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Correlation between the Length of Kanamycin Therapy and Hearing Threshold Shift in Multidrug Resistant Tuberculosis (MDR-TB) Patients

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ABSTRACT

Indonesia are in the top eight for MDR-TB in the world. WHO recommends the use of second-line injectable drugs, aminoglycoside, in enhancing therapeutic efficacy and mandatory incorporation into standard MDR-TB therapy regimens. Kanamycin is the most widely used in Indonesia, particularly Dr. Mohammad Hoesin Palembang. Since kanamycin is ototoxic, audiological monitoring is required in evaluating hearing impairment occurring in MDR-TB patients. Objective: To determine the correlation between the length of kanamycin therapy and hearing threshold shift in MDR-TB patients. This cross-sectional study was conducted on 33 subjects of MDR-TB patients who had been diagnosed and in kanamycin treatment in the Pulmonology Division of the Department of Internal Medicine at Dr. Mohammad Hoesin Palembang. The subjects were consecutively collected from January to April 2017. Anamnesis, ear nose throat physical examination, tympanometry, Otoacoustic Emissions, and pure tone audiometry were done to all subjects. Results: Most patients (90.9%) experienced hearing impairment due to ototoxicity based on ASHA and 54.5% on Brock's criteria. The correlation analysis showed there was a significant correlation between the length of kanamycin therapy and hearing threshold shift at 4000 Hz (r = 0,441) and 8000 Hz (r = 0,362). The multivariate analysis found that the hearing threshold shifts, particularly high frequency (4000 Hz - 8000 Hz) were also influenced by decreased creatinine clearance, increased AST and ALT levels, as well as baseline threshold. There is a significant correlation between the length of kanamycin therapy and hearing threshold shift, especially high frequrencies, in MDR-TB patients.

Keywords: Hearing Loss, Aminoglycoside, Kanamycin, Ototoxicity, MDR-TB

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INTRODUCTION

MDR-TB is defined as tuberculosis which is resistant to isoniazid and rifampicin, with or without resistance to other antituberculosis drugs. MDR-TB is found in more than 100 countries and estimated more than 400,000 new cases are developing each year. According to WHO, MDR-TB cases in Indonesia are in the eighth place, whereas MDR-TB from TB cases treated has reached 12% and new cases of MDR TB are 1.9%. Based on WHO's latest guidelines, the use of second-line injectable drugs, aminoglycosides, enhance therapeutic efficacy and a mandatory incorporation into standard MDR-TB therapy regimens. The treatment of MDR-TB uses a more toxic regimen resulting in many side effects, one of which is hearing loss. Research conducted by Rafique *et al.,* (2012) showed that 15 out of 38

(39.5%) patients with MDR-TB had hearing loss after 1 month of receiving streptomycin injection. Meanwhile, according to Reviono *et al.,* (2013), 15.4% of MDR-TB patients experienced hearing loss in the first month of kanamycin therapy. Based on data from the MDR-TB clinic of Dr. Hasan Sadikin Hospital Bandung during 2013, 127 MDR-TB patients obtained second-line antituberculosis drugs with aminoglycoside injections of kanamycin. As many as 11.8% (15 patients) had hearing loss after 3-6 months of therapy [1-7].

In developing countries, audiological examination is only aimed at people who have complaints in communicating. According to the Integrated Management Guidance on Tuberculosis Control of Drugs by Indonesian Health Minister in 2013, auditory evaluation using audiometry is performed prior to administration of antituberculosis drugs and subsequently as indicated. If this strategy is applied in assessing the hearing of patients receiving MDR-TB injectable therapy, hearing loss will only be detected when irreversible damage to a certain degree occurs at the critical frequency of communication. Until now there has been no uniformity of practical and rational methods in monitoring the administration of ototoxic drugs. The ASHA considers ototoxicity as a 20 dB threshold elevation at a specific frequency, a 10 dB threshold elevation at two consecutive frequencies, or absent responses at three consecutive frequencies after therapy testing. While Brock attributes number values (0 to 4) to various types of hearing loss due to ototoxicity, as seen in Table 1. In the other hand, as addition there is no therapy to cure the damage due to ototoxic drugs [6-8].

Based on the background above, this study is expected to detect the hearing threshold shift caused by the second-line MDR-TB injection drug so that the therapeutic regimen can be adjusted to prevent the progression of hearing loss. And ultimately the quality of life of patients with MDR-TB can be maintained. This research is also expected to be a source of knowledge and foundation for further research, as well as new guidelines in the audiology monitoring of MDR-TB patients.

