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CORRELATION BETWEEN ETHAMBUTOL THERAPY DURATION AND ZINC SERUM LEVEL WITH COLOUR VISION DEFICIENCY IN TUBERCULOSIS PATIENTS

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ABSTRACT

Tuberculosis is one of the most common disease in Indonesia. Ethambutol is one of the main regiment therapy for patient with tuberculosis. Duration of ethambutol therapy depends on what category of tuberculosis patient. Ethambutol intake can cause optic neuropathy with colour vision deficiency as an early symptom. Ethambutol therapy can also cause decrease of zinc serum level and it is cause by zinc chelate that can be found in ethambutol. The purpose of this study was to determine the correlation between duration of ethambutol therapy and zinc serum level with colour vision deficiency which examined with Farnsworth Munsell 100 Hue in tuberculosis patients. This is an observational explorative study. Colour vision is xamined with Farnsworth Munsell 100 Hue and zin serum level is detected by blood sample. Data was analyzed by correlation study. Correlation statistic between ethambutol therapy duration with colur vision using Spearman coreelation study found that r = 0,5 and p = 0,00, whereas in correlation between zinc serum level with colour vision found that r = 1,68 and p = 0,32. There is significant correlation and positive direction between ethambutol therapy duration with colour vision deficiency. Even though there is no significant correlation between zinc serum level with colour vision deficiency, there is a strong correlation.

Keywords: Tuberculosis, Ethambutol, Colour Vision, Zinc serum level

1. INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by one of three species of mycobacteria, namely: *Mycobacterium tuberculosis, Mycobacterium bovis, and Mycobacterium africamum.* M. Tuberculosis is the biggest cause of TB in humans.[1] Tuberculosis bacteria can attack any part of the body, and most often is the lungs. Can spread through the air, when an infected patient coughs, sneezes, or talks. Inhalation of very small amounts of bacilli can cause M. tuberculosis infection.[1,2]

In the early 1990s the WHO had developed a TB control strategy known as the Directly Observed Treatment Short-course (DOTS) strategy, and it has proven to be the most economically effective coping strategy, the proper implementation of the DOTS strategy, in addition to quickly suppressing dispersal and also preventing the development of MDRs -TB (Multi Drugs Resistance-TB) Anti-tuberculosis (OAT) drug guidelines used by the National

Tuberculosis Control Program in Indonesia are provided in packages in the form of fixed-dose combination drugs (OAT-KDT), in the form of a combination of ethambutol (EMB), isoniazid, rifampicin and pyrazinamide, the amount of the dose depends on body weight. For a period of time, OAT can have various side effects in various organs of the body including the eye, known as ocular toxicity.[1,3]

Toxicity to the optic nerve is a result of complications from ethambutol therapy. Carr and Henkind, in 1962, reported the dose effect of ethambutol toxicity. Several studies reported the incidence of retrobulbar neuritis in 18% of patients who received> 35mg / kg / day, 5-6% with 25mg / kg / day and <1% with 15mg / kg / day on the use of Ethambutol hydrochloride (EMB) for more than 2 months. No safe dose has been reported, with the toxicity effect studied under doses of 12.3 mg / kg.[4-14] In Hong Kong the dose used in adults and children is 15 mg / kg. Ethambuthol is an effective first-line drug used in the management of tuberculosis. Optic nerve toxicity resulting from the use of ethambutol is well known as a therapeutic complication. Wang and Sadun estimate that about 100,000 new cases of toxic optical neuropathy are caused by ethambutol each year. Ezer et al estimated vision improvement in 22.5 / 1000 people on ethambutol therapy, with permanent loss of vision occurring in 2.3 / 1000 people. The mechanism of toxicity is not yet fully known. A mechanism related to the effect of chelating on ethambutol in mitochondria that contains enzymes.[15]

