

Clinical Research

Correlation between peripapillary retinal nerve fiber layer thickness and visual function changes in patients receiving ethambutol

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ABSTRAK

Latar belakang: Terdapat beberapa studi yang telah menunjukkan adanya penurunan jumlah sel ganglion retina pada hewan yang diberikan etambutol. Studi ini bertujuan mengevaluasi efek etambutol pada ketebalan serabut saraf retina peripapil manusia. Selain itu studi ini juga ingin melihat korelasi antara perubahan ketebalan retina tersebut dengan perubahan beberapa parameter fungsi penglihatan.

Metode: Studi kohort pada 29 subyek penderita tuberkulosis yang berobat di salah satu pusat pengobatan tuberkulosis di Jakarta. Seluruh subyek menjalani pemeriksaan ketebalan retina menggunakan optical coherence tomography (OCT) dan beberapa parameter fungsi penglihatan (tajam penglihatan, sensitivitas kontras, sensitivitas warna dan lapang pandangan) sebelum dan dua bulan setelah mengkonsumsi etambutol. Perbedaan parameter tersebut sebelum dan setelah konsumsi etambutol dianalisis menggunakan uji T-berpasangan ataupun uji Wilcoxon. Hubungan antara perubahan ketebalan retina dan perubahan fungsi penglihatan dinilai dengan uji Spearman.

Hasil: Sebelum dan setelah pengobatan dengan etambutol terdapat perubahan bermakna pada ketebalan retina di kuadran superior (147 dan 141 μm , $p = 0,001$), nasal (92 dan 88 μm , $p = 0,045$), dan rerata seluruh kuadran (116,77 dan 112,65 μm , $p = 0,001$). Tidak terdapat hubungan antara perubahan ketebalan retina ini dengan perubahan fungsi penglihatan.

Kesimpulan: Konsumsi etambutol selama dua bulan dalam dosis yang dianjurkan dianggap masih aman terhadap retina manusia dan terhadap fungsi penglihatan.

ABSTRACT

Background: Recent animal studies revealed the decreased amount of retinal ganglion cells after treatment with ethambutol. The aim of this study was to evaluate the changes of peripapillary retinal nerve fiber layer (RNFL) thickness in patients receiving ethambutol therapy, as well as to know the correlation of RNFL thickness changes with the changes of visual function.

Methods: This was a cohort study on 29 subjects at one tuberculosis treatment center, Jakarta. Subjects underwent RNFL thickness measurement using optical coherence tomography (OCT) and several visual function parameters (visual acuity, contrast sensitivity, color sensitivity and visual field) before and two-months following ethambutol therapy. Statistical comparison between pre- and post-ethambutol measurements were done using either paired T-test or Wilcoxon test. Correlations between anatomical and functional changes were assessed with Spearman correlation test.

Results: There were significant changes of peripapillary RNFL thickness in superior (147 and 141 μm , $p = 0.001$), nasal (92 and 88 μm , $p = 0.045$) quadrants and average RNFL thickness (116.77 and 112.65 μm , $p = 0.001$). No significant correlation between RNFL thickness changes and the changes of visual function parameters ($p > 0.05$).

Conclusion: Ethambutol consumption for two months in recommended dose is still considered safe to human retina and visual status.

Keywords: ethambutol, optical coherence tomography, optic neuropathy, retinal nerve

pISSN: 0853-1773 • eISSN: 2252-8083 • <http://dx.doi.org/10.13181/mji.v24i1.1065> • Med J Indones. 2015;24:19-23

• Received 10 Sept 2014 • Accepted 20 Feb 2015

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Ethambutol is one of the first line drugs used in treating tuberculosis (TB) together with isoniazid, rifampicin, pyrazinamide and streptomycin.¹ According to WHO report of 2011, Indonesia is in the fourth-highest number of TB infection in 2010, followed with India, China and South Africa² One of the serious side effects caused by ethambutol consumption is ocular side effect known as ethambutol optic neuropathy (EON).

The incidence of EON varies from 1.5-10% of all patients consuming ethambutol, depending on the dosage and duration of drug consumption.^{3,4} Leibold⁵ found an incidence of 11% in patients consuming 35 mg/kgBW/day of ethambutol, and only 2% in patients consuming less than 30 mg/kgBW/day.

The clinical manifestation of EON involves central fibers damage leading to loss of visual acuity, color vision, contrast sensitivity and field defect (mainly central scotoma).⁶⁻⁸ This ocular toxicity has variable prognosis from reversible to permanent disturbance.^{9,10} Early detection is generally considered to improve prognosis.³

Various studies performed in animal have shown decreased amount of retinal ganglion cells in animals treated with ethambutol.^{11,12} So that nowadays retinal ganglion cell damage is more widely believed to cause EON.

