CORRELATION BETWEEN SUPEROXIDE DISMUTASE SERUM AND SENSORYNEURAL HEARING DISORDER IN PATIENTS WITH MULTI DRUG RESISTANCE TUBERCULOSIS

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ABSTRAK

*Pendengaran merupakan fungsi penting bagi kehidupan manusia. Untuk dapat berkomunikasi dengan lancar diperlukan pendengaran yang baik. Gangguan pendengaran dapat disebabkan oleh berbagai macam obat atau bahan yang bersifat toksik diantaranya gangguan pendengaran akibat autotoksik adalah Kanamisin. Pengaruh toksik dari Kanamisin mengakibatkan penurunan pendengaran tipe sensorineural. Gangguan pendengaran sensorineural umumnya terjadi pada frekuensi tinggi dan dapat juga mengenai frekuensi percakapan. kejadian ini keterkaitan dengan efek pasca terapi Kanamisin pada penderita Multi Drug Resistance Tuberculosis (MDRTB). Gangguan pendengaran bersifat permanen, progresif, bilateral dan kadang-kadang disertai dengan tinitus. Oleh karena itu untuk menilai adanya gangguan pendengaran sensorineural, maka dievaluasi dengan audiometri nada murni (ANM) dan pemeriksaan kadar serum superosida dismutase (SOD) merupakan antioksidan endogen sebagai lini pertama yang dapat melindungi fungsi pendengaran.Penelitian ini bertujuan menganalisis hubungan antara kadar serum SOD dengan gangguan pendengaran tipe sensorineural pada penderita MDRTB. Dilakukan penelitian cross sectional pada penderita MDRTB pasca terapi Kanamisin. Penelitian dilakukan di poli MDRTB RSUD Dr. Soetomo Surabaya. Penelitian dimulai dalam kurun waktu 3 bulan dimulai bulan Pebruari sampai bulan April 2012. Pemeriksaan yang dilakukan meliputi THT-KL, audiometri nada murni, timpanometri dan kadar serum SOD. Pada penelitian ini dilakukan pemeriksaan pada 17 penderita MDRTB yang memenuhi kriteria penelitian terdiri dari 8 orang laki-laki (47,10%) dan 9 wanita (52,90%) dengan rasio laki-laki dan perempuan hampir berimbang. Hasil ANM dengan intensitas ≥ 30 dB lebih banyak terjadi pada frekuensi tinggi (4000 Hz, 6000 Hz dan 8000 Hz). Hubungan antara kadar serum SOD dengan gangguan pendengaran menggunakan uji korelasi Pearson, Pada penelitian ini tidak terdapat hubungan bermakna antara kadar serum SOD dengan gangguan pendengaran tipe sensorineural. Berdasarkan hasil ANM pada frekuensi 4000 Hz p = 0,076, frekuensi 6000 Hz p = 0,809, frekuensi 8000 Hz p= 0,974. Berarti, didapatkan perbedaan tidak bermakna (p > 0,05). Hasil pemeriksaan kadar SOD berdasarkan derajat intensitas gangguan pendengaran dengan menggunakan uji korelasi Spearman's didapat p = 0,628. Berarti didapatkan perbedaan tidak bermakna (p > 0,05). Kesimpulan penelitian ini yaitu tidak terdapat hubungan bermakna antara kadar serum SOD dengan gangguan pendengararan tipe sensorineural.**(FMI 2013;49:42-50)***

Kata kunci: *superoksida dismutase, serum, sensorineural, multidrug resistance tuberculosis*

