

Evaluation of Contrast Sensitivity Assessment for Optic Nerve Toxicity Caused by Ethambutol Therapy in Tuberculosis Patient

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Abstract: *To study the optic nerve toxicity caused by ethambutol therapy in patients with tuberculosis and to evaluate contrast sensitivity assessment in tuberculosis patient correlated with age, sex, dose and duration of ethambutol therapy. Therapy duration divided into less than 2 months and more than 2 months. Eighty patients were examined in visual acuity, tonometry, confrontation, funduscopy, contrast sensitivity. Decreased contrast sensitivity was found in 16,25% and correlated with duration of therapy for more than 2 month. We didn't found the correlation of age, sex, and dose with decreased contrast sensitivity.*

Keywords: Tuberculosis, Ethambutol, Contrast Sensitivity

1. Introduction

Management of Tuberculosis has been developed for more than 50 years, and Ethambutol is one of the treatment in tuberculosis. Ethambutol was first introduced as the first line of tuberculosis therapy in 1961. Carr and Henkind. found ethambutol can cause neuropathy optic for the first time in 1962, but the real mechanism is still unknown until now.^[1,2]

Central scotomas are the common visual field defect in neuropathy optic, but bitemporal defects and peripheral field constriction have also been reported.^[3] Pupillary abnormalities can be subtle, and visual evoked potential may be needed to confirm the diagnosis.^[4] Contrast sensitivity assessment and color test has also been found effective in detecting subclinical toxicity.^[5]

Ethambutol-related damage to the visual function can be reversible several months after discontinuing treatment. However, some studies report that even after ethambutol stoppage, 40–50% patients experienced permanent visual loss (irreversible).^[3,4] However, these reports all have one thing in common: the diagnosis of ethambutol-induced ocular toxicity was made after symptom manifestation. Early diagnosis can prevent ethambutol-induced ocular toxicity which is correlated with the reversibility of visual function damage.^[5] Therefore, early detection of ethambutol-induced ocular toxicity before symptom manifestation will be helpful for preventing permanent visual loss. Reversibility of the toxicity depends on early detection. Visual acuity, contrast sensitivity, color vision, and visual fields that are the usual tests recommended to evaluate ocular effects may not detect cases of early and subclinical toxicity.^[5] Early detection and immediate therapy discontinuation are the only effective management that can halt the progression of vision loss and allow recovery of vision.^[5]

2. Literature Survey

Many researches reported that ethambutol related damage to visual function. Salmon et al studied contrast sensitivity assessment in tuberculosis patients using ethambutol for more than 2 months. They found 38,2% tuberculosis patients experienced decreased contrast sensitivity who used ethambutol for three months. He suggest that contrast sensitivity assessment can be used to rule out the damaged optic nerve.^[6,7]

Garg et al in India reported that ethambutol can make visual function damage related the dose and duration of ethambutol therapy. Josephina and Walandow reported a case from Manado, Indonesia, in 2013 that the ethambutol toxicity was related to the dose and duration of ethambutol therapy. Whitney et al reported also that there was manifestation of ocular toxicity caused by ethambutol in tuberculosis patients.^[8-10]

3. Problem Defenition

We want to know the correlation age, sex, dose and duration of ethambutol therapy and contrast sensitivity assessment in tuberculosis patients.

4. Method

This was an observational analytic study of 80 tuberculosis patients in ethambutol therapy took dose regimen 15–20 mg/kg/day in tuberculosis patients which presenting in kombipak tablet (@275 mg Ethambutol per tablet). Examinations were done in two group patients. when ethambutol therapy less than or equal 2 months and after 2 months of starting the therapy. All the cases was diagnosed with pulmonary tuberculosis at the medical out patient Respiratory Hospital in Medan.

Detailed ophthalmic evaluation included anterior segment evaluation, visual acuity assessment, refraction, funduscopy, confrontation assessment, contrast sensitivity assessment. Exclusion criteria included any other ocular or systemic

diseases that may have affected the parameters being evaluated. Subjects with best corrected vision less than Snellen's 6/9, with preexisting color vision defects, or taking any other drugs known to cause optic neuropathy were excluded from the study. Patient with cataract, glaucoma, diabetic retinopathy, retinopathy hypertension, and any ocular inflammation and retinal disease were excluded. Contrast sensitivity was assessed using the Pelli-Robson CS chart at 1 m distance monocularly and binocularly (Normal limits = 1,80-1,95). Color vision was tested using Ishihara test under monocular viewing conditions in the same room under similar lighting conditions. Confrontation assessment after measuring the intraocular pressure with Schiötz tonometry. The pupils were dilated with 1% tropicamide. The fundus was examined by direct ophthalmoscopy (Keller Ophthalmoscope).

