

## **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**

**Introduction.** to determine the correlation between duration of ethambutol and copper levels in serum with color vision disorder examined with Farnsworth Munsell 100 Hue (FM100) in patients with tuberculosis.

**Methods.** 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.

**Results.** There was a significant difference of FM100 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  $\text{Cu}^{2+}$  level before and after in category I ( $p=0.005$ ) with decrease of  $\text{Cu}^{2+}$  level  $15.57+5.04$  mg/dL or category II ( $p=0.005$ ) with decrease of  $\text{Cu}^{2+}$  level  $31.66+7.35$  mg/dL. There was significant correlation between color vision and duration of ethambutol ( $p=0.000$ ), but there was no significant correlation of  $\text{Cu}^{2+}$  with color vision ( $p>0.05$ ).

**Conclusion.** The duration of Ethambutol was related to changes in color vision examined with FM100.

**Keywords.** color vision, copper ( $\text{Cu}^{2+}$ ), ethambutol, Farnsworth Munsell 100 Hue, tuberculosis

### **Introduction**

Tuberculosis is one of public health problem. One third of population is infected by Mycobacterium tuberculosis. World Health Organization (WHO) estimated 2-4 people are infected with TB every second, and nearly 4 people every minute died from TB. In Indonesia, there are a quarter million cases and 140,000 deaths occur annually, and TB is number one

killer among infectious diseases and number three after heart disease and acute respiratory disease in all ages. Data taken from the 2014 Palembang City Health Profile shows the number of cases of pulmonary TB was 1972 cases.<sup>1-5</sup>

Ethambutol is used in initial TB therapy. Its side effects, optic neuropathy, have been known since 1960. Optic neuropathy depends on dose and duration of ethambutol treatment. This side effect of ethambutol can occur in patients who have used the least medication 2 months, whereas symptoms generally appear between 4 months to one year. Kumar, reported that ethambutol toxicity was 42.2% within 10-12 months after giving ethambutol. Robert reports that administration of ethambutol 15 mg / kg / day for 4-8 months of therapy cause optic neuropathy in 1.6% of cases and when given at a dose 25 mg / kg / day causes optic neuropathy in 2.48% of cases.<sup>4-5,7,8-9</sup>

Toxicity of ethambutol using is still hypothetical. This hypothesis try to prove toxicity occurs through oxidative phospholiration disorders in Mitochondria of Retinal Ganglion Cells (RGCs) are also disrupted. The latest study conducted on the role of Cu in ethambutol toxicity. Cu triggers mitochondrial apoptosis in RGCs.<sup>8-9,15-26</sup>

Copper (Cu) is an essential trace element. It is an important element in growth and development almost in all microorganisms. In the eye, Cu plays a role in maintaining vision.<sup>26-29</sup> Cu is one of element in ethambutol. Cu can interfere oxidative phosphorilation and mitochondrial functions. Long-term effect of Cu is induce apoptosis. Color vision function i can also occur if there is a decrease in serum levelss disturbed in patients with pulmonary tuberculosis. In several studies conducted by Koyonagi et al, Cu serum levels in patients who using anti-tuberculosis drugs is significantly decreased. Abdonasser et al reported that after 10 days of Ethambutol treatment, Cu levels in pulmonary tuberculosis patients were significantly decreased.<sup>27-31</sup>

## Methods

This is a prospective study that aim to assess the ratio between serum copper levels and visual color impairment in patients with pulmonary tuberculosis before and after administration ethambutol in category I and category II Tb therapy. This study was undertaken in November 2017 to January 2018. There were 20 patients who met the inclusion and exclusion criteria. The protocol has been approved of Ethics Committee, Faculty of Medicine Sriwijaya University.

After an interview to assess clinical data, we perform ophthalmological examination. Color vision function is assessed by Farnsworth Munsell 100 Hue examination. Examination of Copper serum level is by taking blood samples as much as 3 cc and examined at the Biomolecular Laboratory, Faculty of Medicine Sriwijaya University.

All data are described in univariate table and graph. Data analysis was performed using SPSS. We use Shapiro Wilk to assess normality distribution. Comparison of each group was tested using Mann-Whitney test. Correlation in this study was tested by Pearson test (parametric data) and Spearman test (non parametric).