Table 1: Brock's Hearing Loss Grades [13]

Grade	Hearing Threshold
0	< 40dB at all frequencies
1	≥ 40 dB only at 8.000Hz
2	≥ 40 dB starting at 4.000Hz
3	≥ 40 dB starting at 2.000Hz
4	≥ 40 dB starting at 1.000Hz

MATERIALS AND METHODS

This cross-sectional study was conducted on 33 subjects of MDR-TB patients who had been diagnosed and in kanamycin treatment in the Pulmonology Division of the Department of Internal Medicine at Dr. Mohammad Hoesin Palembang. The subjects were consecutively collected from January to April 2017. Anamnesis, ear nose throat physical examination, tympanometry, Otoacoustic Emissions (OAE), and pure tone audiometry were done to all subjects. Baseline audiograms before drug administration were collected as secondary data from medical records, while on treatment audiograms being performed in this study. Patients with acute and chronic inflammation of the outer ear and middle ear, and also are not cooperative in evaluation of hearing function were excluded.

The correlation between the length of kanamycin therapy and the hearing threshold shift of the subject was analyzed using Pearson's correlation test when the data was normally distributed. If the data was not normally distributed or in the form of categorical data, Spearman correlation test was used. P value is considered significant if $p < 0.05$ with 95% confidence interval. Multivariate analysis was done to control confounding variables, that was for categorical data used logistic regression while for numerical data used linear regression. Multivariate analysis aims to analyze factors related to hearing loss in patients with MDR-TB, such as age, gender, body mass index, history of previous antituberculosis drugs, comorbidity, AST and ALT titer, and creatinine clearance. We assisted with *SPSS software for windows version 21.0* for the data analysis.

RESULTS

Thirty three patients treated with injectable kanamycin in MDR-TB therapy were included in the analysis. Baseline characteristics are shown in Table 2. Participants complained about hearing loss, tinnitus, and vertigo. Based on these clinical

symptoms, most participants complaint were tinnitus (63.7%). While 15 participants (45.5%) had hearing loss, only a few participants complained of vertigo (12.1%).

Table 2: Baseline demographics (percentages in parentheses)

Variables	Value
Mean Age ± SD (years)	39.6 ± 10.9
Gender: Male Female	 18 (54.5%) 15 (45.5%)
Body Mass Index	18.76 ± 4.1
Mean Kanamycin Therapy ± SD (months)	3.73 ± 2.18
Kanamisin Dosage 500 mg 750 mg 1000 mg	 6 (18.2%) 13 (39.4%) 14 (42.4%)
History of Previous Antituberculosis Drugs: 1st Category 2nd Category 1st & 2nd Category No previous drugs	 21 (63.6%) 2 (6.1%) 6 (18.2%) 4 (12.1%)
Comorbidity 1. Hypertension 2. Diabetes Mellitus 3. HIV No comorbidity	 1 (3.0%) 6 (18.2%) 1 (3.0%) 25 (75.8%)
Mean AST Titer ± SD (U/L)	25.21 ± 8.68
Mean ALT Titer ± SD (U/L)	11.52 ± 13.6
Mean creatinine clearance ± SD (%)	85.79 ± 37.77

Table 3 describes the results of tympanometry, OAE, baseline and on treatment pure tone audiometry. All of patients showed type A tympanogram. Whereas out of 66 ears, pass result of OAE were 47 ears and only 19 ears were refer. Overall in every frequency, descriptively on treatment hearing threshold were higher than baseline. The highest shifts were on high frequencies (6000 Hz and 8000 Hz).

Fourteen out of 33 patients showed bilateral normal hearing on baseline audiograms. While 4 patients were found to have bilateral sensorineural hearing loss, 5 patients had bilateral conductive one. Then on treatment audiograms showed that only 3 patients left with bilateral normal hearing. And patients with bilateral sensorineural hearing loss on treatment audiograms were more than baseline as seen on Table 4.

Based on ASHA criteria out of 33 patients, ototoxicity was observed in most of patients (90.9%). Meanwhile according to Brock's, only about half patients experienced ototoxicity. Table 5 describes the proprotion of ototoxicity.