ABSTRACT

*Hearing is one of the most vital functions in life. In order to maintain communication, normal hearing is crucial. Hearing loss can be caused by various drugs or agents that are toxics, one of mentioned is autotoxicity of Kanamycin. Such drug effect can cause sensorineural type of hearing loss. High frequency sensorineural hearing loss is the consequence of post Kanamycin administration in Multi Drug Resistance Tuberculosis (MDRTB) patients. The characteristics of hearing loss are permanent, progressive, bilateral and sometimes accompanied by tinnitus. The objective of this study is to analyze the correlation between superoxide dismutase (SOD) serum level and sensorineural hearing loss in MDRTB patients. The cross-sectional study was conducted in 17 ears of MDRTB patients post Kanamycin administration. Six ears were normal and 11 ears suffered from hearing loss. This study was carried out in MDRTB outpatient department, Dr. Soetomo Hospital of Surabaya, from February to April 2012. The examinations included pure tone audiometry, tympanometry, 10 mm blood from cubital vein in vacuum tube that was sent directly (<1 hour) for SOD serum level check in Laboratory of Dr. Soetomo Hospital, Surabaya. In this study, from total of 17 patients post Kanamycin admisnitration, those who met the criteria consist of 8 men (47,10%) and 9 women (52,90%). Mean pure tone audiometry with intensity ≥ 30 dB were in high frequencies (4000 Hz, 6000 Hz and 8000 Hz). The result of correlation between SOD serum level and hearing loss by Pearson correlation test, based on audiogram were p = 0,076 in frequency 4000 Hz, p = 0,809 in frequency 6000 Hz, and p = 0,974 in frequency 8000 Hz, which showed no significant differences (p > 0,05). There were no correlation between SOD serum level and sensorineural hearing loss in high frequencies. The hearing test results based on intensity level of hearing loss and SOD serum level check by Spearman's correlation test was p = 0,628, that showed no significant differences (p > 0,05). In conclusion, this study showed that there was no correlation between Pure Tone Average (PTA) at frequencies, 4000 Hz, 6000 Hz, and 8000 Hz, or PTA based on intensity level of hearing loss, with SOD serum level in MDRTB patients. **(FMI 2013;49:42-50)***

Keywords: *superoxide dismutase, serum, sensorineural, multidrug resistance tuberculosis*

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INTRODUCTION

Hearing is an important function for human life. To be able to communicate well needed good hearing. Hearing loss can be caused by various drugs or toxic materials including autotoxic -induced hearing loss is Kanamycin. Kanamycins lead to toxic influence of the type of sensorineural hearing loss. Hearing loss associated with autotoxicity is often found as granting Kanamycin, Gentamicin, Streptomycin, occurs slowly and severity comparable to the old, the amount of drug administered. The incidence of aminoglycoside autotoxicity caused ketutulian in some countries as many as 66%, 18% to 17% for Gentamicin Kanamycin and 2% Netilmicin, Neomicin, Amikacin mainly affects the auditory system, while Dibekacin cause vestibular dysfunction. Tobramycin, Gentamicin can damage both organs (Brummett and Fox 1989, Garetz and Schacht 1996).

Kanamycin can damage the outer hair cells of the cochlea from base to progressive hearing loss occurs stale so start high frequency. Oxidative stress that causes an increase in reactive oxygen species (ROS) is several times higher than normal after Kanamycin therapy.

Kanamycin through ROS generation due to several factors such as the cochlea is due to a very high metabolism to meet the needs of high energy with the consequence of higher ROS formation as well. Apart from that occurring blood flow to the cochlea which decreases the impact of ischemia. This situation triggers the formation of superoxide generation more. To fix a decrease in blood flow to the cochlea then the formation of superoxide generation as a result of the increasing availability of other oxygen in the process in mitochondria. The first level of defense mechanisms is the role of superoxide dismutase (SOD) as an antagonist of ROS, thus preventing excessive ROS activity and ultimately may prevent the activation of cell death pathways. Superoxide dismutase (SOD) superoxide anion will change into hydrogen peroxide which is dangerous but if immediate detoxification, this reaction has benefits for the cell. The side effects of Kanamycin as aminoglycosides are nephrautoxic and autotoxic. Cochlear toxicity resulted in a decrease in high-frequency hearing begins, next to the irreversible damage to the outer hair cells of organ of Corti, especially in the basal part of the cochlea (Mudd 2008). Kanamycin is more toxic to the cochlea than streptomycin (Selimoglu 2007).

Multi Drug Resistance dual resistance Tuberculosis (MDRTB) is the biggest problem of the prevention and eradication of TB world. In 2003 the World Health Organization (WHO) declared MDRTB incidence gradually increased an average of 2% per year. In 2005, the United State Centers for Disease Control and Prevention (CDC) and the WHO study published in 2006 of 49 countries is as much as 20% MDRTB. In the United States in 1993-2006 there were 3% MDRTB. WHO reported on a survey of more than 90,000 TB patients in 81 countries, it turns MDRTB rate is higher than expected. The six countries with a high incidence of MDRTB in the world is Estonia, Kazakhstan, Latvia, Lithuania, part of the Russian Federation and Uzbekistan. WHO estimates there are 300,000 new cases of MDRTB per year. In developing countries MDRTB prevalence ranged from 4.6%-22.2% (Soepandi 2010). Research conducted in Oupatient Clinic Dr. Soetomo Hospital by Pakpahan 2007 showed that MDRTB cases as much as 7.27%. Data were taken at the Oupatient Clinic in 2009 to 2010 showed that MDRTB was 26%. In Indonesia, the results of global surveillance found that the anti-tuberculosis drugs (ATD)-resistant *Mycobacterium tuberculosis* has spread and threaten TB control programs in various countries. ATD-resistant tuberculosis germs will be many more, this time 79% of MDRTB is "super strains" resistant to at least 3 or 4 ATD (Soepandi 2010). One therapeutic option for patients with MDRTB is aminoglycoside ie Kanamycin group. Kanamycin is an antibiotic derived from *Streptomyces kanamycetius* that has activity against *Mycobacterium tuberculosis*.