## Results

In the period November 2017 to January 2018., there were 20 patients who met the inclusion and exclusion criteria. Examination of color vision with Farnsworth Munsell 100 Hue proved the highest color discrimination is obtained in 12 subjects (60%) and others had average color discrimination as many as 8 subjects (40%).

**Table 1.** Comparison of Copper Level Before Ethambutol Treatment.

	<b>Cu Serum</b>	<b>P*</b>
First Category	80.40±3.07 µg/dL	0.07
Second Category	75.62±5.49 µg/dL	

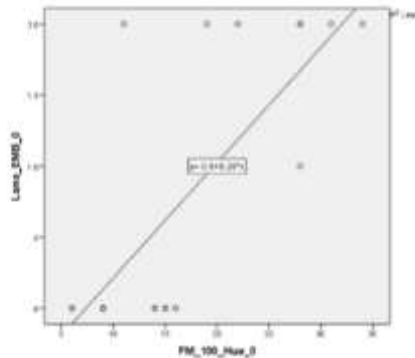
**Table 2.** Comparison of Copper Level After Ethambutol Treatment.

	<b>Cu Serum</b>	<b>P*</b>
First Category	64.83±5.39 µg/dL	0.00
Second Category	43.96±5.94 µg/dL	

**Table 3.** Comparison FM<sub>100</sub> Examination Before and After Ethambutol Therapy

	Before Treatment	After Treatment	ΔFM100	
First Category	11.30±3.89	23.10±7.79	11.80±5.31	0.000
Second Category	24.40±6.72	39.40±8.38	15.00±7.41	0.000

Paired T test ( $p < 0.05$ )



**Figure 1.** Correlation of FM100 examination before and after ethambutol therapy

Correlation between FM100 examination before and after ethambutol therapy was assessed by Pearson's correlation test. Obtained the value of  $r = 0.580$ . P value 0.000 means there is a moderate strength correlation and has a positive statistically significant result. There was significant correlation between color vision and duration of ethambutol ( $p=0.000$ ), but there was no significant correlation of  $\text{Cu}^{2+}$  with color vision ( $p>0.05$ ).

## Discussion

In this study, Cu levels before and after ethambutol therapy in category 1 groups decrease  $15.57 \pm 5.04 \mu\text{g} / \text{dL}$ . Based on the analysis of the Wilcoxon test, it found significant differences in Copper content before and after on category 1 with  $p \text{ value} = 0.005$ . In the category 2 group, Cu levels before and after ethambutol therapy decrease of  $31.66 \pm 7.35 \mu\text{g} / \text{dL}$ . Based on the Wilcoxon test analysis, it shows significant differences Cu levels before and after in category 2 with  $p \text{ value} = 0.005$ . Based on non-parametric comparison test, Mann-Whitney test, it shows significant differences after copper levels between the category I groups and category II with  $p \text{ value} = 0.000$ . This study also found an average the value of Cu level after ethambutol therapy in the category I was  $64.83 \pm 5.39 \mu\text{g} / \text{dL}$  and in the category II was  $43.96 \pm 5.94 \mu\text{g} / \text{dL}$ .

Ethambutol interferes oxidative phosphorylation by not binding copper in mitochondria. This situation change mitochondria potential membrane, Research carried out the role of Cu in ethambutol toxicity. It was found that Cu plays a role in the toxicity of ethambutol by triggering mitochondrial apoptosis in RGCs.<sup>26-29</sup>

To obtain the correlation between serum Cu level and Farnsworth Munsell 100 Hue, we performed Spearman's and Pearson's Correlations. The aim is to find out correlation between serum Cu level with color vision impairment. The results are not significant correlations serum Cu level with color vision impairment before and after the category 1 or 2 treatment. Ray's study proved changes serum Cu level in Tb patient. After completing treatment, a significant decreasing in serum Cu levels can occur. Koyonagi et al examined serum Cu and zinc levels in patients with pulmonary tuberculosis, there was decreasing serum Cu level in patients who use. As a metal chelator found in ethambutol, Cu and Zinc can interfere with oxidative phosphorylation and mitochondrial function, and the synthesis is divided into two complexes. Both groups has function in ATP formation which functions as synthesis and metabolism in mitochondria. Damage in the formation of long-term ATP and a buildup of reactive oxygen species (ROS) cause apoptosis.<sup>2,26,30</sup>

## Conclusion

The duration of Ethambutol was related to changes in color vision examined with FM100.

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