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Auditory evaluation with Pure Tone Audiometry and DPOAE in Kanamycin Treatment of Multidrug-Resistant Tuberculosis

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Abstract

Background: Kanamycin treatment is mainly used in multidrug-resistant tuberculosis (MDR-TB) patients. Hearing impairment associated along with the treatment leads to be permanently. Audiology assessments and monitoring may benefits to detect early on hearing loss. This study aimed to determine the evaluation of hearing alteration after kanamycin injection in the first month treatment.

Method: We conducted a prospective study, observational longitudinal analytic with pre and post design in patients treated with kanamycin-based regimens in MDR TB Outpatients Pulmonology Department Dr. Soetomo general hospital Surabaya. Assessment of hearing result using Pure Tone Audiometry and DPOAE, compared between baseline data and after 4 weeks treatments. Statistical analysis for hearing threshold and cochlear dysfunction based on overall frequency and specific frequency DPOAE examination, using Wilcoxon ranks test and Mc Nemar test.

Results: A total of 15 patients (8 males and 7 females) with confirmed diagnosis of MDR-TB were included in this study conducted within 3 months in 2018.There were 15 ears represented with based line and compared to 4 weeks after treatment, showed on Audiometry and DPOAE on overall frequencies, found no significant difference ($p > 0.05$), but in DPOAE at frequency of 10,000 Hertz (Hz) was found a significant difference ($p = 0.002$).

Conclusion: DPOAEat high frequency (10,000 Hz) may benefits for early detection on hearing impairment. A baseline data with DPOAE is recommended, besides Audiometry for ototoxicity monitoring in Kanamycin treatment in MDRTB patients.

Keywords: *Audiometry, DPOAE, kanamycin, multi drug resistant tuberculosis.*

Introduction

Hearing loss in patient with *multidrug resistant tuberculosis* (MDR TB) is suspected due to the effects of long-term kanamycin injection, kanamycin is known affected the permanent damage and the ototoxic remain lasting even after several weeks and months of administration.[1]

Drug ototoxic like aminoglycoside 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.[3,4] Ototoxicity might be without any clinical manifestations on weeks, months, or years after stop or finish the therapy.[5] The hearing damage can be tested using several tools like pure tone audiometry and *otoacoustic emission* (OAE) especially to evaluated the damage of cochlear outer hair cell function.[2]

Peloquin *et al,* described the use of kanamycin given both daily and three times a week. They found that the size or frequency of dosage did not affect toxicity. MDR TB patients experience hearing dysfunction after 5 weeks and weeks.[6]Meanwhile, Sharma *et al*., reported only 18 out of 100 MDR-TB patients who received kanamycin after 6 weeks[7]. 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).[6] The ototoxicity of TB MDR patients begin affecting high frequency and followed by lower frequncy in the end of second week.[8]

The aimed of this study to identify the occurrence of cochlear dysfunction after 4 weeks on MDR-TB patients using DPOAE *baseline* and pure tone audiometry.

Material and Method

This was an observational analytical longitudinal using pre and post test approach without controldesign and conducted at the in the MDR-TB outpatient clinic at Dr Soetomo Hospital Surabayafrom July 2018 until October 2018 which had been ethically legalized before. **Participants:** Subjects were 15 MDR TB patients that received 750 mg Kanamycin injection (i.m) every day for 4 weeks and the age of patients between 17 to 60 years old and not having symptoms that can be 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 (Oral Anti Tuberculosis category 2).

Intervention: Subjects that were received Kanamycin injection after 4 weeks examination hearing DPOAE test with specific frequency (1000 Hz, 2000 Hz, 4000 Hz, 6000 Hz, 8000 Hz and 10000 Hz) using *Audx Pro* with overall criteria 4/6 *pass* and pure tone audiometry with specific frequency (250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 6000 Hz and 8000 Hz). **Outcome:** DPOAE baseline and pure tone audiometry examination were performed to all subject which 15 ears were taken. This study was determined using the Mc Nemar test and Wilcoxon signed rank test with the level of significancy 5% (p=0.05).

Findings: This study selected 15 MDR-TB patients who received Kanamycin injection for 4 weeks after which audiometry and DPOAE examinations were performed to see hearing dysfunction due to Kanamycin injection in MDR-TB patients. In the DPOAE examination only 10,000Hz frequency can detect changes in the patient's hearing impairment but the Audiometry cannot.