The diagnosis of hearing loss due to autotoxic drugs is very important, because with it we can change the dose of medication, drugs or giving drugs to replace autoprotective and provide an explanation to the patient, so that a more severe hearing loss can be avoided and the patient is ready to risk that happening (Rybak & Ramkumar 2007). Examination of the type of sensorineural hearing loss can be evaluated by audiometric examination. Examination of serum levels of SOD can evaluate the relation between SOD and hearing loss. So far in Indonesia, there has been no study on the relationship between serum levels of SOD with the type of sensorineural hearing loss in patients with MDRTB. This study analyzed the relationship between serum levels of SOD with the type of sensorineural hearing loss in patients with MDRTB.

MATERIALS AND METHODS

This study is an observational analytic cross-sectional design (cross-sectional). The study was conducted at MDRTB Oupatient Clinic Dr. Soetomo Hospital, and Clinical Pathology Laboratory Dr. Soetomo Hospital. The study was performed from February to April 2012. Affordable study population was patients who had received therapy for MDRTB Kanamycin at Hospital

Dr. Soetomo Hospital between February-April 2012. The samples were MDRTB patients who received Kanamycin. Acceptance criteria (inclusion) are aged 20 -55 years old and intact tympanic membrane and tympanogram type A.

Rejection (exclusion) criteria is both infections there are abnormalities in the outer ear and the middle ear such as otitis externa, otitis media, there is a history of head trauma, there is a risk factor for systemic diseases such as diabetes mellitus, and history of noise exposure, and an intact tympanic membrane tympanogram type B, C. Sample size appropriate time limit, which began from February 201 to April 2012, and sampling conducted consecutive sampling.The instrument used in this study is a tool-KL ENT examination, screening tools, namely ANM 226 audiometer type AD type, tympanometry screening tools that Tympanometer types GSI 39 Inter acoustic type, drug dose Kanamycin MDRTB is 15-25 mg/kg (im), laboratory tests: Cu/ZnSOD ELISA Kit eBio-science brand and data collection sheets. MDRTB patients were those who received Kanamycin injection at a dose of 15-25 mg/kg/day in the MDRTB Oupatient Clinic Dr. Soetomo Hospital. Atopic Dermatitis-KL ENT examination and selection was according to inclusion and exclusion criteria. If the sample of patients met the study criteria then explained about the purpose of study and examinations to be carried out, if it is willing to follow the study were asked to sign a letter of approval of research. History is recorded by the investigator in the data collection sheet by sheet that has been created by default. Examination of the ears, nose, throat, head and neck was done by researchers. The tympanometry examination, ANM alternately on the right and left ear, done by officers which Oupatient Clinic audiology help researchers came to the MDRTB Oupatient Clinic. Blood sampling was performed by nurses at MDRTB Oupatient Clinic blood taken from the cubital vein of patients using vacuum tubes as much as 3 milliliters. Blood is taken and then immediately (1 hour) was sent to the Oupatient Clinical Pathology Laboratory of Hospital Dr. Soetomo to be examined serum levels of SOD using a coolbox. Each data sheet filled in and kept by the researcher, at the time of data tabulation research subject's name will be withheld. Tabulation of the data obtained will be processed statistically. Otherwise, the patient was excluded from the study sample (drop out) when they withdrew from the study and came not in accordance with a predetermined time (injection schedule). All data collected in the data collection sheets are arranged in the form of tables and processed statistically using the Pearson correlation test and Spearman's correlation test.