Table 3: Results of Tympanometry, OAE, and Pure Tone Audiometry (percentages in parentheses)

Results	Right Ear	Left Ear
Tympanometry Type A	 33 (100%)	 33 (100%)
OAE Pass Refer	 24 (72.7%) 9 (27.3%)	 23 (69.7%) 10 (30.3%)
Pure Tone Audiometry		
250 Hz		
Baseline	38.64 ± 2.20	39.55 ± 2.47
On Treatment	46.82 ± 2.13	54.24 ± 2.37
Decrease	8.18 ± 8.82	14.70 ± 15.81
500 Hz		
Baseline	36.36 ± 2.19	37.12 ± 2.62
On Treatment	44.09 ± 2.63	51.06 ± 2.96
Decrease	7.73 ± 13.98	13.94 ± 17.04
1000 Hz		
Baseline	27.42 ± 2.16	28.94 ± 2.65
On Treatment	35.30 ± 2.99	40.00 ± 2.44
Decrease	7.88 ± 13.11	11.06 ± 9.58
2000 Hz		
Baseline	28.03± 2.47	27.58 ± 2.08
On Treatment	33.18 ± 3.74	36.67 ± 3.50
Decrease	5.15 ± 11.49	9.09 ± 16.46
4000 Hz		
Baseline	34.85 ± 3.78	35.61 ± 3.31
On Treatment	40.91 ± 4.32	46.36 ± 4.34
Decrease	6.06 ± 16.67	10.76 ± 16.59
6000 Hz		
Baseline	38.03 ± 4.57	36.82 ± 4.19
On Treatment	49.70 ± 5.35	52.73 ± 4.76
Decrease	11.67 ± 17.84	15.91 ± 18.48
8000 Hz		
Baseline	35.30 ± 4.74	32.88 ± 4.34
On Treatment	49.24 ± 5.38	52.42 ± 4.59
Decrease	13.94 ± 19.03	19.55 ± 19.62

Table 4. Baseline and On Treatment Audiogram Interpretations

Audiogram Interpretations	*Baseline*		*On Treatment*	
	n	**%**	**n**	**%**
Bilateral Normal	 14	 42.4	 3	 9.1
Sensorineural Hearing Loss	4	12.1	11	33.3
Conductive Hearing Loss	5	15.2	2	6.1
Mixed HearingLoss	0	0	3	9.1
Sensorineural/ Mixed Hearing Loss	5	15.2	6	18.2
Sensorineural/ Conductive Hearing Loss	1	3.0	3	9.1
Mixed/ Conductive Hearing Loss	0	0	3	9.1
Unilateral: Sensorineural Hearing Loss Mixed Hearing Loss Conductive Hearing Loss	 1 1 2	 3.0 3.0 6.1	 0 1 1	 0 3.0 3.0
Total	**33**	**100**	**33**	**100**

Almost all frequencies showed no correlation with the length of kanamycin therapy, but frequency 4000 Hz and 8000 Hz. The coefficient of frequency

4000Hz was 0,441 with moderate positive correlation and statistically significant ($p < 0.01$). And at frequency 8000 Hz showed the same analysis. It weakly and positively correlated with the length of kanamycin therapy (r = 0,362) with p value = 0,039. The longer kanamycin injection administered, the greater hearing threshold shifts at frequency 4000 Hz and 8000 Hz.

Table 5: Ototoxicity Proportion Based on ASHA and Brock's (percentages in parentheses)

Ototoxicity Criteria	ASHA	Brock's
Ototoxicity	30 (90.9%)	18 (54.5%)
Normal	3 (9.1%)	15 (45.5%)
Total	**33 (100%)**	**33 (100%)**

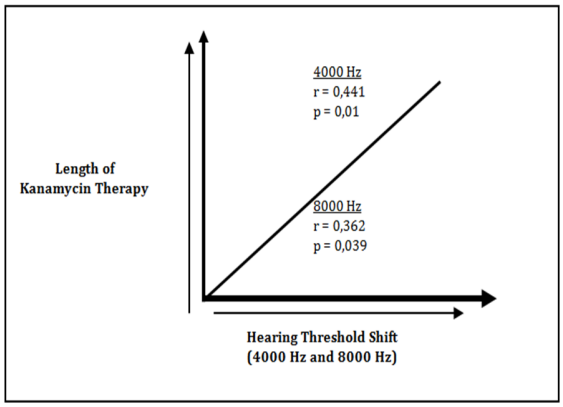

Figure 1: Correlation Between The Length of Kanamycin Therapy and Hearing Threshold Shift on Frequency 4000 Hz and 8000 Hz

DISCUSSION

The most common clinical symptoms of kanamycin ototoxicity is tinnitus, followed by hearing loss and vertigo. We report 63.7% participants complained of tinnitus. Yulianti and Mahdiani (2015) also reported that the most common complaint is tinnitus (73.3%). As many as 53.3% of patients complained of hearing loss and no one complained of vertigo. According to Mustikaningtyas and Purnami (2013), half of patients receiving kanamycin (46.3%) complained of hearing loss. Various literature also supports that kanamycin has major side effects on cochlea, which are tinnitus and hearing loss, whereas vestibular injury is rare [6, 7, 11, 12].