Ethambutol toxicity occurs due to damage of oxidative phosphorylation of the mitochondria in the Retinal Ganglion Cell (RGC) and the presence of chelating metal in ethambutol can block the oxidative phosphorylation process so that zinc cannot be bound to the mitochondrial in the Retinal Ganglion Cell (RGC) and the presence of chelating metal in ethambutol can block the oxidative phosphorylation process so that zinc cannot be bound to the mitochondrial mitochondria in RGC and this process can trigger mitochondrial apoptosis. In RGC there are 3 major cell types, namely: *Parvocellular* which functions to see colours and have a light response, *Magnocellular* which has greater dendritic cells but lacks response to colour and *Koniocellular* which functions to receive input of blue bipolar cone cells and has a response in blue and yellow. Ethambutol toxicity often occurs between three to five months after treatment, is bilateral, progressive, loss of vision without pain and or decreased colour vision. Research in Hong Kong said that ethambutol toxicity did not occur until 1.5 months after administration of therapy.[7]

Signs and symptoms of optic neuropathy caused by ethambutol can be seen at an early stage. Vision abnormality (discromatopsia) is an early sign that can be detected. Blue-yellow (tritan) defects occur earlier than red-green (protan) defects. Vision improvement caused by ethambutol toxicity can return completely by early detection and cessation of ethambutol can prevent permanent blindness and sharp vision can return within a few months.[7-13] There can also be a significant deficit during recovery in the field of view, colour vision, and contrast sensitivity, reported mean sharp vision can improve between 20% to 80%. Age, hypertension, renal dysfunction and daily dose of ethambutol have an association with increased effects of toxicity. The duration of therapy as a risk factor is still controversial.[7]

Colour blindness is a condition where the patient experiences weakness or decreased ability to distinguish between certain colours that should be distinguished by people with normal vision. The three kinds of colour pigments in the retina allow us to distinguish colours. For can see normally, all three cone pigment cells must work well. If one of the pigments is abnormal or absent, colour blindness

occurs. Colour vision deficiency occurs when one or more cone cells in the retina function less than normal, or do not function at all. Of all types of warmth blindness, the most common case is trichomacy of anomalies, especially deutranomalies which reach 5% in men. Actually, the cause of colour blindness is not only due to an abnormality on the X chromosome, but can have links with 19 different chromosomes and other genes. Some inherited diseases such as cone cell dystrophy and acromatopsia can also cause a person to become colour blind. Colour blindness can also be found in macular disease, the optic nerve, while in retinal abnormalities there are relative abnormalities in vision in blue and yellow while in optic nerve abnormalities are found abnormalities in seeing red and green.

The Ishihara test (Ishihara pseudoisochromatic plates) is used for screening colour vision defects in patients with possible ethambutol toxicity, because this test is easy and usually protects defects. The Ishihara test was made with the aim of detecting protan defects in colour vision, and is not ideal for ethambutol toxicity which shows tritan colour vision defects. [11-12, 15-16] The Farnsworth Munsell 100 hue (FM 100) test can be used to measure chromatic discrimination. It can also help identify deficiencies in colour vision in congenitals, and is useful and sensitive for measuring changes in neuronal disease or Possible side effects of medications such as hydrochloroquine, digoxin, ethambuthol and others. This examination can provide detailed information on the defects of protan, deutran and tritan.[11-12, 16-19]

Zinc is an essential micromineral in the human developmental body, development and immune function. Micronutrient deficiencies such as zine deficiency cause immune disorders and increase the likelihood of infections such as tuberculosis. Hassan Ghulam et al reported that the mean value of zinc concentrations in the pulmonary tuberculosis group before treatment seemed to decrease significantly. Compared to control group. Ray M et al. Studied plasma zine status in 50 children with tuberculosis and compared 10 healthy children and 10 malnourished children without tuberculosis with antituberculosis therapy. Children with tuberculosis have lower plasma zine values than healthy ones, regardless of nutritional status. Karyadi et al. Examined the nutritional status of active pulmonary tuberculosis patients and compared with healthy controls and found poor nutritional status and significantly lower serum zinc values in tuberculosis patients compared with controls.[20-25] The purpose of this study was to determine the correlation between the duration of ethambutol administration and serum zinc levels with colour vision disorders examined by Famsworth Munsell 100 Hue in patients with pulmonary tuberculosis.

