

ETHAMBUTOL EFFECT ON RETINAL AND OPTIC NERVE HISTOLOGY DAMAGE IN TOXIC OPTIC NEUROPATHY CASE: A LITERATURE REVIEW

ABSTRACT

Introduction: Ethambutol (EMB) is one of the first-line antituberculosis drugs that reported to cause toxic effects on the ocular. This study aims to elucidate the histological mechanism of retinal and optic nerve damage in toxic optic neuropathy cases. **Reference sources:** The literature search was conducted in the PUBMED and MEDLINE databases using the latest publication of the 2012-2022 series. **Studies selection:** The observational and randomized controlled trial studies analyzing the effect of ethambutol on retinal nerve fiber layer, retinal ganglion layer, inner cell plexiform layer thickness, nerve fiber layer, optic nerve tissue, best-corrected visual acuity (BCVA), color perception, visual evoked response, and patients' visual field were included. **Data extraction method:** Articles that met the inclusion criteria underwent a specific evaluation, whereby the main focus was the ethambutol on retinal and optic nerve tissue. **Results:** The results showed that ethambutol affects the thinning of the Retinal Nerve Fiber Layer (RNFL), decreasing the amount of Ganglion Cells and changing the optic nerve's histological function by damaging the mitochondria and axonal fiber. **Conclusion:** It was concluded that ethambutol has adverse effects on retinal and optic nerve tissue due to several mechanisms and significantly affects the patient's visual outcome.

Keywords: *ethambutol, retina, optic nerve, toxic optic neuropathy, histology damage.*

INTRODUCTION

Ethambutol is a first-line antituberculosis treatment option that is typically used in combination with pyrazinamide, isoniazid, and rifampicin. (1,2) Following oral administration, 75-80% of the dosage is absorbed, and blood levels reach a peak within 2-4 hours. Additionally, a single dosage of 25 mg/kg results in plasma concentrations of 2-5 g/mL. Ethambutol has a serum half-life of 3-4 hours and can last up to 10 hours in individuals with severe renal failure. Furthermore, between 20% and 30% of the medication binds to plasma proteins. (3)

In a 10-year survey of 4.803 patients newly diagnosed with tuberculosis, it was reported that approximately 1.29% of them developed a case of ethambutol optic neuropathy. (4) Ethambutol has been shown to cause bulbar and retrobulbar neuritis, generally due to visual impairment with painless, subacute, symmetrical, and progressive symptoms. The decrease in visual acuity affects the central or caecocentral scotoma and dyschromatopsia (5). Several studies have also shown that EMB is a risk factor for optic neuropathy and chiasmopathy because of its toxicity to retinal ganglion cells through the excitotoxic pathway. (6) Meanwhile, optic neuropathy was induced by the EMB, which causes the loss of small-diameter axons. The EMB changes the histological function of the optic nerve by damaging the mitochondria as physiology of axon transport and axon-myelin interactions. Hence, it results in a relatively complex series of events, such as damage to an axon. (5,7,8)

The epidemiological study by Sheng et al. (2021) reported that ethambutol optic neuropathy (EON) incidence is approximately 100,000 cases per year. In the early stages, EON is still considered reversible, but when it has occurred for some time and is delayed for a long time, it causes permanent loss of vision. (9) The degree of ocular toxicity of EMB depends on the dose and the individual duration. Furthermore, the incidence was 5–6% of cases in patients that was administered EMB at 25 mg/kg/day, 3% at 20 mg/kg/day, and 1% at 15 mg/kg/day. Optic neuropathy was reported at a dose of 3.6 mg/kg/day over 6 months of treatment. This incident further reinforces that there is no longer a supposedly safe dose. (10–13)

Optical coherence tomography (OCT) is a well-known examination used to measure any changes in retinal tissue. In the case of EON, OCT helps to identify the loss of nerve fibers in patients with early symptoms of toxicity before the fundal changes become more pronounced. Therefore, OCT was used as an additional objective test in monitoring patients treated with ethambutol. (12)

Moreover, other examinations such as visual-evoked potentials (VEP), neural magnetic resonance imaging (MRI), and pattern electroretinography (PERG) are used as choices to screen retinal and optic neuropathy damage due to ethambutol-induced toxic optic neuropathy. (14)

METHODS

Search strategy

A literature search was conducted on 12 February 2022 in the PUBMED and MEDLINE databases using either of the following keywords, ((ethambutol) AND ((retinal layer) OR (retinal cell) OR (retinal tissue) OR (optic nerve) OR (optic nerve tissue))). The latest references in the 2012-2022 series were used, but other valuable studies were consulted as complementary and supporting sources. Furthermore, the selected article was then managed by Mendeley®'s citation manager for further analysis and usage.

