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COMPARISON OF COPPER LEVEL AND COLOR VISION IN PULMONARY TUBERCULOSIS PATIENTS BEFORE AND AFTER ETHAMBUTOL TREATMENT IN CATEGORY I AND II

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ABSTRACT

Copper as a metal chelator in ethambutol may interfere oxidative phosphorylation and mitochondrial function that are useful in the formation of ATP, so that long-term damage can cause apoptosis and interfere color vision. This study aims to determine the correlation between duration of ethambutol and copper levels in serum with color vision disorder examined with Farnsworth Munsell 100 Hue (FM_{100}) in patients with tuberculosis. This study was an explorative observation of 20 samples during November 2017 - January 2018 period. Comparative analysis using independent t-test, paired t-test, Wilcoxon test and Mann-Whitney test, while correlation analysis using Spearman's test and Pearson's test. There was a significant difference of FM_{100}value before and after in category I (p=0.000) with increase of total error value 11.80+5.31 or category II (p=0.000) with increase of total error value 15.00+7.41. There was significant difference of Cu^{2+} level before and after in category I (p=0.005) with decrease of Cu^{2+} level 15.57+5.04 mg/dL or category II (p=0.005) with decrease of Cu^{2+} level 31.66+7.35 mg/dL. The duration of Ethambutol was related to changes in color vision examined with FM_{100}.

Keywords: color vision, copper (Cu^{2+}), ethambutol, Farnsworth Munsell 100 Hue, tuberculosis

1. INTRODUCTION

Tuberculosis is an important public health problem because one third of the world's population is infected by the Mycobacterium tuberculosis bacteria. The World Health Organization (WHO) in 1993 declared tuberculosis a global concern that must be addressed jointly by all countries in the world. WHO also estimates that as many as 2-4 people are infected with TB every second, and nearly 4 people every minute die of TB. TB facts in Indonesia to date there are a quarter million cases and 140,000 deaths occur annually, and TB in Indonesia is the number one killer among infectious diseases and number three after heart disease and acute respiratory disease in all ages. Data taken from the Palembang City Health Profile in 2014 showed the number of pulmonary TB cases of 1972 cases.[1-5]

In line with the increase in TB cases, in the early 1990s WHO and IUATLD developed a TB control strategy known as the DOTS (Directly Observed Treatment Short-course) strategy. The main focus of DOTS is the discovery and healing of patients, priority is given to infectious type TB patients. This strategy aims to break the chain of TB transmission and thereby reduce the incidence of TB in the community and prevent the development of MDR-TB (Multi Drugs Resistance-TB). The treatment that isused by the National Program for TB Control by the Government of Indonesia using the DOTS strategy is the use of Anti Tuberculosis Drugs (OAT). Commonly used drugs are Isoniazid, Etambutol, Rifampicin, Pirazinamid, and Streptomycin. This group of drugs is referred to as primary or first-line drugs. [3,4,6]

Ethambutol is one of the drugs used in the initial line of TB therapy, and its side effects in the form of optic neuropathy have been known since the first use of TB drugs in 1960.9 Optic neuropathy that occurs in the use of ethambutol depends on the dose and duration of use of ethambutol. Side effects caused by the use of ethambutol can occur in patients who have used the drug for at least 2 months, while symptoms generally appear between 4 months to one year. Kumar, reported that ethambutol toxicity occurred was 42.2% within 10-12 months after administration of ethambutol. Robert reported that administration of ethambutol 15 mg / kg / day for 4-8 months of therapy can cause optic nuropathy in 1.6% of cases and if given at a dose of 25 mg / kg / day cause optic neuropathy in 2.48% of cases. [4-5,7,8,9]

Ethambutol has a toxic effect on nerve fibers in the retinal ganglion. The onset of complaints in the eye is usually slow, can be months after starting therapy (on average between 3-5 months, some even up to 12 months), rarely appearing acutely. Affected patients will complain of a sharp decrease in vision in both eyes without pain, a decrease in contrast and color sensitivity and visual field disturbances. On inspectionphysically, the disturbance that occurs in both eyes is symmetrical. Discromatopsia (color perception abnormalities) is usually the earliest sign of toxicity, classically shown by a decrease in red-green color perception that is assessed using ishiara. Contrary to this, Polak et al reported that blue-yellow defects were the most common initial defects in patients without symptoms of visual impairment. But the blue-yellow defect can only be detected using the Lantony desaturation panel or using Farnsworth Munsell 100 hue (FM_{100}), not using Ishihara. [8-14]