2. METHODS

This study used exploratory observational methods to determine the correlation between duration of ethambutol administration and serum zinc levels with colour vision deficiency in patients with pulmonary tuberculosis. The study was conducted at the Eye Clinic of the Neuropthalmology subdivision Mohammad Hoesin Hospital, Palembang on October 2015 – January 2016. The research sample was taken by consecutive sampling. The inclusion criteria were all pulmonary TB sufferers who receive Ethambutol therapy at Mohammad Hoesin Hospital Palembang and age between 18-50 years. The exclusion Criteria were patients with TB with congenital colour blindness, patients with pulmonary TB who are difficult to do the examination, and patients with toxic optical neuropathy due

to other causes. Data analysis using SPSS version 18 statistical to assess the correlation between duration of ethambutol administration and serum zinc levels with Farnsworth Munsell 100 Hue in patients with pulmonary tuberculosis using Spearman's test. This research approved by Health Research Review Committee of Mohammad Hoesin Central Hospital and Faculty of Medicine, Sriwijaya University with ethical clearance number: 447/kepkrsmhfkunsri/2015.

3. RESULT

The research has been conducted at the Eye Clinic of the Neuropthalmology subdivision of Mohammad Hoesin Hospital Palembang, consisting of 36 pulmonary tuberculosis patients who have met the admission criteria. Based on sex, from a total of 36 subject, the subjects in this study were dominated by males, as many as 22 people (61.1%), while female subjects amounted to 14 subjects (38.9%). Research subjects had an age range of 18 to 50 years, with an average age of 37.92 years. The most age group is 50-59 years with 13 subjects (36.1%) and the lowest age group in the 14-19 year with 3 subjects (8.3%). On the subject of research, the highest level of education is 18 subjects (50%), while the smallest number is found in the elementary education group of 7 people (19.4%). On the most occupational research subjects were 17 private employees (47.2%). Most of the study subjects had underweight BMI of 23 subjects (63.9%) followed by a normal weight of 13 subjects (36.1%). The baseline vision of patients with the study was carried out using LogMAR with the most basic vision was <0.5 as many as 34 subjects (94.4%), and in 2 subjects (5.6%) with refractive anomalies. After the best correction (Best Correction Visual Acuity / BCVA), the subject's vision <0.5 with LogMAR became 36 subjects (100%). Examination of colour vision with Farnsworth Munsell 100 Hue is divided into superior, moderate colour discrimination. In the research subjects, the most colour discrimination was superior colour discrimination in 20 subjects (55.6%). In the study subjects, normal colour vision was found in 20 subjects (52.8%), red-green colour disturbance by 3 subjects (8.3%) and blue-yellow colour disturbance in 13 subjects (36.1%). The duration of use of Ethambutol is divided into 0 - 2 months,> 2 - 4 months, and> 4 months. Each research subject as many as 12 people so that the percentage of each is 33.3%. Characteristics of research subjects were presented in Table 1 below.

Table 1. General Characteristics of Research Subjects

Characteristics	Frequency (n)	Percent (%)
Sex		
Male	22	61.1
Female	14	38.9
Age		
14-19 years	3	8.3
20-29 years	8	22.2
30-39 years	5	13.9
40-49 years	7	19.4
50-59 years	13	36.1
Education		
Primary School	7	19.4
Middle School	11	30.6
High School	18	50.0

Occupation		
Does not work	3	8.3
PNS / Profession	1	2.8
Private employees	17	47.2
Housewife	5	13.9
Labor	4	11.1
Student	6	16.7
BMI		
Underweight	23	63.9
Normal weight	13	36.1
Basic vision (LogMAR)		
<0.5	34	94.4
0.5 – 1.0	2	5.6
Visus after BCVA (LogMAR)		
<0.5	36	100
Farnsworth Munsell		
Superior	20	55.6
Average	16	44.4
Red-green deficiency	3	8.3
Blue-yellow deficiency	13	36.1
Duration Ethambutol Consumption		
0 -2 month	12	33.33
>2 – 4 months	12	33.33
4 months	12	33.33