Optical coherence tomography (OCT) is a non-contact examination technique, which shows cross-sectional images of the retina. Assessing retinal thickness quantitatively, either in the macula or peripapillary region, has been made possible with this device. Evaluating peripapillary retinal nerve fiber layer (RNFL) is popular in optic neuropathy cases especially glaucoma.¹³

There have been some cross-sectional studies evaluating peripapillary RNFL in patients with EON. Those studies revealed RNFL thinning in patients diagnosed with EON.^{10,14,15} This condition is assumed to happen due to damage in retinal ganglion cells in the disease. Cross-sectional data of RNFL thickness is considered not sufficient in making conclusion of RNFL thinning among patients with EON, due to the highly variable baseline RNFL thickness. This study aimed to evaluate the course of peripapillary RNFL

thinning after patients consume ethambutol and also to evaluate the correlation with some visual function parameters. In the future it is expected that OCT scanning of peripapillary RNFL can be used as an alternative diagnostic procedure among patients with possible EON.

METHODS

This was a cohort study on 30 individuals newly diagnosed with TB infection, conveniently recruited from PPTI (*perkumpulan pemberantasan tuberculosis* Indonesia) clinic, DKI Jakarta region beginning from March - July 2013 (including two-month follow-up). Anti-tuberculosis regimens were all given in the form of a fixed dose combination (FDC) consisting of ethambutol, isoniazid, rifampicin and pyrazinamide, in accordance to WHO guideline for TB treatment. Inclusion criteria were patient age 18-60 year-old, agree to not consuming alcohol during the course of study, and agree to sign the study consent. While patients with visual acuity less than 6/6, defect in color sensitivity, intra-ocular pressure (IOP) > 21 mmHg, presence of retinal defect, optic nerve abnormality or any opacity in the visual axis which may contribute to poor OCT results, were excluded.

All subjects underwent complete ophthalmological and OCT examination before and two months after consuming ethambutol. Each examination included an assessment of visual acuity using the early treatment diabetic retinopathy study (ETDRS) Chart, color sensitivity using the hardy-rand-rittlér (HRR, Richmond products, US) pseudoisochromatic plates, and Pelli-Robson chart was used for contrast sensitivity test. Humphrey 24-2 standard automated perimetry using the Swedish Interactive Test Algorithm strategy (Carl Zeiss Meditec, Dublin, California, USA) was performed at each visit. OCT Stratus (Carl Zeiss Meditec, Inc, Dublin, CA) was used to examine peripapillary RNFL on both eyes of each patient using the retinal nerve fiber layer analysis protocol, as has been described elsewhere. Patients who were not able to attend the scheduled follow-up time, were considered lost to follow up.

Statistical analysis were performed using Statistical Package for the Social Sciences software (SPSS, Inc. version 11.0). Statistical

differences between pre- and post-ethambutol consumption were assessed using the paired T-test or Wilcoxon test. Correlations between anatomical and functional changes were assessed with Spearman correlation test. P value less than 0.05 is considered significant. The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No. 48/H2.F1/ETIK/2013).

RESULTS

There were initially 30 subjects enrolled in the study, one subject dropped out before the second examination owing to stopped continuing TB treatment that only 29 subjects included in the study analysis. Patient's body weight was also recorded to get a more precise dosage received according to body weight. There were 21 (72.4%) male subjects and 8 (27.6%) females subject enrolled in the study, with age ranging from 18 to 55 years old (median 37 years old). The mean calculated dosage of ethambutol received per body weight in the study was 16.44 mg/kgBW/day.

Table 1. Visual function changes associated with two months ethambutol consumption

	Before ethambutol median (min-max)	After ethambutol median (min-max)	p*
Visual acuity [†]	0 (0-0.14)	0 (0-0.12)	0.022
Color sensitivity	19 (13-20)	19 (14-20)	0.001
Contrast sensitivity	1,95 (1,35-1,95)	1,95 (1,5-1,95)	0.737
Mean deviation	-4 (-25-0)	-2.29 (-23.73-0.2)	0.001

* Wilcoxon test, p < 0,05 significant

[†] logMar

Effects of ethambutol consumption here were divided into 2, functional and anatomical effects, as seen in table 1 and table 2. There are statistically significant changes of visual acuity, color sensitivity and visual field after consuming ethambutol (p < 0.05) (Table 2). Two out of 58 eyes examined (from 2 different subjects) were revealed suitable for the EON diagnostic criteria. One has decreased contrast sensitivity and the other has decreased color sensitivity. On both subjects, ethambutol consumption has been discontinued after the second examination. There are no statistically significant correlation between mean peripapillary RNFL thickness change and all visual function parameters changes as expressed in table 3.