Data were analyzed using Statistical Package for the Social Sciences Version 22 (SPSS-22) Software and Microsoft Excel 2016. P value less than 0.05 regarded as significant.

5. Result

Mean age of the 80 subjects (160 eyes) included in the study was 40.33 years. Most of them (82%) were in the age group 36-45. Among them 53 subjects (66.2%) were men and 27 subjects (33.8%) were women (table 1).

Table 1: The Distribution of Age and Sex in Tuberculosis Patients

Age (years)	N	%
0 -5	0	0
6-11	0	0
12 - 16	1	1,25
17 - 25	15	18,75
26 - 35	16	20
36 - 45	20	25
46 - 55	15	18,75
56 - 65	11	13,75
> 65	2	2,5
Sex		
Male	53	66.2
Female	27	33.8
Total	80	100

Table 2 shows that dosage of ethambutol for 15-20 mg/kg/day presenting in 550 mg (2 kombipak tablet), 825 mg (3 kombipak tablet), 1100 mg (3 kombipak tablet) and 1375 mg (5 kombipak tablet). Duration of ethambutol therapy divided into two group for less than 2 months for 37 patients (46,3%) and more than 2 months for 43 patients (53,7%). From 80 subjects, 13 subjects (16,25%) had decreased contrast sensitivity, the other 67 subjects (83,75%) had normal contrast sensitivity.

Table 2 Described that the ethambutol doses were divided into 4 variables, 550 mg, 825 mg, 1100 mg, 1375 mg. Many subjects were in 1100 mg for 44 patients (55%), and subjects with 550 mg were 3 patients (3.75%), 825 mg for 30 patients (37.5%), and 1375 mg for 3 patients (3.75%).

Table 2: Characteristics Subjects Based on Dose, Long Term Ethambutol Therapy and Contrast Sensitivity Assessment

Dose Ethambutol (@275 mg in Kombipak Tablets)	N	%
550 mg	3	3,75
825 mg	30	37,5
1100 mg	44	55
1375 mg	3	3,75
Duration of Treatment Ethambutol		
≤ 2 Months	37	46,3
> 2 Months	43	53,7
Contrast Sensitivity Assessment		
Decreased	13	16,25
Normal	67	83,75
Total	80	100

From table 2, we can see that subjects who used ethambutol for more than 2 months were 43 patients (53.7%), and less or equal than 2 months for 37 patients (46.3%). The subjects who experienced decreased contrast sensitivity were 13 patients (16.25%) and subjects who did not experience decreased contrast sensitivity were 67 patients (83.75%).

The correlation between age and contrast sensitivity assessment. According to Two-Sample Kolmogorov-Smirnov Test, p value was 0,572. It can be concluded that from table 3, there is no correlation between age and decreased contrast sensitivity in tuberculosis patients.

Table 4 described that male in this research was higher than women in decreased contrast sensitivity assessment, but p value was 0,200 according to Fisher's Exact Test. From the data above it can be concluded that there is no correlation between sex and decreased contrast sensitivity assessment in tuberculosis patients.

Table 5 described the correlation between dose and decreased contrast sensitivity assessment in tuberculosis patients. According to the Two Sample Kolmogorov-Smirnov Test, p value was 0.996. It can be concluded that there was no correlation dose regimen 15-20 mg/kg/day and decreased contrast sensitivity assessment in tuberculosis patients. We found only 13 patients (16.25%) who experienced in decreased contrast sensitivity assessment. Subjects who used 1100 mg (8 patients) dose regimen were the higher patients who experienced in decreasing contrast sensitivity assessment. Based on statistical calculations there was no significant correlation between dose regimen ethambutol therapy and decreased contrast sensitivity assessment in tuberculosis patient.

Table 6 described the correlation between the duration of ethambutol treatment in tuberculosis patients. According to Pearson Chi-Square Test and we found p value at 0.0001. It was concluded that from 80 tuberculosis patients, thirteen patients were experienced decreased contrast for more than 2 months.