RESULTS

We had conducted research on the relationship between serum levels of superoxide dismutase with the type of sensorineural hearing loss in patients with Multi Drug Resistance Tuberculosis (MDRTB) who came to MDRTB Clinic and Clinical Pathology Laboratory Dr. Soetomo Hospital Surabaya. The sample selection is done by consecutive sampling without control until the sample size is met. Pure tone audiometry examination (ANM), was performed on all study subjects after kanamycin treatment of 17 patients and blood samples (SOD). This study is an observational analytic cross-sectional design (cross-sectional) statistical test significant if $p < 0.05$.

In this study, the age of the youngest 20 years old and the oldest 50 years of age. The mean age was 33.19 years (SD = 7.75). While the distribution by sex showed 47.10% of men and women are almost equal number 9 52.90%. The ratio of men compared to women is 1:1. The degree of interference at a frequency of 6000 Hz hearing, and 8000 Hz which degrees were earned by 4 patients (36.4%). At a frequency of 4000 Hz, 6000 Hz and 8000 Hz is the degree of weight gained as much as 3 patients (27.3%) while the mild and very severe degree obtained at a frequency of 4000 Hz, 6000 Hz and 8000 Hz with a balanced percentage as much as 18.2% (Table 1).

Table 1. Hearing loss by frequency

Frequency (Hz)	Degree of hearing loss				Total
	Mild	Moderate	Severe	Very Severe	
4000	1(50%)		1(50%)		
6000		3(60%)	1(20%)	1(20%)	
8000	1(25%)	1(25%)	1(25%)	1(25%)	
Total	2(18.2%)	4(36.4%)	3(27.3%)	2(18.2%)	11(100%)

Table 2. Hearing loss is based on intensity

Intensity (dB)	Degree of hearing loss				
	Mild	Moderate	Severe	Very Severe	Total
30	1(100%)				1
35	1(100%)				1
45		3(100%)			3
50		1(100%)			1
70			1(100%)		1
80			2(100%)		2
85				1(100%)	1
110				1(100%)	1
Total	2(18.2)	4(36.4%)	3(27.3)	2(18.2)	11

Hearing loss is based on the intensity ranged between 30-110 dB. Hearing loss was found in degrees by 4 patients (34.6%), the degree of weight gained as much as 3 patients (27.3%), whereas the mild and very severe degree obtained the same value, namely 18.2% (Table 2). From this data, the evidence shows that the distribution of hearing loss with the intensity of 30-110 dB, the highest obtained in moderate to severe.

ANM examination results at a frequency of 250 Hz conversations obtained a mean 18.52 (SD = 7.018), frequency of 500 Hz obtained a mean 22.64 (SD = 6.873), the mean frequency of 1000 Hz obtained 21.76 (SD = 7.894), frequency of 2000 Hz obtained a mean 19.11 (SD = 13.71). Examination results at a frequency of 4000 Hz ANM obtained a mean 30.00 (SD = 22.77), the mean frequency of 6000 Hz obtained 40.88 (SD = 24.44) obtained a mean frequency of 8000 Hz 33.88 (SD = 30.89) (Table 3).SOD Examination Results obtained in this study averaged 172.29 (SD = 80 082). Based on statistical analysis using Pearson correlation test between serum levels of SOD by ANM at a frequency of 250 Hz conversations obtained p = 0.619, frequency of 500 Hz obtained p = 0.718, frequency of 1000 Hz obtained p = 0.627, frequency of 2000 Hz obtained p = 0.735. Whereas at high frequencies, ie the frequency of 4000 Hz obtained p = 0.076, frequency of 6000 Hz obtained p = 0.809, frequency of 8000 Hz obtained p = 0.974. Means, the serum levels of SOD by ANM at all frequencies obtained correlation was not significant (p > 0.05).

ANM normal workup was as many as 6 people (35.03%). While the results of ANM based on the degree of hearing loss mild degrees obtained by 2 patients (11.08%), moderate by 4 patients (23.05%), the degree of weight as much as 3 patients (17.06%) and very severe degree by 2 patients (11.08%), hearing loss that occurs while 64.97% obtained results ANM ratio between normal and hearing impaired is 1: 2 (Table 5).

Table 3. ANM examination results on the frequency and frequency -specific conversations

	ANM speech frequency (Hz)				ANM high frequency (Hz)		
	250	500	1000	2000	4000	6000	8000
Mean	18.52	22.64	21.76	19.11	30.00	40.88	33.82
SD	7.018	6.873	7.894	13.71	22.77	24.44	30.89

Table 4. The relationship between serum levels of SOD by ANM at a specific frequency and frequency conversation.