Analysis data of DPOAE Test:

Table 1. The distribution and statistic analysis of DPOAE overall frequencies

DPOAE Result	Baseline	After Kanamycin Injection	p
Pass	15 (100%)	11 (73.3%)	0,12
Refer	0 (0%)	4 (26.67%)	
Total	**15 (100%)**	**15 (100%)**	

Based on the table 1, all of patients did not experience hearing impairment before Kanamycin injection treatment but after Kanamycin injection 4 weeks there were 4 patients who had hearing loss with using DPOAE. From the results of the MC Nemar test p = 0.12 which means there is no significant change in DPOAE as screening hearing in patients who experience hearing loss after Kanamycin injection for 4 weeks.

Table 2. The distribution and Statistical analysis of DPOAE each frequency.

Frequency (Hz)	Baseline			After kanamycin injection			P
	Pass	Refer	Total	Pass	Refer	Total	
1000	13 (86.6%)	2 (13.3%)	15	12 (80%)	3 (20%)	15	1.00
2000	14 (93.3%)	1 (6.6%)	15	14 (93.6%)	1 (6.6%)	15	1.00
4000	15 (100%)	0 (0%)	15	12 (80%)	3 (20%)	15	0.25
6000	12 (80%)	3 (20%)	15	9 (60%)	6 (40%)	15	0.37
8000	13 (86.6%)	2 (13.3%)	15	9 (60%)	6 (40%)	15	0.21
10000	14 (93.3%)	1 (6.6%)	15	5 (33.3%)	10 (66.6%)	15	0.002*

Based on the table above showsthat DPOAE with a frequency of 10,000Hz can identify hearing impairment in MDR-TB patients after Kanamycin injection for 4 weeks. Only 1 patient (6.6%) was previously detected as having problems *Refer*, but after therapy, DPOAE detected 10 patients (66.6%). The results of the McNemar test obtained p = 0.002 which means there is a change in the number of patients who experience hearing impairment after Kanamycin injection treatment using DPOAE.

Analysis data of Audiometry test:

Table 3. The distribution and statistic analysis of Audiometry each frequencies

Frequency (Hz)	Baseline			After kanamycin injection			p
	Normal	Hearing loss	Total	Normal	Hearing loss	Total	
250	15 (100%)	0 (0%)	15	15 (100%)	0 (0%)	15	1.00
500	15 (100%)	0 (0%)	15	15 (100%)	0 (0%)	15	1.00
1000	15 (100%)	0 (0%)	15	15 (100%)	0 (0%)	15	1.00
2000	15 (100%)	0 (0%)	15	15 (100%)	0 (0%)	15	1.00
4000	15 (100%)	0 (0%)	15	15 (100%)	0 (0%)	15	1.00
6000	15 (100%)	0 (0%)	15	14 (93.3%)	1 (6.3%)	15	0.317
8000	15 (100%)	0 (0%)	15	15 (100%)	0 (0%)	15	1.00

From table 3. it was found that all subjects baseline none of the patients were detected as having hearing impairment using audiometry at all frequencies. After Kanamycin injection for 4 weeks, only 6000Hz frequency can detect as many as 1 patient (6.3%) who have hearing impairment but from statistic result p=0,3017 that means there's no significant change in audiometry as hearing screening in patients with hearing impairment.

Table 4. The distribution mean Audiometry result each frequency

Frequency (Hz)	Baseline		After kanamycin injection	
	Mean	Total	Mean	Total
250	24.66	15	24.66	15
500	23.00	15	23.00	15
1000	23.00	15	23.00	15
2000	20.66	15	20.66	15
4000	25.00	15	25.00	15
6000	28.66	15	29.00	15
8000	23.33	15	23.33	15

From the table 4. an average Intensity of 28.6 dB can be heard with a frequency of 6000Hz from baseline using audiometry and after injection of Kanamycin 4 weeks, the average intensity is 29 dB. 26-40dB is categorized as mild deaf.