The toxicity that occurs in the use of ethambutol is still hypothetical. This hypothesis links toxicity to occur through oxidative phospholiration disorders so that metabolism in the mitochondria of Retinal Ganglion Cells (RGCs) is also disrupted. Mitochondria play an important role in the process of anaerobic respiration, which produces ATP as a source of cellular energy. The latest research conducted on the role of Cu in ethambutol toxicity found that Cu plays a role in ethambutol toxicity by triggering the occurrence of mitochondrial apoptosis in RGCs. [8-9,15-26]Copper (Cu) is a metal called the "essential trace element" which is an important element in the growth and development of almost all

microorganisms, including bacteria. The function of Cu in the eye plays a role in maintaining vision. [26-29] As a metal chelator found in ethambutol, Cu can interfere with oxidative phospholiration and mitochondrial functions that are useful in the formation of ATP.

Therefore,color vision disorders can also occur if there is a decrease in serum Cu levels in patients with pulmonary tuberculosis. In several studies conducted by Koyonagi et al, found serum Cu levels in patients using anti-tuberculosis drugs significantly decreased. Abdonasser et al reported that after 10 days of Ethambutol treatment, the level of Cu in pulmonary tuberculosis patients decreased significantly. They also state that these results support the hypothesis that Ethambutol with Cu can make complex chemical reactions in the body and cause changes in Cu concentration. [27-31]

Based on the above data it can be said if the use of ethambutol can reduce Cu levels which ultimately can cause color vision disorders.The purpose of this study was to determine the comparison of serum copper levels and color vision disorders in patients with active pulmonary tuberculosis before and after ethambutol administration of category I and category II.

2. METHODS

This study is a prospective study that aims to assess the comparison between serum levels of copper and color vision disorders in patients with pulmonary tuberculosis before and after administration of category I and category ethambutol. This research was conducted at Mohammad Hoesin Hospital Palembang and Merdeka Public Health Center. The entire implementation time starts from November 2017 to January 2018. The target population is all pulmonary TB sufferers who seek treatment at the Internal Medicine Clinic of RSMH and Merdeka Public Health Center in Palembang.The sample selection method used is consecutive sampling.

The inclusion criteria of this study were (a) all pulmonary TB patients who received category I and category II ethambutol therapy. (b) Willing to follow the stated research by signing an informed consent letter (c) Age between 18-69 years. While the exclusion criteria are TB sufferers with congenital color blindness (b) Lung TB patients who are difficult to do the examination. Patients with toxic optic neuropathy for other reasons. (c) Patients who have anterior segment abnormalities. Patients who have posterior segment abnormalities.

All data is displayed in the form of tabulated data and performed statistical analysis using a computer program with the SPSS program. For the general characteristics of research subjects, the normality test with Shapiro-Wilk will be used. Comparisons before and after the use of category I and category II use the paired t test (parametic) and the Mann-Whitney test (nonparametric). Correlation in this research will be analyzed using Pearson test (parametric) and Spearman test (nonparametric).

3. RESULT

General characteristics of research subjects are presented in Table 4.1 below.

Table 1. General Characteristics of Research Subjects

Characteristics	Frequency (n)	Percent (%)
Sex		
Male	10	50
Female	10	50
Age		
20-29 years	5	25
30-39 years	10	5
40-49 years	2	10
50-59 years	2	10
60-69 years	1	5
Education		
Primary School	2	10
Middle School	8	40
High School	9	45
Bachelor	1	5
Occupation		
Does not work	1	5
Housewife	3	15
labour	4	120
Student	1	5
PNS / Profession	1	5
Private employees	10	50
BMI		
Underweight	12	60
Normal weight	8	40
Basic vision OD		
<0.5	15	75
0.5 – 1.0	5	25
Basic vision OS		
<0.5	17	85
0.5 – 1.0	3	15
Ishihara		
Normal	20	100
Abnormal	0	0
Farnsworth Munsell		
Superior	12	60
Average	8	40
Red-green deficiency	2	10
Blue-yellow deficiency	6	30
Duration Ethambutol Consumption	10	50
0 -2 month	3	15
>2 – 4 months	7	35
4 months		