PNS: Pegawai Negeri Sipil; BCVA: Best Corrected Visual Acuity; BMI: Body Mass Index

Correlation analysis using Spearman's test showed that the correlation of duration of use of Ethambutol with the Farnsworth Munsell 100 Hue has significant with moderate correlation (p=0.000 and r=0.558). These statistical results indicate that the duration of use of ethambutol will increase the risk of colour vision disorders in patients with pulmonary tuberculosis. Whereas the correlation between the value of the use of ethambutol were not found to be significant correlation and the direction of correlation is positive (p=0.613 and r=0.087). The results were presented in Table 2 below.

Table 2. Correlation of Duration Ethambutol Consumption with Farnsworth Munsell 100 Hue and Zinc Level

		Farnsworth Munsell 100 Hue	Zinc Levels
Duration Ethambutol Consumption	Correlation coefficient (r)	0.558	0.087
	p	0.000	0.613

Correlation power, from correlation coefficient: 0 (no correlation); 0.00-0.199 (very weak); 0.20-0.39 (weak); 0.40-0.59 (medium); 0.60-0.79 (strong); 0.80-1.0 (very strong)

Reciprocally, the correlation between serum zinc values with Farnsworth Munsell 100 Hue and serum zinc level was is no statistically significant correlation (p =

0.326 and r = 0.168). The analysis was presented in Table 3 below.

Table 3. Correlation of Farnsworth Munsell 100 Hue and Zinc Level

		Zinc Levels
Farnsworth Munsell	Correlation coefficient (r)	0.168
	p	0.326

Correlation power, from correlation coefficient: 0 (no correlation); 0.00-0.199 (very weak); 0.20-0.39 (weak); 0.40-0.59 (medium); 0.60-0.79 (strong); 0.80-1.0 (very strong)

4. DISCUSSION

Most of the subjects of this study were 61.1% male, while 38.9% female. This finding is similar to research from Joubert et al in 1986 where the majority of research subjects were men as much as 83.3%. Karyadi's research in June 2000 in Jakarta found that the majority of men were 62.2%. Then Karyadi et al continued their research in September 2000 with a total of 82 subjects and obtained a majority of men as much as 60.9%. Reyes et al in 2013 conducted a study in the Philippines with 105 subjects getting a percentage of male subjects by 73.3%.[22,23]

Men are considered to be more susceptible to exposure to mycobacterium tuberculosis not only by biological function but also due to higher mobility and activity than women. Can also be caused by the impact of risk factors from exposure such as smoking, employment, industrial exposure and others. Vulnerability of men to tuberculosis exposure is not only happening in Indonesia. According to data from the World Health Organization (WHO), other Southeast Asian countries also have the same case, namely pulmonary tuberculosis is more experienced by men. According to WHO data in Thailand, in 2006 had 29,081 new cases of positive tuberculosis with 70% were male. Likewise, in Myaumar, 66% of tuberculosis sufferers in the country are male. [3,32]

The results of this study are consistent with the research of Reyes et al who examined the research subjects at the age of 16-68 years with an average age of 37.1 years. In the study of Cruz et al also found the average age of research subjects was 38.67 years. And also, in the study of Rao et al found that the most age group in the group 40-60 years as many as 47 people at least under the age of 20 years as many as 7 people and the average age of 45 years. This shows that pulmonary tuberculosis is more common in adult patients. So, based on the age of patients with tuberculosis, the rate of transmission of this disease is higher in the productive age because it more often interacts with the surrounding environment. In contrast to research by Karyadi et al in which the most subjects were in the age group 21-30 years as many as 41 people (46%). Whereas in the research of Joubert et al, it was found that the average age of the research subjects was 52 years. [4-13,15,22,32]

The level of education of the research subjects was mostly high school / equivalent as many as 18 people (50.0%) with junior high / equivalent of 30.6% and elementary / equivalent 19.4%. The subject of this study has a high percentage of secondary education. WHO states that pulmonary tuberculosis not only attacks people at productive age, but also attacks people with low education. This is because the level of education influences the level of public knowledge on information about

fulfilling balanced nutrition and the prevention and treatment of pulmonary tuberculosis.