Because of kanamycin major side effects on cochlea, particularly outer hair cell, OAE can be very helpful. Based on OAE examination, we had 47 out of 66 ears were pass and only 19 ears were refer. Meanwhile, all ears showed a type A tympanogram. In Rakhmawati (2015) study, DPOAE examination was performed in ototoxic protocols ranging from 1,500 Hz to 10,000 Hz on 76 ears. Cochlear disorders characterized by refer result in frequency 8000 Hz as much as 5 ears and 9 ears at 10,000 Hz. While at frequencies less than 8,000 Hz there was no interference marked by pass results. The majority of timpanometry examination showed type A (66 ears) and the others (10 ears) were type As. In contrast to Mustikaningtyas and Purnami (2013) research, the OAE examination showed refer on 54.9% ears and pass on 23 ears (28%) [6, 12].

This 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 Hz. And administration of kanamycin injection for 2 months or more was considered to have risk for ototoxicity. According to Yulianti and Mahdiani (2015), 72 of 86 participants (83.7%) had normal hearing, 11.6% sensorineural, 1.2% conductive, and 3.5% mixture hearing loss on baseline audiometry. During the course of therapy, 20.8% of normal hearing participants change into sensorineural hearing loss. The biggest change occurs at high frequencies above 4000 Hz. Sagwa *et al.,* (2015) showed that 55.6% MDR-TB patients receiving kanamycin injections had hearing loss with varying degrees ranging from high frequency (4000 - 8000 Hz). Reviono *et al*., (2013) reported 15.4% MDR-TB patients experienced a hearing loss in the first month of kanamycin therapy. In the other hand, based on data of MDR-TB clinic of Internal Medicine Dr. Hasan Sadikin Hospital Bandung for one year (January - December 2013) found that as many as 11.8% (15 patients) of 86 patients who received kanamycin injection experienced hearing loss after 3-6 months of therapy [2, 6, 7, 10].

Based on ASHA criteria, almost all of the participants (90.9%) showed kanamycin ototoxicity. Whereas based on Brock's, half of participants (54.5%) had experienced ototoxicity. This result exceeds study performed by Harris *et al*., which showed 57% of patients had ototoxicity according to ASHA criteria. Meanwhile, Sharma *et al*., (2016) reported only 18 out of 100 MDR-TB patients who received kanamycin after 6 weeks

showed ototoxicity based on ASHA and did not show improvement after 1 year of discontinuation. In addition, no research literature has reported Brock's in determining the otoxicity of MDR-TB treatment so far. The American Academy of Audiology recommends the use of the ASHA criteria in classifying ototoxicity in MDR-TB treatment [13, 14].

We found a positive correlation between the length of kanamycin therapy with the hearing threshold shift at frequency 4000 Hz to 8000 Hz. And so the decreased of creatinine clearance, the increased of ALT and ASPT levels, as well as the baseline threshold also correlated to the hearing threshold. Sagwa *et al.,* (2015) reported that old age, low body weight (40-59 kg), HIV coinfection, duration of treatment, and especially impaired renal clearance had a higher risk of hearing loss due to long-term use of kanamycin. In a literature, Chang pointed out that typically the toxicity of the cochlea first affects the high frequency then the damage will extend to a lower frequency depending on the duration of exposure and the given dose. Haris *et al.,* (2012) studied on animals and it showed a correlation between the effects of aminoglycosides nephrotoxicity with drug accumulation. And according to Adriztina *et al.,* (2014), the ototoxic effect could be minimized in young tuberculosis patients with good kidney function, while disturbed liver function could lead to disruption of drug metabolism and ultimately accumulation of drugs in the body. However, it is also possible that in MDR-TB therapy using a combination of complex and toxic drugs, side effects such as liver disorders, renal impairment, or hearing loss can occur simultaneously and actually do not affect each other. Although statistically obtained a significant correlation [9-11, 14].

This research has limitation, such as the use of OAE screening tool which can only detect in frequency 1000 Hz to 5000 Hz. So in this research the results of OAE examination were dominantly pass. Pure tone audiometry limited up to frequency 8000 Hz was also a constraint in the study. Many literatures such as Seddon (2012) and Sharma (2016) suggest that ototoxicity was determined by comparing baseline audiogram data obtained before ototoxic drug administration with monitoring audiograms during and after therapy. Hearing threshold shifts found in serial pure tone audiograms are the most effective indicators in detecting hearing loss due to ototoxicity, especially when using ultra-high frequencies. Audiological monitoring for ototoxicity recommends an audiometry evaluation one to two times a week and may also use OAE [13-15].