		ANM speech frequency			ANM high frequency			
		250Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz	6000 Hz	8000 Hz
SOD	r	0.130	0.094	0.127	0.089	0.442	0.063	0.009
	p	0.619	0.718	0.627	0.735	0.076	0.809	0.974
	n	17	17	17	17	17	17	17

Pearson correlation test, *: significant (p < 0.05) r = correlation coefficient, p = significant value, n = sample size

Table 5. ANM examination MDRTB patients after Kanamycin therapy

ANM Result	Degree	%
Normal		6 (35.03)
Hearing loss	Mild	2 (11.08)
	Moderate	4 (23.05)
	Severe	3 (17.06)
	Very Severe	2 (11.08)
Total		17 (100)

Table 6. The relationship between serum levels of SOD and post the results ANM MDRTB patients Kanamycin therapy with degree of hearing loss based on the intensity tinggiSOD

Degree of hearing loss	n	Mean (SD)	p
Normal	6	126.0 (47.36)	
Mild	2	258.0 (90.51)	
Moderate	4	211.5 (68.86)	0.628
Severe	3	170.6 (129.3)	
Very Severe	2	172.1 (80.08)	
Total	17		

Table 7. Relationship between serum levels of SOD by Degrees Hearing Loss

		Degree of hearing loss
SOD	r	0.127
	p	0.628
	n	17

r = correlation coefficient, p = significant value,
n = sample size

With Spearman's correlation test the relationship between serum levels of SOD and hearing loss in the total sample obtained p = 0.628. Mean, there was no association between serum levels of SOD with the degree of hearing loss in the total sample of this study (Table 7). The mean serum levels of normal SOD obtained 126.0 ng/ml (SD = 47.36), mild degrees earned 258.0 ng/ml (SD = 90.50), the degree was obtained 211.5 ng/ml (SD = 68, 86) ng/ml, the degree of weight gained 1700.6 ng/ml (SD = 129.3) and very severe degree of 172.1 ng/ml (80.08). Based on Spearman's correlation test between the degree of hearing loss with serum levels of SOD obtained p = 0.628. Meaning, there is no relationship between the intensity of the degree of hearing loss with serum levels of SOD ($p > 0.05$).

DISCUSSION

In this research, statistical calculations on the ear 17 MDRTB patients after therapy made Kanamycin and grouping characteristics by age and sex. The results of this study showed that the age distribution of patients with MDRTB post Kanamycin therapy, obtained youngest age is 20 years old and the oldest 50 years old, with a mean age was 33.19 years (SD = 7.75). Largest age group is 20-35 years of age was 58.82% (10 patients). This is consistent with research Duggal and Sarkar (2007) conducted a study of 64 patients aged between 17 and 65 patients with a mean age of 40 years (SD = 13.5). In that study there type of sensorineural hearing loss at high frequencies of 18.75%, whereas the frequency of conversations about 6.25%. In another study conducted by Jager and Altena (2002), in 31 patients with acquired hearing loss mean age 36 years (SD = 16.0), contrast with Javadi et al (2011) in his study found the average age of patients 39 years (SD = 17.5), with patients with mild sensorineural type hearing loss of 44.83%, patients with moderate sensorineural loss of 17.24%, patients with severe sensorineural loss of 24.14% and patients with very severe sensorineural loss of 10.34%. Age affects the incidence of impaired function of the outer hair cells of the cochlea and the high -frequency sensorineural hearing loss.

Women earned more than men, that women were 9 people (52.10%) and 8 males (47.10%). This is consistent with the literature that more women are 21 men and 20 men (Javadi et al 2011). The same opinion is supported by other studies (Forge& Van De Water 2008) said women are more vulnerable to stress than men, because of excessive production of free radicals.

Frequency hearing loss are based on frequency 4000 Hz and 8000 Hz with a mild degree by 2 persons (18.2%), at a frequency of 8000 Hz with 6000HZ and moderate as many as 4 people (36.4%), at a frequency of 4000 Hz, 6000 Hz and 8000 Hz with a weight of as much as 3 degrees (27.3%), while very severe degree 2 (18.2%) contained at 6000 Hz and a frequency of 8000 Hz. Based on these results, it seems that moderate degrees of hearing loss and the percentage is much more severe than the mild and severe degrees of 11 patients. This is consistent with research Javadi et al (2011) 11 of 18 patients with moderate degrees of hearing loss in as many as 24, 14% and 10.34% severity. Research by Brummett and Fox (1989) due to autotoxic hearing loss occurs at a high frequency (4000 Hz, 6000 Hz and 8000 Hz). Hearing loss is based on intensity, in this study showed a decrease $\geq$ 30 dB, illustrates the effects of autotoxicity Kanamycin therapy marked a shift in hearing threshold value. Based on the degree of hearing loss, moderate and severe degrees had the highest value (36.4% and 27.3%). This is consistent with research by Duggal and Sarkar (2007) autotoxic effects can be detected in the intensity $\leq$ 20 dB at 1 frequency decrease or a decrease of 10 dB at two adjacent frequencies as well as the loss of frequency response at 3.