Discussion

The gender distribution of MDR TB patients who received kanamycin injections in this study hearing impairment occur more in male patient as many as 8 patient (53.3%) than female patient as many as 7 patient (46.6%). Gender can correlated with cochlear dysfunction or hearing impairment found by Kavalieratos (2012) and Rakhmawati (2015). Therefore it can be concluded that cochlear function disorders associated with hearing impairment in MDR TB patients is not influenced by gender.The WHO study in 2015 reports that the prevalence of pulmonary TB in male was 1.7 times than female. Manbeing more active and have contact with other frequently than woman. Many woman are often late and less interested in visiting health care centers than men, according to research conducted by Nakagawa.[8-10]

The age distribution of MDR TB patients who received kanamycin injections in this study was mostly in the age group 26 to 35 years as many as 5 patients, and age group 36-45 years as many as 5 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%). 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.[8,9]

Tinnitus was a symptommostly occurs in research subjects after injection of Kanamycin 4 weeks. DPOAE amplitude in patients with Tinnitus symptom showed a slight different. Cochlear function disorder that leads into tinnitus symptoms are characterized by a decrease in DPOAE amplitude at high frequencies above 4,000 Hz. Gouveris (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).[11]

The subjects of this study have the same dose injection in 15 MDR TB patients. They all received kanamycin injection of 750 mg. The duration and dose of kanamycin injection increased the risk of hearing impairment significantly. The dose and duration of therapy play an important role in hearing loss, as well as the cumulative total dose is associated with decreased hearing.[8, 12,13]

DPOAE is believed to be very useful in monitoring specific ototoxic effects on cochlear dysfunction and other effects especially on outer hair cells. DPOAE examination basically describes the motility activity of outer hair cells that show its function.[14] The examination results show that DPOAE detects as many patients who were previously detected as having disorders *Refer*only 1 patient after DPOAE therapy detected 10 patients who referred at 10,000Hz frequency.The results of the DPOAE on other study in 2016, from 52 MDR TB patients who received kanamycin injections for 4 weeks in the Kwazulu hospital, South Africa was found that 29 right ears and 30 left ears *pass* at baseline and 12 right ears and 14 left ears became *refer* after kanamycin injection.[15]

Examination using DPOAE with a frequency of 10,000Hz detected hearing impairment in MDR-TB patients after receiving a 4-week Kanamycin injection. The results of the statistical test found $p = 0.002$ ($p < 0.05$) which means that there are significant changes in patients who experience hearing loss after receiving therapybut was not significant at frequencies of 1000 Hz, 2000 Hz, 4000 Hz, 6000 Hz and 8000 Hz (table 3). Related with the result of this study was found the significant difference on DPOAE examination at frequency of 10,000Hz in high frequency as early detection. Hearing loss in those treated with aminoglycosides and polypeptides usually starts with high-frequency loss first[16]

From the Audiometry examination only 6000Hz frequency can detect as many as 1 patient (6.3%) who has hearing loss (table 6). The average Intensity that can be heard is 28.6 dBfrom baseline data and 29 dB after getting a 4-week Kanamycin injection. From the statistical results obtained $p = 0.317$ which means there are no significant specific changes in audiometry as hearing screening in patients with hearing imparment. However other frequency is not significant such as 250Hz, 500Hz, 1000Hz, 2000Hz, 4000Hz and 8000Hz.

The previous study reported that 14 people (42.4%) had normal hearing based on baseline audiometry. Meanwhile, audiometry on treatment found that only 3 people (9.1%) had normal hearing, most of them (90.9%) had hearing impairment. Mostly the hearing threshold shift at high frequencies, 6000 Hz and 8000 Hzand administration of kanamycin injection for 2 months or more was considered to have risk for ototoxicity.[17]The reason why audiometry is not maximally used as a screening for hearing loss is because the injection of Kanamycin for only 4 weeks has not given the ototoxic effect of kanamycin. 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.[17] Another reason is that Audiometryc examination is only performed at the beginning of the baseline and after getting a 4-week Kanamycin injection. Audiological monitoring for ototoxicity recommends an audiometry evaluation one to two times a week[18]

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 otoacoustic emission process.[18, 19]

Conclusion

This study concludes that cochlear dysfunction occurs at a specific frequency of 10,000 Hz after 4 weeks Kanamycin injection, but not in overall frequency while in audiometry it cannot detect. Auditory evaluation at 4 weeks is considered not able to detect hearing impairment due to ototoxic drug MDR-TB. The useof ultra-high frequencies is recommended and may also use combination with OAE.

Conflict of Interest: There was no conflict of interest in this study.

Ethical Clearance: This study was received ethical approval from the Health Research Ethics Committee Dr. Soetomo Hospital Surabaya.

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