and other effects specifically on outer hair cells. The DPOAE examination basically describes the pre neural motility activity of outer hair cells that depicts its function (Chang 2014). Evaluation of DPOAE examination is based on the results of the pass or refer at each frequency examined from each ear.

The results of the DPOAE baseline examination correlating the overall frequency of 30 ears showed that after kanamycin injections, there were changes in 4 right ears and 1 left ear into refer (table 1). These results indicate that after kanamycin injection, there is a cochlear function disorder in some MDR TB patients. It is similar with the study by Rakhmawati on 38 MDR TB patients who received kanamycin injections after 4 weeks of obtaining 4 right ears and 5 left ears into refer after previously DPOAE baseline 38 right ears and 38 lefts ear pass (Rakhmawati et al 2015).

Study by Appana et al in 2016 of 52 MDR TB patients who received kanamycin injections for 4 weeks in the Kwazulu hospital, South Africa depicted that 29 right ears and 30 left ears pass at baseline and 12 right ears and 14 left ears became refer after kanamycin injection.

The changing in DPOAE results for each frequency at 30 ears after kanamycin injection mostly stand at a frequency of 10,000 Hz followed a frequency of 8,000 Hz (table 2b), the biggest change to refer is in the right ear as many as 7 ears and 6 left ears at 10,000 Hz while the 6 right ears became refer at a frequency of 8000 Hz. The results of this study are different from the study on 68 MDR TB patients who only got 21 right ear pass at the baseline became refer is only 1 right ear after 4 weeks of kanamycin injection (Kavalieratos 2012).

The changing of 15 ears with the best DPOAE baseline after administration of kanamycin injections obtained 4 ears to refer and it is indicating that the results of DPOAE statistical analysis at the overall frequency was not significant ($p > 0.05$) (Table 3), while the biggest DPOAE changes for 9 ears with statistical analysis showed significant results ($p < 0.05$) at a high frequency of 10,000 Hz but was not significant at frequencies of

1000 Hz, 2000 Hz, 4000 Hz, 6000 Hz and 8000 Hz (Table 4).

The results of this study are not in accordance with the Study in 201216 conducted on 68 MDR TB patients at Murchison Hospital in South Africa. The number of DPOAE baseline examination results is 34 left ears for pass and 34 (50%) right ears for refer while 34 (50%) right ears are pass and 34 (50%) left ears are refer. In DPOAE examination after administration of kanamycin injection for 1 month, the number of left ears pass are 32 (47%) and refer are 36 (53%), while the right ear that passed are 33 (49%) and refer are 35 (51%). The analysis was measured at high frequency changes of 4000 Hz, 6000 Hz and 8000 Hz from each ear and showed a statistically significant ($p < 0.05$) change at the pass result into a refer after kanamycin injection.

Research in 2017 conducted on 33 MDR TB patients at Dr. Mohammad Hoesin Palembang Hospital, attained the DPOAE baseline pass examination in 47 ears and refer in 19 ears , after kanamycin injections are found changing in the frequency of 8000 Hz by 5 ears and 9 ears at a frequency of 10,000 Hz on refer results17. Research in 2015 on 38 MDR TB patients also showed the occurrence of OHC disorders after administration of kanamycin injections for 1 month which was marked by changing in DPOAE values at high frequencies (8,000 Hz and 10,000 Hz). As much as 76 ears was analyzed for 1 month, it was found that there was impaired OHC function at the frequency of 10,000 Hz on right and left ear started from day 19 to 21, whereas at frequencies of 8,000 Hz and 10,000 Hz, there was an impaired OHC function in the right ears started on day 25 to 27. Based on DPOAE examination of 76 ears, there were found 2 refer and 36 pass in right ears, whereas 3 refer and 35 pass in left ears (Rakhmawati et al 2015).

The statistical analysis results based on the overall frequencies in this study were not significant but the statistical analysis based on each frequency is similar with the literature that supporting DPOAE examination was quite sensitive to alter OHC function at high frequencies associated with cochlear dysfunction.

The insignificant statistically results of this study are because the DPOAE examination protocols based on 4/6 pass criteria, 6 frequencies are examined for the minimum DP that passed were at least 4 out of 6 frequencies, so that in this study there were more MDR TB patients. It was concluded that cochlear function was still within normal limits because only one frequency that was statistically significant (10,000 Hz) had cochlear dysfunction. Statistical analysis in other studies that analyzed alteration in DPOAE at high frequencies (above 4000Hz) also led to different results compared to this study. Giving the same dose of 750 mg kanamycin injection to all patients also lead non meaningful results similar to the literature which states that the total cumulative dose affects the occurrence of cochlear function disorders and hearing function. Other confounding factors in this study were not analyzed such as intracellular antioxidants involving enzymatic and non-enzymatic antioxidants such as superoxide dismutase, catalase and glutathione peroxidase. It also lead of the insignificant results of the study, according to the literature that mentions ROS-induced hair cell apoptosis prevented through the mechanism of reactive detoxification to support cochlear cell recovery.

The effect of cochlear toxicity usually occurs first at high frequencies which then extend towards a lower frequency depending on the length of exposure and dose given (Sharma et al 2016). Early exposure of ototoxic drugs can usually affect the basal cochlea. Further exposure causes the spread of damage towards the apex. Therefore, cochlear toxicity initially affects high frequencies and then extends to lower frequencies. Cochlear damage that occurs in outer hair cells leads to high frequency hearing loss and affects the autoacoustic emission process (Sharma et al 2016, Seddon et al 2012).

The results of DPOAE examination in this study are similar to the explanation about ototoxicity due to kanamycin causes damage to hair cells at the basal cochlea so that cochlear dysfunction arises first at high frequencies. Ultra high frequency (>8,000 Hz) is not checked routinely, therefore the incidence of hearing loss due to administration of kanamycin is often overlooked (Irwan et al 2017).

CONCLUSION

This study conclude that on ototoxicity monitoring there was no cochlear dysfunction after 4 weeks Kanamycin injection but cochlear dysfunction occurs at a specific frequency of 10,000 Hz. Suggested for further evaluation of cochlear function in TB MDR patients who treated with injections of kanamycin should be routinely done every month until completion of kanamycin injections administration and 6 months after finishing the treatment.

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