Table 3: The Correlation between Age and Contrast Sensitivity Assessment in Tuberculosis Patients

Age (Years)	Contrast Sensitivity Assessment		Total	P Value
	Decrease	Normal		
0-5	-	-	0	0,572
6-11	-	-	0	
12-16	-	1	1	
17-25	-	15	15	
26-35	3	16	19	
36-45	3	20	23	
46-55	1	15	16	
56-65	5	11	16	
> 65	1	2	3	
Total	13	67	100	

Table 4: The Correlation between Sex and Contrast Sensitivity Assessment in Tuberculosis Patients.

Sex	Contrast Sensitivity Assessment		Total	P value
	Decrease	Normal		
Male	11	42	53	0,200
Female	2	25	27	
Total	13	67	80	

Table 5: The Correlation between Dose and Contrast Sensitivity Assessment in Tuberculosis Patients

Dose (mg)	Contrast Sensitivity Assessment		Total	P value
	Decrease	Normal		
550	1	2	3	0,996
825	3	27	30	
1100	8	36	44	
1375	1	2	3	
Total	13	67	80	

Table 6: The Correlation Duration Of Treatment and Contrast Sensitivity Assessment

Duration of Ethambutol Treatment	Contrast Sensitivity Assessment		Total	P value
	Decrease	Normal		
> 2 Months	13	37	50	0,0001
≤ 2 Months	0	30	30	
Total	13	67	80	

6. Discussion

This study took 80 patients with tuberculosis patients who had been assessed in inclusion criterias. In this study we found that the most subjects were men, the most ages were 36-45 years old and the most patients used ethambutol at 1100 mg (15-20/ kg in /day) for 44 patients from 80 tuberculosis patients.

This study found no correlation between age and decreased contrast sensitivity assessment. The different result was found by Bansback C in Spain that there was no correlation between age and decreased contrast sensitivity.^[11]

This study also found that there was no significant correlation of sex and decreased contrast sensitivity assessment. Bensback C in Spain reported that decreased contrast sensitivity assessment was not correlated with sex in age macular degeneration (AMD) patients that were not consuming ethambutol. Gella Laxmi et al in Indian population found the same result that there was no

correlation between sex and contrast sensitivity assessment in patients consuming ethambutol.^[11]

We also found that there was no correlation between dose regimen 15-20 mg/kg/day and decreased contrast sensitivity in tuberculosis patients, but we found decreased contrast sensitivity assessment in each gradation of dose regimen. Same result with Addington Whitney and Kwok that they found decreased contrast sensitivity in tuberculosis patients at any dose gradation.^[8-10]

Previous studies also revealed that there were correlation between the duration of ethambutol treatment and decreased contrast sensitivity in tuberculosis patients.^[7,13,14] Salmon et al reported from 100 patients tuberculosis in ethambutol therapy, 38.2% patients experienced optic neuropathy in patients who took ethambutol for 3 months, and 36.7% for patients who took ethambutol for 6 months.^[7]

This study has limitations in the research's method. Researchers only used observational analytic to determine the role of contrast sensitivity assessment in detecting early optical damage caused by ethambutol in tuberculosis patients but could not explain when the exact time of optic nerve damage although in the literature it was explained that ethambutol toxicity can occur two until eight months during ethambutol therapy.^[15]

It is also reported that if toxic optic neuropathy due to ethambutol had occurred in the initial phase and etambutol still continued, the damage would spread anteriorly to optic chiasm, and gave a bitemporal hemianopsia with Humphrey perimetry.^[15]

7. Future Scope

Further research is needed with cohort methods to find out when the exact time of the decreased contrast sensitivity occurs in tuberculosis patients, especially MDR tuberculosis patients who need ethambutol therapy for 24 months.

Contrast sensitivity assessment can be used as an initial screening because it is a simple and easy assessment for medical workers to determine the optic nerve damage caused by ethambutol toxicity as in literature it can become an irreversible blindness.

Monitoring of long-term ethambutol therapy must be carried out considering the side effects. For this reason it is necessary to cooperate between the related departments in detecting early ethambutol toxicity and preventing blindness.

8. Conclusion

There was no significant correlation between age and decreased contrast sensitivity in tuberculosis patients. There was no significant correlation between sex and decreased contrast sensitivity in tuberculosis patients.

There was no significant correlation between the dose regimen and decreased contrast sensitivity in tuberculosis patients. *There was significant correlation between the*

duration of ethambutol therapy and decreased contrast sensitivity in tuberculosis patients.

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