Articles criteria

The inclusion criteria for the article are 1) use of observational and randomized controlled trial design; 2) The use of English language; 3) The exposure is ethambutol; and 4) The outcome is retinal nerve fibre layer, retinal ganglion layer, inner cell plexiform layer thickness, nerve fiber layer, optic nerve tissue, visual acuity, color perception, visual evoked response, and visual field. Meanwhile, the exclusion criteria were: 1) No abstract, 2) The unavailability of full text, 3) Unmatched article type, and 4) Wrong or unmatched population, such as using the animal as study subject.

Study selection and data extraction

Deep review process was used to choose articles that matched the inclusion criterias. The data extracted include first autor's name, the year of publication, the study's design, the study's location, characteristic of the participant, sample size, exposure, study examination outcome, patients' clinical outcome, research results, and conclusion.

RESULTS

A total of 9 studies from articles discovered in Pubmed and Medline were included in this review. The effects of ethambutol on retinal tissue and optic nerve damage in individuals with toxic optic neuropathy were reviewed in all of the papers. The total population of the 9 inclusion studies was 343 patients. Among these inclusion studies, five studies assessed the effect of ethambutol on the Retinal Nerve Fiber Layer (RNFL) and Ganglion Cells Inner Plexiform Layer (GCIPL), two articles specifically assessed the effect of ethambutol on the Retinal Nerve Fiber Layer (RNFL), and two studies also specifically assessed the effect of ethambutol on Ganglion Cells Inner Plexiform Layer (GCIPL). There are five studies (by Mandal et al., Sheng et al., Teng et al., Lee et al., and Han et al.) were assessed the RNFL and GCIPL tissue thickness after ethambutol administration. Furthermore, three studies showed reduced RNFL and GCIPL thickness, One of them had "subclinical toxicity" in 46% of the eyes, which was measured by an increase in VER latency of more than 2 SD (more than 125 ms) at a dose of 18.5-7.3 mg/kg per day. Moreover, one study on the administration of ethambutol at a dose of 15 mg/kg/day showed no significant thickness changes in RNFL, but there was a decrease in thickness in GCIPL.

The central scotomas, cecentral scotomas, and hypochromatopsia were observed. In another study, ethambutol increased RNFL tissue thickness at a dose of 15-20 mg/kg/day, decreased GCIPL tissue thickness, and resulted in the persistence of a small paracentral scotoma in the left eye. 2022/3/8 There are 2 inclusion studies by Jin et al. and Taffner et al. that assessed ethambutol's effect on RNFL tissue thickness. According to the results of the study by Jin et al., ethambutol at a dose of 14.72 ± 3.07 mg/day/kg caused an increase in RNFL tissue thickness, and there was no clinical change as assessed by BCVA, color vision, and contrast sensitivity in individuals with toxic optic neuropathy. In contrast, the study by Taffner et al. showed an increase in the thickness of the RNFL tissue and a decrease in visual acuity as measured by the Ishihara test. (18,19)

Furthermore, 2 other inclusion studies by Lee et al and Vieira et al assessed the effect of ethambutol on GCIPL tissue thickness. Ethambutol was shown to reduce tissue thickness when taken

at doses of 17.8 to 20 mg/kg daily, and 35 mg/kg three times weekly. (20,21) The assessment and descriptions of the papers included in this evaluation of literature are presented in Table 1.