CONCLUSION

The long-term use of kanamycin in MDR-TB treatment led to a high risk of hearing loss caused by ototoxicity. The longer kanamycin injection administered, the greater hearing threshold shifts, particularly at high frequencies (≥ 4000Hz) Administration of kanamycin injection for 2 months or more was considered to have risk for ototoxicity than 2 months lesser. The hearing threshold shift was also affected by creatinine clearance, ALT and AST level, and baseline threshold itself. A periodic auditory examination as audiological monitoring is necessary for the evaluation of hearing loss resulting from the use of kanamycin, especially when administered for minimum two months. The examination of liver and kidney function is also required routinely. And first of all, we recommed that patients and families should be well informed about ototoxicity risk prior to kanamycin administered in MDR-TB treatment.

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The author(s) declare that they have no competing interests.

REFERENCES

1. World Health Organization. Key point. WHO Report 2012: Global Tuberculosis Control 2012 surveillance, planning, financing. Geneva, Switzerland: WHO, 2012.
2. Reviono W, Harsini AJ, Sutanto YS. Streptomisin dan insidens penurunan pendengaran pada pasien Multidrug Resistant Tuberculosis di Rumah Sakit Dr. Moewardi. Surakarta. J Respir Indo. 2013; 33(3):167-72.
3. Peraturan Menteri Kesehatan Republik Indonesia. Pedoman Manajemen Terpadu Pengendalian Tuberkulosis Resistan Obat.

Jakarta: PerMenKes RI. 2013: 13.
4. Kusnanto P, Eko V, Pakiding H, Nurwidiasih D. Multidrug resistant tuberculosis (MDR-TB): tinjauan epidemiologi dan faktor risiko efek samping obat anti tuberkulosis. Majalah Kedokteran Bandung. 2014; 46(4):189-96.
5. Rafique A, Dastgir M, Jamalullah M, Maqbool S, Basher S, Rashid M. Streptomycin associated hearing loss in patients treated for multidrug resistant tuberculosis. Isra Med Journal. 2012; 4:139-42.
6. Rakhmawati L, Agustian RA. Peluang Kejadian Ototoksisitas pada Penggunaan Kanamisin dalam Pengobatan Tuberkulosis Resisten Obat Ganda Selama 1 Bulan. Majalah Kedokteran Bandung. 2015; 47(4):224-30.
7. Yulianti Y, Mahdiani S. Gangguan pendengaran penderita Tuberkulosis Multidrug Resistant. Oto Rhino Laryngologica Indonesiana. 2015; 45(2):83-9.
8. Taneja MK, Varshney H, Taneja V, Varshney J. Ototoxicity, drugs, chemicals, mobile phones and deafness. Indian Journal of Otology. 2015; 21(3):161-4.
9. Sturdy A, Goodman A, José RJ, Loyse A, O'donoghue M, Kon OM, Dedicoat MJ, Harrison TS, John L, Lipman M, Cooke GS. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice. Journal of Antimicrobial Chemotherapy. 2011; 66(8):1815-20.
10. Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Leufkens HG, Mantel-Teeuwisse AK. Comparing amikacin and kanamycin-induced hearing loss in multidrug-resistant tuberculosis treatment under programmatic conditions in a Namibian retrospective cohort. BMC Pharmacology and Toxicology. 2015;16(1):36.
11. Chang KW. Ototoxicity. In Bailey's Head & Neck Surgery Otolaryngology 5th ed. Philadelpia: Lippincott Williams & Wilkins, 2014: 2542-2548.
12. Mustikaningtyas E, Purnami N. Hearing disorder in multidrug-resistant tuberculosispatients atthe outpatients unit, pulmonary department, Dr. Soetomo Hospital Surabaya. Folia Medica Indonesiana. 2013; 49(4):263-7.
13. Durrant JD, Campbell K, Fausti S. American Academy of Audiology Position Statement and Clinical Practice Guidelines. Am J Audiol. 2009.
14. Sharma V, Bhagat S, Verma B, Singh R, Singh S. Audiological Evaluation of Patients Taking Kanamycin for Multidrug Resistant Tuberculosis. Iranian Journal of Otorhinolaryngology. 2016; 28(86):203-8.
15. Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis. European Respiratory Journal. 2012; 40(5):1277-86.