ANM examination results on the frequency of other conversations between the mean frequency of 250 Hz obtained 18.52 (SD = 7.018), frequency of 500 Hz obtained a mean 22.64 (SD = 6.873), the mean frequency of 1000 Hz obtained 21.76 (SD = 7.894), frequency of 2000 Hz obtained a mean 19.11 (SD = 13.71), the high frequency of 4000 Hz was obtained averaged 30.00 (SD = 22.77), the mean frequency of 6000 Hz was obtained 40.88 (SD = 24.44) and obtained at a frequency of 8000 Hz averaged 33.88 (SD = 30.89). From the results of ANM mean hearing threshold at each frequency varies from 18.52 dB to 40.88 dB. In this study the mean SOD 172.29 (SD = 80.82). These results were consistent with the research Duggal and Sarkar (2007) who examined the three groups (Amikacin, Kanamycin, Capriomisin). ANM is obtained based on the frequency of Kanamycin group, the mean hearing threshold of the study is the frequency of 4000 Hz was 27.5 (SD = 10.4), the frequency of 6000 Hz was 30 (SD = 7.9), and a frequency of 8000 Hz is 33, 75 (SD = 16). Kanamycin therapy was evaluated during the study ≥ 6 months of usage.

Statistical test with Pearson correlation between the results of ANM with serum levels of SOD, at a frequency of 250 Hz obtained p = 0.619, frequency of 500 Hz obtained p = 0.718, frequency of 1000 Hz obtained p = 0.627, frequency of 2000 Hz obtained p = 0.735, at a frequency 4000 Hz obtained p = 0.076. At a frequency of 6000 Hz obtained p = 0.809, at a frequency of 8000 Hz obtained p = 0.974. Means, at these frequencies are not significantly different p > 0.05. The results of this study are not in accordance with Ryback and Whiteworth (2005) SOD protects cochlear outer hair cell damage from toxic effects. Research on guinea pigs was done to prove that SOD provides protection against deafness. In this study found no association between sensorineural hearing loss with serum levels of SOD, this is not in accordance with the theory mentioned by Forge and Van De Water (2008), SOD is part of the first line of cellular defense against free radicals. SOD catalizing changes of superoxide radicals into hydrogen peroxidation which is then degraded by the enzyme peroxide. Damage to the outer hair cells of the cochlea causes a decrease in sensorineural sensitive at high frequencies because the basal area electrifying sound at high frequencies (Martini et al 2007).

ANM examination shows a more comprehensive function of the entire auditory system. Outer hair cells have a high sensitivity of the ear with a lot of receptors on the nerve fibers. While the hair cells are responsible for the resolving power of the better but with a higher stimulus threshold. ANM examination after therapy there Kanamycin normal and hearing disturbances seen by the intensity, the intensity of light as much as 11.08% (2), the intensity was as much as 23.05% (4 people), the intensity of the weight as much as 17.06% (3 people), very heavy as much as 11.08% (2), in this study of 17 patients with normal hearing obtained as much as 35.03% (6 people), and who have a hearing loss as much as 64.97% (11 people) showed ANM with an intensity of 30 dB to 110 dB and the average distribution of the frequency of 4000 Hz, 6000 Hz and 8000 Hz. This is consistent with research conducted by Duggal and Sarkar (2007) hearing loss at high frequencies with the criteria ≤ 20 dB at three frequencies of 4000 Hz, 6000 Hz, 8000 Hz. Another study by Javadi et al (2011) post- therapy Kanaminsin hearing loss was detected at 20 dB or greater at a single frequency, 10 dB or greater decrease in the frequency or loss of response 2 to 3 consecutive frequencies, decrease standards vary up to 50 dB.