DISCUSSION

Ethambutol was introduced and marketed in the 1960s as a bacteriostatic agent against *Mycobacterium tuberculosis*. This agent is used as a chelating compound that interferes with the other metal-containing enzyme systems in the mycobacterial nucleic acid structure. (12) Unfortunately, this drug had been reported to cause ocular toxicity, a condition known as bulbar and retro-bulbar neuritis, resulting in painless, symmetrical, progressive vision loss, and central or cecentral scotoma as well as dyschromatopsia. (11,18)

The prolonged use of ethambutol is one of the main risks of thinning the RNFL. Spectral-domain OCT is the most common test to assess the RNFL and the macula. (9,10,22) In a study by Varan et al. (2020), RNFL values recorded a statistically significant increase in thinning after 2 years of administering the ethambutol treatment compared to the pre-treatment RNFL value. The thickness of the RNFL decreased in all quadrants, with the temporal quadrant showing the major loss. (23) Therefore, the RNFL thickness quickly decreases in the disease process. An electrophysiological test such as the visual evoked potential (VEP) detects anterior visual pathway involvement before symptoms develop. (11)

Ethambutol also affects the retinal ganglion cells (RGCs), where the layer of ganglion cells was significantly reduced. The loss of ganglion cells is a sign of irreversible retinal damage. (24) Study in monkey showed that RGCs were significantly damaged by EMB-induced optic neuropathy, functionally and morphologically. (25) Additionally, the toxic impact of ethambutol on the retina also has an effect on other cell types, such as amacrine and bipolar cells, which are clarified in some studies.(10)

In humans, the first symptom and earliest indicator of EMB-induced optic neuropathy is dyschromatopsia or altered color perception. Ethambutol also causes a blue-yellow color defect in the early stages of the disease. (11) A dose of 35, 50, and 100 mg/kg/day administered to an experimental group of rabbits for 12 weeks resulted in vacuolation and demyelination, which were assessed by measuring histological changes. This condition shows that optic nerve toxicity is dose and duration dependent. (26)

The ocular toxicity caused by ethambutol is reversible on discontinuing the drug. Optic neuropathy due to this drug is usually described as reversible with full recovery over a few weeks or months of stopping treatment. However, there is also evidence of deterioration in vision after EMB discontinuation. Hence, it causes patients to experience mild to moderate visual impairment, but some suffer severe to permanent vision loss even after taking standard doses. (27)

EMB is known to cause a permanent decrease in visual acuity and color vision impairment due to damage to the optic nerve. (28) A significant loss of color vision and relatively preserved visual acuity indicates optic neuropathy, which is a cause of visual loss. Therefore, it is essential that color vision is monitored in anti-TB therapy patients to detect early toxicity signs. (29) Ethambutol causes optic neuropathy, which primarily affects the central vision since there is usually a central field detected, while peripheral vision is often unaffected (11). The optic neuropathy caused by EMB presents as bilateral involvement. However, the onset is usually unilateral, but both eyes are affected eventually. Typically, symptoms appear four to twelve months after the administration of EMB but rarely within a few days of starting treatment. (25)

According to Huang et al., EMB increases the flash visual evoked potential (FVEP) test latency in rat retinal ganglion cells (RGCs), inducing apoptosis. (30) Ethambutol and its metabolite 2, 2' ethylene diimino dibutyric acid (EDBA) have been shown to be toxic to retinal ganglion cells both in vitro and in vivo in studies. Furthermore, by decreasing mitochondrial activity, EMB and EDBA improve ganglion cell sensitivity to external glutamate concentrations, which is mediated through the regulation of mitochondrial energy homeostasis. (28).

Ethambutol toxicity causes damage to myelin, a fatty acid layer surrounding axons of the optic nerve produced by oligodendrocytes. The myelin sheath plays a vital role in the rapid transmission of signals through the nerves. Furthermore, the damages to this sheath result in progressive axonal degeneration (27). In this condition, ethambutol affects either the axonal or preaxial parts of the optic nerves by the demyelination process, primarily observed in the optic nerves

and chiasma. (4) Consequently, it is probable that EMB binds to the optic chiasm with high affinity and causes bitemporal visual field abnormalities, which express themselves as toxic symptoms in the eyes. (28)

CONCLUSION

Ethambutol has adverse effects on retinal and optic nerve tissue due to several mechanisms and significantly affects the patient's visual outcome. Ethambutol toxicity causes damage to myelin and cause

Clinical impact to the patients usually described as reversible with full recovery after stopping treatment.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Table 1. Data collection