DISCUSSION

Optic neuropathy due to mitochondrial dysfunction in retinal ganglion cells can happen either acquired or inherited. These diseases are similar in signs and symptoms one with another.¹⁶ Some of the most common cause for acquired mitochondrial optic neuropathies are vitamin deficiency, nutritional deficiency, toxic substance exposure and drug exposures. Some drugs that are well known to cause optic neuropathies include ethambutol, chloramphenicol, linezolid, erythromycin and streptomycin.^{16,17} Ethambutol

Table 3. Correlation between visual function parameters and changes of mean RNFL thickness

	Visual acuity (logMar)	Color sensitivity	Contrast sensitivity	Visual field (MD)
p value	0.142	0.744	0.084	0.515
r value*	-0.195	-0.044	-0.229	-0.087

* Spearman correlation test

Table 2. Changes in peripapillary retinal nerve fiber layer thickness before and two months after receiving ethambutol

Quadrant	RNFL (µm) before (mean ± SD)	RNFL (µm) after (mean ± SD)	Mean difference, (mean ± SD)	p*
Temporal	81 ± 15	78 ± 13	-3.14 ± 12.13	0.054
Superior	147 ± 16	141 ± 16	-5.98 ± 11.98	0.001
Nasal	92 ± 22	88 ± 18	-4.53 ± 16.82	0.045
Inferior	146 ± 21	144 ± 19	-1.60 ± 12.26	0.323
Average	116.77 ± 11.69	112.65 ± 10.63	-4.12 ± 5.62	0.001

RNFL: retinal nerve fiber layer, SD: standard deviation

*Dependent T-test, before vs after ethambutol

as one of first line anti-TB drug, is well known to be able to cause ethambutol optic neuropathy, which was postulated to be related to damage on mitochondria of retinal ganglion cells.¹⁸

Demographic data shows that there are more male subjects with male to female ratio of 2.62.¹⁹ This unequal sex distribution happens in almost all parts of the world, due to several possible reasons. This male-female ratio is also in accordance with WHO report 2011 regarding sex distribution of TB patients in South East Asia.² Mean age of subjects in this study (35 year-old) is also in accordance with WHO report 2011.²

Anti-TB drugs given to all subjects in this study were in the form of fixed dose combination (FDC), which contain 275 mg of ethambutol and was prescribed according to patient's body weight. In this study, subjects received ethambutol with average dose of 16.4 mg/kgBW/day. This dose is in the acceptable range of dose as recommended by WHO, that is between 15-20 mg/kgBW/day, and considered to cause very minimal side effects.

During the study, no patient complained of any visual disturbance. This can be explained since EON (if any) is mostly asymptomatic at the beginning. Decrease of color or contrast sensitivity might happen without any complaint from the patient.^{7,8} This study found statistically significant decrease of RNFL thickness in superior and nasal quadrants. This is similar with earlier studies in animals, that found decreased retinal ganglion cell density among animals fed by ethambutol.^{11,12} However, the reduction is still in the standard deviation range, and is still less than the value considered significant set at the beginning of the study (10 μ m). Recalculation of samples size revealed that the power was less than 80%, so the sample size of this study is considered insufficient. Chung, et al²⁰ and Tang, et al²¹ in their study also did not find any significant RNFL difference two months after ethambutol consumption.

Sadun, et al¹⁷ have previously explained a theory that in mitochondrial optic neuropathy cases, there is a time period where visual function deficit happens without any reduction of ganglion cell axons. This is made possible, due to an earlier compensatory phase in the axons, which is mitochondrial congregation, right before apoptosis start taking place. This compensatory

phase is considered to already be able to cause visual function defects.

Some studies have reported that EON can occur as early as two months after starting ethambutol consumption.^{3,9,18} This duration is different among different studies, with other report mentioning a mean duration 3-5 months of drug consumption and one descriptive study in Korea even reporting that EON cases occurred after nine months of drug ethambutol consumption.³ This study only evaluated patients who consumed the drug for two months, so it is also possible that it is too early to expect some effect in RNFL thickness.

Apart from RNFL thickness, this study found statistically significant reduction of mean acuity, color sensitivity and visual field (expressed with mean deviation). However, the changes of each visual function parameter are clinically considered insignificant. These results are different when compared to earlier study by Menon, et al²² which is able to detect visual function defect in 20% of their subjects.

Some earlier studies (especially in glaucoma field) have found good correlation between RNFL thickness and severity of glaucoma. However, we found no correlation between visual function changes and average RNFL thickness changes. This is thought to be due to the fact that most subjects only suffer a minimum reduction of RNFL thickness (less than 10 μ m), thus, no visual function changes happened yet.

This study has some limitations, in which consecutive sampling method was used and the samples only came from one center. Other limitation is that the HFA result in one-third of all subjects did not meet the required criteria as an accurate result (false positive, false negative and fixation losses index). This has made sensitivity changes difficult to interpret. The short follow-up duration was also considered as a limitation, as it is well known that occurrence of EON is influenced by the duration of drug consumption.

In conclusion, this preliminary study found a significant decrease of RNFL thickness in some patients after two months of ethambutol consumption without changes in visual function parameters. In other words, ethambutol consumption for two months in recommended

dose is still considered safe to human retina and their visual status.

Conflicts of Interest

The authors affirm no conflict of interest in this study.

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