

# Correlation between the Duration of Ethambutol Therapy and the Toxic Optic Neuropathy Occurene in Patients with Multidrug-Ressistance Tuberculosis

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## Abstract

**Background:** Tuberculosis affects one-third of the world's population. Increasing number of tuberculosis cases also leads to the increase of anti-tuberculosis drugs use, such as ethambutol. Ethambutol is one of the most effective and rarely resistant tuberculosis drugs.

**Objective:** To determine the relationship between duration of ethambutol therapy with toxic optic neuropathy in tuberculosis patients

**Method:** This study enrolled MDR-TB patients who visited MDR-TB Unit of Dr. Soetomo General Hospital from July 2014 until the sufficient amount of sample was achieved. The patients enrolled are those who met the inclusion and exclusion criteria. Inclusion criteria consisted of MDR TB patients treated with ethambutol therapy, aged of 20-69 years old, and whose VEP examination results showed extension of P100 latency.

**Results:** The mean of <6 month duration was  $3.24 \pm 1.348$ , while for the  $\geq 6$  months was  $11.71 \pm 5.764$ . This difference was statistically significant with  $p = 0.043$ .

**Conclusion:** There is a correlation between duration of ethambutol therapy with toxic optic neuropathy in patients with MDR-TB.

**Keywords:** *ethambutol therapy, toxic optic neuropathy, multidrug-resistance, visual evoked potentials*

## Introduction

Tuberculosis affects one-third of the world's population. The increasing number of tuberculosis cases leads to the more use of anti-tuberculosis drugs, such as ethambutol<sup>1</sup> Ethambutol is one of the most effective and rarely resistant tuberculosis drugs, and therefore is often used in the case of Multidrug-Resistance Tuberculosis (MDR-TB). However, many researches reported the occurrence of optical toxic neuropathy (TON) with

clinical symptoms of decreased vision until blindness<sup>2</sup>.

The incidence of toxic optic neuropathy associated with ethambutol varies greatly from several studies ranging from 0.5-35% of patients Visual Evoked Potentials (VEP) can be used to determine the toxic effects of ethambutol<sup>3</sup> Of the 14 samples, 5 were showed abnormalities in VEP, where in from the clinical findings only showed abnormal person<sup>4</sup>. A study reported that 42% of patients with permanent vision impairment were dependent on the initial disorder severity. As reported in most cases, toxicity occurs at doses greater than 20mg/kgBW/day. However, not too little toxicity has occurred at a standard dose of 15mg/kgBW/day. For instance is in a case reporting optic neuropathy occurrence at a dose of 12 mg/kgBW/day. The duration of drug use that causes toxic effects is averagely one to six months. However, it has been reported that the fastest duration in which

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visually impaired due to ethambutol occurs in the use duration of only three days.

Toxic optic neuropathy can provide symptoms of progressive decrease in vision, which might get worse until blindness occurs. Although the loss of vision is reversible when ethambutol is lowered or terminated, some patients experience permanent vision impairment even with standard drug doses<sup>5</sup>. Some cases of progressiveness continue to run even though the drug has been stopped. Imperfect improvement was often found. Some even experienced permanent blindness<sup>6</sup>. The mechanism of optic neuropathy due to ethambutol is thought to be caused by impaired function of the mitochondria<sup>7</sup>. One study found a vacuole change from the cytoplasm of ganglion cells in animals injected with ethambutol. Ethambutol is a metal chelator, which can interact with zinc, copper and iron that cause damage to the mitochondria<sup>8</sup>. Studies conducted on animals have demonstrated the toxic effects of ethambutol on electrophysiological visual systems as well as histopathology<sup>4</sup>.

Toxicity can be detected earlier by VEP, even before the emergence of complaints from patients. This is very useful because by detecting TON earlier, can be stopped or replacement of drugs before clinical symptoms appear. In addition, knowing the occurrence of TON and drug termination will inhibit the progression of the disease and thus permanent loss of vision can be prevented. Aim to determine the relationship between duration of ethambutol therapy with toxic optic neuropathy in tuberculosis patients.

## **Method**

This is an observational analytic study. The samples are MDR-TB patients who received ethambutol therapy who came in MDR-TB Unit of Dr. Soetomo General Hospital from July 2014 until the sufficient amount of samples was achieved. They all met the inclusion criteria consisted of MDR-TB patients who received ethambutol therapy, aged of 20-69 years old, VEP examination results obtained extension of P100 latency. The exclusion criteria consisted of the subjects with diabetic retinopathy, hypertensive retinopathy, renal failure, hepatic dysfunction, history of stroke, history of intracranial infection, multiple sclerosis history, cerebral

neoplasm history, eye abnormalities, and those who were unwilling to participate in the study.