The results of the post- therapy ANM Kanamycin normal and indicates the degree of hearing loss based on the mean serum levels of SOD, the normal mean obtained 120.0 (SD = 47.36), mild serum levels of SOD obtained mean 258.0 (SD = 90.50), degree of mean serum levels of SOD was obtained 211.5 (SD = 68.86), the mean severity of serum levels of SOD obtained 170.67 (SD = 129.3), very severe degree of mean serum levels of SOD obtained 148.0 (SD = 25.4). Statistical analysis by Spearman 's correlation between the degree of hearing loss and serum levels of SOD each degree obtained p = 0.628. Means, hearing loss based on normal, mild, moderate, severe and very severe there was no significant difference (p > 0.05). This data does not describe a decrease in serum levels of SOD after Kanamycin therapy.

Based on the theory Forge and Van De Water (2008) the survival of hair cells can be influenced by the expression of specific genes coding for proteins involved in the inactivation of free radicals. In mice that have a gene expression has implications in the gene encoding SOD in protecting cochlear hair cells against the effects of Kanamycin toxicity and noisy. The results of this study do not conform with Keithley el al (2005) in transgenic mice and control mice examined ABR and then histopathological examination in the absence of SOD cochlear turns result in deafness. Hearing loss in transgenic mice was significantly greater than B6 mice, transgenic mice because of degeneration is greater than B6 mice, because of the low SOD will result in greater susceptibility to deafness (Keithley et al 2005).

Enzymes-antioxidant enzymes, such as Cu/ZnSOD, protect the outer hair cells of the cochlea to the toxic effects of ROS. SOD is important for the survival of cochlear neurons and vascular stria, even half or half the amount of SOD is sufficient, while excessive amounts

does not give better protection against deafness. SOD is an enzyme that is essential for cell survival-the outer hair cells of the cochlea. Another study by Rarey and Yao (1996) Immunohistochemical examination can identify SOD in the spiral ganglion cells in mice. Although most of the stria vaskularis contain SOD, catalase and glutathione peroxidase activation can prevent the degeneration that great. Perhaps the absence of SOD and other enzymes play a role to prevent cell damage vascular stria of superoxide.

In this study the relationship between the degree of hearing loss based on the intensity of the serum levels of SOD statistical test $p = 0.628$ means, not found significant correlation ($p > 0.05$). Thus, the hypothesis of a relationship between serum levels of SOD with the type of sensorineural hearing loss in patients with MDRTB is not proven. The results of this study are not consistent with studies conducted by Sha et al (1999) over-expression of SOD provide protection against the effects of autotoxicity caused by Kanamsisin, which is observed in B6 mice that received antioxidant therapy can maintain the outer hair cells of the cochlea and degeneration of hair cells. Another study by Kawamauto et al (2004) SOD expression in mice with certainty protects the outer hair cells of the cochlea of autotoxic, besides some reports showed overexpression of SOD also protects the outer hair cells from oxidative stress.

Kawamauto et al (2004) conducted a study in mice in the experimental group and the control group, the extent of degeneration of outer hair cells in the cochlea and is calculated starting from the apex to the basal, the percentage of hair cells missing is lacking gradually increased from the basal to the apex. Damage to the outer hair cells of the cochlea causes a decrease in high-frequency sensorineural. Research conducted on one guinea pig ears ear without therapy and those receiving SOD has a tendency protection than the contralateral ear.

Overexpression of SOD effectively protect cochlear hair cells and auditory outside of Kanamycin autautoxicity. Ten of the 48 guinea pigs were studied (20.9%) had a hearing threshold change $\leq$ 20 dB at a frequency of 20000 Hz. The loss of outer hair cells of the cochlea increased gradually from the basal to apical and larger changes in hearing thresholds at high frequencies. Cellular level, the damage caused by aminoglycosides started by ROS formation. Protection by SOD can prevent the effects of autotoxic aminoglycosides can increase ROS. After the reduction of molecular oxygen to superoxide, which is a slow reacting radical, a more aggressive ROS can be formed as radical chain. Prove the hypothesis that the excessive production of free radicals is a major factor and the start of the damage due to autotoxic hearing loss, trauma, noise and aging. The benefits of SOD is to protect superoxide against proradical hydrogen peroxide (H2O2) and then inactivated into oxygen and water by catalase (Kawamauto et al 2004).