PNS: Pegawai Negeri Sipil; BMI: Body Mass Index

Based on the non-parametric comparison test using the Mann-Whitney test, the results showed that there were no statistically significant differences in Cu levels before Ethambutol therapy in the category I and category II with a p value = 0.075. While, based on the non-parametric comparison test using the Mann-Whitney test, the results showed that there was a statistically significant difference in Cu levels after between the category I and category II groups with a value of p = 0,000

Table.2 Comparison of Cu levels before and after in category I and II

Cu Before	p*	Cu After	p**
80.40±3.07 µg/dL	0.075	64.83±5.39 µg/dL	0.000
75.62±5.49 µg/dL		43.96±5.94 µg/dL	

*Mann-Whitney Test (p<0.05)
**Paired T Test (p<0.05)

In the category 1 group, it was found that changes in Cu before and after were equal to 15.57 ± 5.04 µg / dL. Based on the analysis of the Wilcoxon test the results show that there are statistically significant differences in Cu levels before and after in category I with a value of p = 0.005. In the category II, it was found that changes in Cu levels before and after ethambutol therapy were 31.66 ± 7.35 µg / dL. Based on the analysis of the Wilcoxon test it was found that there were statistically significant differences in Cu levels before and after ethambutol therapy in category II with a p value = 0.005.

Table. 3 Comparison of Cu levels in Category I and II

	Cu Before	Cu After	Difference	p***
Category I	80.40±3.07 µg/dL	64.83±5.39 µg/dL	15.57±5.04	0.000
Category II	75.62±5.49 µg/dL	43.96±5.94 µg/dL	31.66±7.35	0.005

***Wilcoxon Test (p<0.05)

In this study the results showed that the results of FM100 examination before ethambutol therapy in category I were 11.30 ± 3.89 while in category 2 it was 24.40 ± 6.72. Based on the parametric comparison test using the unpaired T test shows that there are results a statistically significant difference before the FM_{100} examination results between the category I and category II groups with a value of p = 0,000.

Table 4. Comparison of the results of the FM_{100} before and after in categories I and II

	p**	FM_{100} After	p**
Category I	0.000	23.10±7.79	0.000
Category II		39.40±8.38	

**Paired T Test (p<0.05)

In the category I group, there was an increase in the total error value before and after, which was 11.80 ± 5.31. Based on the analysis of paired T test results obtained that there are significant differencesof FM100 examination results before and after in category I with a value of p = 0,000.In the category II group, an increase in the total error value before and after was equal to 15.00 ±7.41. Based on the analysis of the paired T test results showed that there were statistically significant differences in the results of the FM_{100} examination before and after in category II with a value of p = 0,000.

Table. 5 Comparison of FM_{100} in Category I and II

	FM_{100} Before	FM_{100} After	Difference	p**
Category I	80.40±3.07 µg/dL	64.83±5.39 µg/dL	11.80±5.31	0.000
Category II	75.62±5.49 µg/dL	43.96±5.94 µg/dL	15.00±7.41	0.000

**Paired T Test (p<0.0

4. DISCUSSION

The distribution of the subjects of this study was based on gender, that is not found differences, male and female 10 subjects each (50%). The results of this study differed from the findings of Nazari et al in 2009 that were 26 subjects (43.3%) female and 34 subjects (56.7%) male. Reyes et al in 2013 in the Philippines also found that 105 subjects were male by 73.3% .[28-29]

The findings of this study that there are no differences in sex might be influenced by several factors. Men can be considered more susceptible to mycobacterial tuberculosis microbial exposure 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 Myanmar, 66% of people with tuberculosis in the country are male.[3,4]

Other studies in several developing countries say that tuberculosis patients suffer more women than men. Because most of the population are poor families, while the fact is that in the process of cooking food, many women are exposed to smoke from firewood or biogas (cow dung which is burned as fuel in the room. Due to the dominant role in the household, poor women often dwell in homes with poor lighting and ventilation. [3,4]