The sampling method of the study was conducted according to the consecutive case (sampling from consecutive admission) until the sample size was determined. The study instrument was visual evoked potentials. The duration of ethambutol therapy was the duration (within months) of patients taking ethambutol during the MDR program, calculated from the first day of drug use until the VEP examination with short duration of <6 months, and long duration of ≥6 months.

Toxic optic neuropathy is an abnormality in vision function due to optic nerve damage caused by toxic substances diagnosed from an extension of P100 latency from the normal limit of VEP examination with a 116 ms cutoff point. TON occurred when the obtained P100 latency is >116 ms, and it is considered normal when the normal P100 latency is ≤116 ms. VEP is the electrical potential of the visual stimulus recorded from the scalp to assess the integrity of the afferent visual path. The examination was done by Cadwell Sierra Wave in Electromyography of Dr. Soetomo General Hospital. The results will be interpreted by a neurophysiologist consultant. All subjects included in the inclusion criteria and the family responsible for the patients were given an explanation of the purpose, usefulness and risk of the study, and were asked to be involved in the study. The identity and characteristics of the subjects signing the consent were recorded in the form. Data collection of research subjects was conducted through anamnesis, careful physical examination and neurology, selection of samples for the cases according to inclusion and exclusion criteria. The eligible samples and all necessary clinical data were recorded. VEP examination was performed in the EMG of Dr. Soetomo General Hospital. All the recording results were collected for further data tabulation and statistical analysis.

The data obtained from the data collection sheets were then analyzed. The correlation between duration of ethambutol therapy and optic neuropathy was calculated and analyzed using the appropriate statistical tests. This study will be proposed as an ethical feasibility study to the Research Ethics Committee of Dr. Soetomo Teaching Hospital Surabaya.

## Result

**Table 1. The difference in the proportion of duration of ethambutol therapy in each group of subjects**

Characteristics	TON		p	RO (IK 95%)
	Cases N (%)	Control N (%)		
Age	43.29 ± 11.58	38.82 ± 10.06	0.239	
Gender				
Male	7 (41.2%)	13 (76.5%)	0.03	0.215 (0.049-0.946)
Female	10 (58.8%)	4 (23.5%)		
Education				
Elementary, Junior High School	7 (41.2%)	6 (35.3%)	0.724	0.779 (0.195 - 3.118)
Senior High School, College	10 (58.8%)	11 (64.7%)		
Diabetes Melitus				
Yes	7 (41.2%)	6 (35.3%)	0.724	1.283 (0.321 – 5.134)
No	10 (58.8%)	11 (64.7%)		
Ethambutol dose (mg/day)				
≥1200	7 (41.2%)	10 (58.8%)	0.303	0.49 (0.125 – 1.921)
800-1199	10 (58.8%)	7 (41.2%)		
Ethambutol therapy history (year)				
≤ 1	7 (41.2%)	6 (35.3%)	0.271	2.275 (0.518 – 9.989)
>1	10 (58.8%)	11 (64.7%)		
Ethambutol therapy duration				
≥6 months	12 (70.6%)	5 (29.4%)	0.016	5.76 (1.317-25.187)
<6 months	5 (29.4%)	12 (70.6%)		

All subjects underwent eye examination in MDR-TB and VEP units in the EMG section of Department of Neurology, Dr. Soetomo General Hospital Surabaya from July to December 2014. In this study, there were 34 subjects consisting of 17 normal subjects with normal Visual Evoked Potential (VEP) results referred to as controls and 17 subjects with VEP prolonged latency P100 results hereinafter referred to as cases. Table 1 shows the characteristics of the study subjects. In the case group there were 7 male subjects (41.2%) which were less than in control group with 13 male subjects (76.5%). There was a difference of sex proportions between each group, and this difference was statistically significant with  $p = 0.037$ . The mean of the subjects' age in the case group was  $43.29 \pm 11.58$  years, while in the control group was  $38.82 \pm 10.06$  years old. However, this difference was not statistically significant with  $p = 0.239$ . In the case group, However, this difference was not statistically significant with  $p = 0.724$ . Characteristics

of subjects based on dose of ethambutol  $\geq 1200$  mg / day in case group there were 10 people (58.8%) more than control group that was 7 people (41.2%). However, this difference was not statistically significant with  $p = 0.303$ . Characteristics of subjects based on history of ethambutol therapy  $\leq 1$  years showed that in the case group there were 7 people (41.2%), which was more than the control group with 4 people (23.5%). However, this difference was not statistically significant with  $p = 0.271$ .

The difference in the proportion of duration of ethambutol therapy in each group of subjects can be seen in Table 1. In the case group, there were 12 subjects (70.6%) with ethambutol therapy duration of 5 months, which is more than the control group with only 5 subjects (29.4%). Meanwhile, in group <6 months duration there were 5 subjects in case group (29.4%), which is less than in control group with 12 people (70.6%). This difference was statistically significant with  $p = 0.016$ . Odd ratio of

5.76 (95% IK 1.317-25.187) was also obtained. Logistic regression of sex and duration indicated a significant correlation between duration of ethambutol therapy and TON with  $p$  value = 0.043 and an odds ratio of 4.93 (95% IK 1.053 - 23.082). Thus, subjects with duration of ethambutol therapy  $\geq 6$  months had 4.93 times higher risk of TON compared to subjects with ethambutol therapy duration of  $< 6$  months. This suggests that the study is clinically and statistically significant.