The BMI variable of this study subject was the most in the underweight group of 23 people (63.9%), followed by normal weight in 13 people (36.1%). The study of Karyadi et al in 2000 found 57 patients (underweight BMI) (63.3%). Then Karyadi et al continued the research in 2002 and got underweight research subjects as many as 51 people (63.7%). Research Cruz et al found that underweight as many as 41 people (64.1%), followed by normal weight 19 people (29.6%) and overweight in 4 people (6.3%). Nutritional status is one of the factors that influence the outbreak of pulmonary tuberculosis that is actively experiencing weight loss and decreased appetite. Also followed, in developing countries where there are still many poor people, so there is a lack of micronutrient intake.[12]

Baseline Visual Examination of patients with Snellen Chart that was converted to LogMAR and obtained the most vision results was <0.5 ie 34 people (94.4%) and 2 people (5.6%) had a baseline vision 0.5-1.0 at two research subjects were found refractive anomalies. So the best correction was performed on the subject and the vision was <0.5 after correction. All subjects were screened for colour vision screening with Ishihara and normal results were obtained. Where this examination is easier to do and easy to interpret. Usually this tool is also used to detect congenital colour vision abnormalities and red-green colour vision disorders. This tool has flaws in assessing blue-yellow colour vision disorders. Ishihara is also able to assess protan defects in colour vision but this tool is not ideal for assessing tritan defects that occur in the use of ethambutol. Inspection with Farnsworth Munsel 100 Hue is a gold standard for examining colour vision because it is more sensitive and can analyze quantitatively. In the study subjects, the results of the assessment of superior colour vision in 20 subjects (55.5%) and moderate colour vision in 16 subjects (44.4%). Examination abnormalities are divided into red-green colour vision disorders and blue-yellow colour vision disorders. Red-green colour vision was found in 3 people (8.3%) and blue-yellow colour vision disorder in 13 people (36.1%). In the study of Kaimbo et al, the examination of all research subjects found normal Ishihara examinations, while the examination with Farnsworth Munsell found 15 people (36%) had a total scorehigh error. Kaimbo et al then grouped colour vision disorders, so that red-green colour vision problems were found at 13.1% and blue-yellow colour vision disorders by 7.5%. The results from Kaimbo et al's study said that blue-yellow colour vision disorder is an early symptom of ethambutol intoxication, while red-green colour vision disorder is a symptom that can be found afterwards. This colour change can occur despite the sharp vision of normal patients. Colour vision disorders are a sensitive indicator of early optic neuropathy symptoms due to ethambutol. [10-11]

Colour vision disturbances can occur several weeks after using ethambutol, but there are also those that occur after 5 months of therapy. Therefore, in this study the duration of use of ethambutol was divided into 3 groups namely 0-2 months, groups> 2-4 months and> 4 months. Zinc levels in serum are examined in the laboratory using an Atomic Absorption Spectrophotometer (AAS). In this study, a minimum value of 13.7 pumol / L was obtained and a maximum value of 58.1 umol / L. Whereas in the study of Karyadi et al obtained values of zinc levels in serum 10.7 - 22.9 umol / L. So, in this study the researchers searched for a cut-off point for zinc levels in serum and obtained a figure of 32.3 umol / L with a sensitivity of 68% and a specificity value of 70%. After obtaining the default limit value, grouping

is carried outserum zinc levels. Levels lower than 32.3 μmol are grouped into zinc levels less than normal and when greater than 32.3 μmol / L are classified as normal serum zinc levels.