The most subjects in this study were the age group of 30-39 years, with 10 subjects (50%), while the least age group was 60-69 years, amounting to 1 person (5%). The age of the oldest study subjects was 62 years and the youngest at the age of 24 years and the average age of the study subjects was 36.35 years. 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. Research Cruz et al also showed the average age of the study subjects was 38.67 years. This shows that pulmonary tuberculosis is more common in adult patients. So, based on the age of tuberculosis patients, the rate of transmission of this disease is higher in the productive age because it interacts more frequently with the surrounding environment.[8,14,15,17,28]

The distribution of the education level of the subjects of this study is 1 subject (5%), 9 subjects (45%) high school, 8 subjects (40%) and 2 subjects (10%) of elementary school. These results are in accordance with the research of Karyadi et al. 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. Other studies by Suswati showed that there was no relationship between education levels in tuberculosis patients.

In this study, the most types of work were private employees, namely 10 subjects (50%) while 1 subject (5%) who did not work and 3 subjects (15%) became housewives. The same thing in the study of Karyadi et al found that the type of work the subject of research was private workers by 23 people (40%). The type of work a person influences on family income. Because family income will have an impact on the quality and patterns of daily living including consumption of nutritious food and health care. In this study as many as 12 subjects (60%) had underweight nutritional status while 8 other subjects (40%) had normoweight nutritional status. These results are consistent with the findings of the study of Karyadi et al in 2000 to get patients with underweight IMT as many as 57 (63.3%). Then Karyadi et al continued research in 2002 and obtained underweight research subjects of 51

people (63.7%). Research Cruz et al showed the results of underweight subjects as many as 41 people (64.1%), followed by normoweight of 19 people (29.6%) and overweight in 4 people (6.3%). Nutritional status is one of the factors that influences the development of active pulmonary tuberculosis which experiences weight loss and decreased appetite. Also followed, in developing countries where the population is still poor, there is a lack of micronutrient intake.[14.29]

Examination of subjects with Snellen Chart converted to LogMAR and obtained 15 subjects (75%) for the right eye and 17 subjects (85%) for the left eye had <0.5, while 5 subjects (25%) with refractive anomalies having sharp basic vision of 0.5-1.0.All subjects were screened for color vision screening before and after the use of category I and category II Ethambutol with Ishihara and normal results were obtained. Where this examination is cheaper and easier to interpret. Usually this tool is also used to detect congenital color vision abnormalities and red-green color vision disorders. This tool has a deficiency in assessing disturbances in assessing visual impairment in blue and yellow. Ishihara can also assess protan defects in color vision but this tool is not ideal for assessing tritan defects that occur in the use of ethambutol, so we need to use the Farnsworth Munsell 100 Hue tool to detect color disturbances that occur in pulmonary TB patients using ethambutol.[8, 31-35]

Examination with Farnsworth Munsel 100 Hue is the gold standard for checking color vision because it is more sensitive and can analyze quantitatively. In the study subjects, the results of the assessment of superior color vision were 12 subjects (60%) and average color vision in 8 subjects (40%). Examination disorders are divided into visual disturbances in red and green and blue-yellow in vision. Red-green color vision impairment in 2 people and blue and yellow color vision disorder in 8 people. Based on Mira Tetiana's research, the examination of all research subjects obtained normal ishihara examination, while the Farnsworth Munsell 100 Hue examination found 16 people (44.4%) there was a moderate error value. Tetiana Mira, Azri Wahyuni Devi, Saleh Irsan, Rasyid Ahmad categorized the visual impairment of red-green as much as 8.3% and 44.4% of the blue-yellow visual impairment. Based on research Kaimbo et al said that the disorder blue-yellow color vision is an early symptom of ethambutol intoxication, while red-green color vision disorder is a symptom that can be found afterwards. Changes in color can occur despite the sharp vision of normal patients. Color vision disturbance is an early sensitive indicator of optic neuropathy symptoms due to ethambutol.[8,9,12,13]

The distribution of research subjects based on the length of use of ethambutol obtained as many as 10 subjects (50%) using ethambutol for 0-2 months and as many as 7 subjects (35%) using ethambutol for> 4 months. Color vision disorders can occur in a few weeks after using ethambutol, but some also 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.[8,17]