## Discussion

The gender characteristics of a total of 34 samples 20 (58%) male and 14 (42%) female. A population-based study in Taiwan found more male with 65.8%. Similarly, in studies that linked ethambutol therapy to another TON, there were more male subjects than females 71%<sup>9</sup>.

The mean age of the subject of the case group was  $43.29 \pm 11.58$  years old while in the control group was  $38.82 \pm 10.06$  years old, as seen in the older average age group. These demographic data were compared with studies that correlated the dose of ethambutol with TON obtained in the mean age of  $55.4 \pm 14.4$  years old<sup>5</sup>. The study of TON incident, the obtained the mean of age range was  $58.23 \pm 16.68$  years<sup>10</sup>. Characteristics of subjects based on risk factors of diabetes mellitus in case group was 7 people (41.2%) slightly more than control group 6 people (35.3%), but this difference was not statistically significant with  $p = 0.742$ .

The dose of ethambutol of  $\geq 1200$  mg/day in the case group was obtained in 10 subjects (58.8%) more than in the control group with 7 subjects (41.2%). While the dose of 800-1199 mg/day were found in case group with 7 subjects (41.2%) less than control group that was 10 subjects (58.8%), was not statistically significant. The study with 231 TON samples was 49.8% dose  $< 800$  mg, 38.1% dose 800-1199 mg, 12.1% dose  $\geq 1200$  mg/day (3). Based on the history of ethambutol therapy of  $\leq 1$  years, in case group there were 7 subjects (41.2%), which is more than control group with 4 subjects (23.5%). However, this difference was not statistically significant with  $p = 0.271$ .

The previous studies have not reported about the history of the use of ethambutol before, possibly because the previous studies involved a sample of TB patients category 1, whereas in this study the samples are MDR-TB patients who had previously received etambutol

therapy. In the case group, the number of subjects with ethambutol therapy duration of  $\geq 6$  months was 12 (70.6%), more than in control group with 5 subjects (29.4%). Meanwhile in the control group, the number of subjects with ethambutol therapy duration of  $< 6$  months is 12 (70.6%) which is more than in the case group with 5 people (29.4%). The mean of  $< 6$ -month-duration was  $3.24 \pm 1.348$ , while for the  $\geq 6$ -month-duration was  $11.71 \pm 5.764$ . This difference is significant statistically with  $p = 0.043$ , and clinically with odds of 4.93 (95% I 95% 955-23.082).

This study was conducted using the cut-off of  $> 3$  months. In case group, there were 143 subjects (61.9%) with 3-month duration and 88 subjects (38.1%) with  $\leq 3$ -month duration, with odds ratio of 1.35 (1.02-1.86)<sup>11</sup>. The case series performed by Griffith et al. found that the duration of ethambutol in the case group was 1-16 months ( $6.7 \pm 5.8$  months), with a tendency for longer duration using ethambutol with optical neuropathy<sup>9</sup>.

Long duration of ethambutol therapy might cause TON. This can be analyzed from the following explanation: ethambutol is a metal chelator, this agent is able to strongly bind metals especially zinc required in axonal transport, and citric acid cycle. Ethambutol bonding to these metals results in calcium influx, mitochondrial dysfunction, and ultimately leads to decreased ATP, ganglion cell death, and papillomacular bundle damage. If this process lasts longer then most likely will occur more bonds causing the increased risk of TON. However, this does not occur easily. Some factors are also influential and therefore a person might develop TON while the others do not. These factors include the use of other toxic substances such as isoniazid, chloroquine, chloramphenicol, amiodarone, cyclosporine, the use of these drugs are not found in the study subjects. Isoniazid, in particular, is reported to have toxic effects as on the eyes, but the incidence is very small. When starting this MDR-TB treatment program patients are not given isoniazid therapy because MDR-TB patients are resistant to isoniazid. However, most of the patients had received isoniazid therapy previously during the DOTS program. This could have an effect but is not analyzed. In addition, systemic disorders such as kidney and liver disorders that are likely to cause drug accumulation have also been excluded. Other factors that are also influential and not examined in this study are malnutrition conditions, and zinc deficiency.

## Conclusion

There is a correlation between duration of ethambutol therapy with toxic optic neuropathy in patients with MDR-TB.

**Conflict of Interest:** There is no conflict of interest.

**Source of Funding:** This study is self-funded.

**Ethical Clearance:** This study was approved by Ethical Commission of Health Research Faculty of Medicine University of Airlangga.

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