In this study, an analysis with Spearman Correlations was conducted to see whether there was a significant correlation between the duration of use of ethambutol with the examination of Farnsworth Munsell 100 Hue. The results show that there is a significant relationship with the value of p = 0.00 (p <0.05) with moderate correlation strength (r=0.558). So, it can be said that the use of ethambutol will increase the risk of colour vision disorders in patients with pulmonary tuberculosis. On the scatter dot chart found a higher point that is in the administration of long ethambutol (18 months), still obtained superior colour vision. This can be caused by factors of good patient nutrition and young age. Cruz et al obtained the results of research that on the use of ethambutol for 39 days can cause visual impairment in colour, although there are also subjects who experienced colour vision problems after 5 months of use. [10-12]

To obtain a correlation value between serum zinc levels and Farnsworth Munsell 100 Hue also performed with Spearman Correlations. The aim is to find out whether there is a correlation between serum zinc levels and colour vision disturbance on the Farnsworth Munsell 100 Hue examination. The results obtained p=0.326 (> 0.05) and r = 0.168, so there is no significant correlation between zinc levels in serum with colour vision disturbances at Farnsworth Munsell 100 Hue with strong correlation strength. Research Bhandari et al and research Muhsin et al said that zinc deficiency is known to be an important factor that causes disruption of immune cells that can increase the incidence of tuberculosis. There can be a decrease in serum zinc levels in patients with active tuberculosis and an increase in serum zinc levels after an improvement in administration of anti-tuberculosis drugs and an increase in nutritional status. Ray's research says that there can be changes in serum zinc and copper levels in patients using anti-tuberculosis drugs. After finishing treatment, there can be a significant increase in serum zinc levels. where the serum copper levels decrease with tuberculosis treatment. Koyonagi et al examined zinc levels in serum and copper in patients with pulmonary tuberculosis, there was an increase in serum copper levels and copper / zinc ratio compared to normal individuals, where zinc levels in serum decreased compared with the control group. Serum copper levels in patients using anti-tuberculosis drugs are significantly reduced. The reason for the increase in serum copper levels in patients with pulmonary tuberculosis which is very important is the presence of homeostasis from copper due to its ability to move through the pump, so that copper exits the cell before it damages intracellular components. As a metal chelator found in ethambutol, zinc and copper can interfere with oxidative phosphorylation and mitochondrial function, and the synthesis is divided into two complexes. Complex I is that which contains zinc and complex IV which contains copper and other ingredients. Both of these complexes can be used for the formation of ATP which functions as mitochondrial synthesis and metabolism. If there is damage in the long-term ATP production and a buildup of reactive oxygen species (ROS), it can cause apoptosis. Therefore, there can also be colour vision disturbances if there is a decrease in serum copper levels in sufferers of pulmonary tuberculosis. [2,20,24-25]

In this study there are still limitations because there are still other factors that can affect the interference with colour vision in patients with pulmonary tuberculosis using ethambutol.

5. CONCLUSION

Based on the research that has been done, it can be concluded that there is a correlation between the duration of ethambutol administration and colour vision examined by Farnsworth Munsell 100 Hue in patients with pulmonary tuberculosis in Mohammad Hoesin General Hospital Palembang. There was no significant correlation between serum zinc levels and colour vision in patients with pulmonary tuberculosis at Mohammad Hoesin General Hospital Palembang, so it was concluded that the longer use of ethambutol could cause colour vision disorders. In addition to colour checking with Ishihara, it is necessary to do a more sensitive examination to assess colour vision disorders using Farnsworth Munsell 100 Hue. It is necessary to evaluate zinc levels in patients with pulmonary tuberculosis to prevent colour vision problems. Further research needs to be done with more samples and more time to use ethambutol to evaluate colour vision disorders that occur. Further research needs to be done to see the scraping of copper levels that affect colour vision disorders in patients with pulmonary tuberculosis.

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