In this study, subjects in category 1 groups were obtainedexperiencing changes in Cu levels before and after namely a decrease of 15.57 ± 5.04 μg / dL. Based on the analysis of the Wilcoxon test the results show that there are statistically significant differences in Copper content before and after in category 1 with a value of p = 0.005. In the category 2 group, there was a change in Cu levels before and after, ie a decrease of 31.66 ±7.35 μg / dL.Based on the analysis of the Wilcoxon test the results show that there are statistically significant differences in Cu levels before and after in category 2 with a value of p = 0.005. Based on the non-parametric comparison test using the Mann-Whitney test, the results showed that there were statistically significant differences in Copper levels after between the category I and category II groups with a p value = 0,000. In this study also obtained an average value of Cu levels after the use of ethambutol in the category I group of 64.83 ± 5.39 μg / dL and in the category II group of 43.96 ± 5.94 μg / dL. Cu levels lower than 63.7 μg / dL are classified into Cu levels less than normal and Cu levels 63.7 μg / dL-140.12 μg / dL are classified as normal Cu levels.

Copper contained in ethambutol interferes with oxidative phosphorylation, by not binding copper by mitochondria in the formation of ATP. This situation results in a change in the mitochondrial membrane potential, which then results in an increase in mitochondrial tissue fragmentation resulting in the formation of vacuoles in the mitochondria. [18,21-23] The function of Cu in the eye plays a role in maintaining vision. The latest research conducted on the role of Cu in ethambutol toxicity found that Cu plays a role in ethambutol toxicity by triggering the occurrence of mitochondrial apoptosis in RGCs. [26-29]

In several studies conducted by Koyonagi et al, that in patients with pulmonary tuberculosis, serum Cu levels were obtained in patients using anti-tuberculosis drugs significantly decreased.Abdonasser et al reported that after 10 days of Ethambutol treatment, the level of Cu in pulmonary tuberculosis patients decreased significantly. They also state that these results support the hypothesis that Etambutol with Cu can make complex chemical reactions in the body and cause changes in concentration*n*.[28-30]

In the category 1 group, there was an increase in the total error valuethrough FM_{100} examination before and after, which is 11.80±5.31. Based on the analysis of paired T test results obtained that there are statistically significant differences in the results of the FM_{100} examination before and after in category 1 with a value of p = 0,000. In the category 2 group, there was an increase in the total error value through FM_{100} examination before and after, which was 15.00±7.41. Based on the analysis of paired T test results obtained that there were statistically significant differences in the results of the FM100 examination before and after in category 2 with a value of p = 0,000. Based on the unpaired T test shows the results that there is a statistically significant difference in the results of the FM_{100} examination after between the category 1 and category 2 groups with a value of p = 0,000. Polak et al reported that blue-yellow defects were the most common initial defects in

patients taking ethambutol therapy without symptoms of visual impairment. But the blue-yellow defect can only be detected using the Lantony desaturation panel or using Farnsworth Munsell 100 hue (FM $_{100}$), not using ishihara.[8,12,32]

5. CONCLUSION

Based on the research that has been done, it can be concluded that there is a significant comparison between FM_{100} examination before and after the use of ethambutol in category I and 2 in lung patients and also obtained a significant comparison between Cu levels before and after the use of ethambutol in category I and II on pulmonary sufferers, so it can be concluded that the longer use of ethambutol can cause color vision disorders and a decrease in serum copper levels in the blood.This study found no significant correlation between the examination of Cu and FM100 Hue levels before and after the use of category I and category II ethambutol, this shows that the decrease in color vision was not only influenced by serum Cu levels but also influenced by several other factors.In addition to a color check with Ishihara, it is necessary to do a more sensitive examination with Farnsworth Munsell 100 Hue to assess color vision disorders in patients with pulmonary tuberculosis who are given ethambutol therapy.It is necessary to evaluate copper levels in patients with pulmonary tuberculosis to prevent color vision problems.Provision of antioxidant supplements containing copper preparations in pulmonary TB patients receiving ethambutol can help reduce the effects of color vision changes.Need further research on pulmonary TB patients who use ethambutol for more than 6 months as in MDR TB patients to evaluate the deficiency of color disorders that occur.

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