Studies in vivo and in vitro by Sha (2005), oxidative stress is suspected as an important event in the process of Kanamycin -induced hearing loss in the long term. Oxidative stress is caused by an imbalance between ROS and antioxidant defense system of the cell. SOD, catalase and glutathione inactivate ROS. If the system loses balance both overproduction of ROS or antioxidant deficiency, the amount of ROS can oxidize very many cell targets, including lipids, DNA, proteins and can cause severe cell damage. Other studies were also done by Priuska and Schacht (1995), Lesniak and Schacht (2005). The hypothesis proved that amino-glycosides cause oxidative stress and have demonstrated the presence of a redox active compound kanamycin-iron-fat, there is the possibility of the production of ROS and ROS also triggered by aminoglycosides.

Kanamycin causes damage to the outer hair cells of the cochlea from the basal to the apex. In larger doses Kanamycin also causes degeneration of the vascular stria, spiral ganglion and hair cell damage if it reaches the apex. Many things can be a factor that is induced autotoxicity cumulative dose, long-term administration (about 6 months), the technique of administration, individual susceptibility variation, extreme age, previous hearing loss, anemia, history of radiation, and the use of other autotoxic drugs.

Free radical theory of aging theory or the latest version of the mitochondria. Based on this hypothesis, aging is associated with improved bioenergetic function caused by the accumulation of mtDNA mutations and increased production of ROS. ROS are oxygen-derived species consisting of unpaired electrons so it is very unstable. Free radicals will react with the nearby molecules to replace the lost electrons to become stable molecules. As a consequence, more free radicals are formed. Free radical theory of aging is caused by the production of ROS by mitochondria and accumulation results from damage to biological macromolecules that lead to decreased function (Martini et al 2007). Meanwhile, according to the mitochondrial theory of aging, mtDNA mutations accumulate progressively during life and are directly responsible for the oxidative phosphorylation system deficiency function (OX-PHOS). Defects in the respiratory chain will lead to increased production of ROS that would be causing the accumulation of mtDNA damage. Be part of the aging process improvement cycle of oxidative damage, which triggered the crisis bioenergetics, metabolic and physiological changes,

such as activation of apoptosis and loss of cell -type specific, tissue dysfunction and increased sensitivity to disease (Martini et al 2007).

Individual susceptibility variations also affect the outer hair cell function impairment in patients with cochlear hearing loss after Kanamycin therapy in patients with MDRTB. The mechanism of cell death in the cochlea due to Kanamycin is through necrosis and apoptosis induced caspase activation. The mechanism depends on the stimulus to cell death and damage caused by one of two mechanisms. Each of these mechanisms is likely to have reduced its potential in some cases to prevent cell death. Protection of auditory sensory cells occurs at the molecular level through three mechanisms that prevent the formation of ROS, neutralization of toxic products, and blockade of apoptotic pathways. Some genes regulate the differentiation of cochlear hair cells and supporting cells from precursor cells embryogenesis. Prevention of ROS formation and neutralization of toxic products can be influenced by endogenous antioxidant in the body of each individual, so as to prevent damage to the outer hair cells of the cochlea.

According to Sha and Schacht (1999), in vivo treatment with visible Kanamycin immune from 4-hydroxynonenal is a marker of lipid peroxidation in the rat cochlea. By Garetz and Schacht (1996) SOD can suppress the effects of ROS, SOD protects the Kanamycin-induced hearing loss in guinea pigs and rats. Protection of SOD is effective in various forms of toxicity. Overexpression of SOD in mice, as anti-oxidants which can detoxify ROS due to the use of Kanamycin. Gene therapy locally as SOD into the cochlea of mice was also reduce autotoxicity. Based on the theory by Ryback and Whitworth (2005) endogen-ous antioxidant enzyme aminoglycoside autotoxicity assist mechanism as autoproteksi.

Antioxidants are compounds electron donor (electron donor). Biologically, the notion antioxidant is a compound that can counteract or reduce the negative impact oxidants in the body. Antioxidants work by donating an electron to the oxidant compounds that are the usual activities of antioxidant compounds inhibited. (Winarsi 2007). SOD protects the body's cells and prevents inflammatory process caused by free radicals. Actually, this enzyme was present in the body, but need the help of mineral nutrients such as manganese (Mn), zinc (Zn), and copper (Cu) in order to work.

CONCLUSIONS

Acquired sensorineural hearing loss with the highest distribution frequency is higher in patients with MDRTB post Kanamycin therapy. There was no significant correlation between serum levels of SOD with the type of sensorineural hearing loss based on the frequency of post-therapy patients with MDRTB Kanamycin. There was no significant correlation between serum levels of SOD with the degree of hearing loss based on the intensity of post-therapy in patients with MDRTB Kanamycin.

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