No	First Autor (year)	Study Design	Country	Participant	Sample Size	Mean Age (range)	Recruit (follow-up) Year	Exposure	Tissues Outcome	Clinical Outcome	Definition of Operational Variable	Summary
1	Mandal (2020)	Cohort Study	India	≥18 years of age with newly and definitely diagnosed pulmonary or extrapulmonary tuberculosis, advised EMB for at least 6 months.	50 people (100 eyes)	>18 years	≥6 months	Ethambutol (17.5±1.3 mg/kg/day)	Decrease RNFL and GCIPL thickness.	No significant change was observed in visual acuity, contrast sensitivity, color vision and mean or pattern SD on HVF at 6 months. Significant increase in VER latency of >2 SD (>125 ms) was observed in 46% eyes on follow-up indicating subclinical toxicity.	Toxicity: VER Latency greater than 2 SD from baseline	The incidence of clinical EMB optic neuropathy was <2%, though subclinical damage in the form of increase in VER latency, and decrease in RNFL and GCIPL on OCT was seen in 46% eyes.
2	Sheng (2021)	Cross sectional study	China	TB patients who complained of ocular discomfort after taking ethambutol at the Zhejiang Chinese Medicine and Western Medicine Integrated Hospital	64 people (126 eyes)	51.00 ± 21.02	-	Ethambutol (15 mg/kg/day)	No significant difference in p-RNFL thickness, decrease GCIPL thickness, decrease average macular thickness.	Hypochromatopsia was detected using the 11-plate Ishihara Colour Test. One patient had a pale optic nerve head in both eyes, whereas the other two exhibited a normal appearance of the optic papilla. The visual field test of all the three patients exhibited prominent defects, such as cecocentral and central scotomas.	A visual field defect was defined as a cecocentral scotoma, central scotoma, peripheral constriction, altitudinal defect, or hemianopsia, etc.	GCIPL measurements using Cirrus-HD OCT detects retinal ganglion cell layer loss following ethambutol treatment, before visual dysfunction. Using p-RNFL and GCIPL thickness parameters, Cirrus-HD OCT helped detect damage patterns in retinal ganglion cells caused by ethambutol, and may indicate ethambutol withdrawal before serious visual impairment occurs.
3	Tang (2018)	Cross sectional study	China	Patients with ethambutol optic neuropathy whose course of disease were within 6mo after clinical onset for	12 patients (23eyes)	43.4 ± 14.1y	-	Ethambutol	No significant difference in p-RNFL thickness, reduce macular thickness, reduced RGCL thickness.	BCVA and VFs also had reliable correlations to average total macular thickness in ethambutol optic neuropathy patients.	VF tests and were evaluated by a Humphrey Field Analyzer II (Carl Zeiss Meditec, Inc., Germany) using Goldmann size III stimulus. The	In conclusion, in the early stage of LHON, the temporal pRNFL thickness decreased, although pRNFL in other quadrants were edema. For EON, we only

				each of both eyes							BCVA was assessed by a Snellen Eye Chart (decimal acuity).	observed the thinning of temporal pRNFL without pRNFL edema in other quadrants. For macular thickness and RGCL thickness, there were the same impairment patterns in LHON and EON, and RGCL in early stage of MON had suffered severe damages.
4	Lee (2018)	Case control study	Korea	Patient who receiving EMB doses for the treatment of pulmonary tuberculosis. Inclusion criteria were as follows: slowly progressive visual loss accompanied by dyschromatopsia after taking EMB, taking EMB for more than 2 months, normal appearance of the optic disc at the first visit, and absence of symptoms associated with optic neuritis, such as pain on ocular movement.	21 patients (42 eyes)	59 ± 12 years	7 years	Ethambutol (17.8 6 2.3 mg/kg)	In inner temporal GCIPL, a 10- μ m-thickness loss in the initial OCT was associated with a 0.5 decrease in the amount of logMAR visual acuity recovery at 12 months and a 10- μ m-thickness reduction between follow-up visits was associated with a 0.5 decrease in the amount of logMAR visual acuity recovery	As duration of medication use increased, the degree of visual acuity recovery decreased 3, 6, and 12 months after stoppage of EMB (all P < 0.001). Also, the lower the initial BCVA was at the first visit, the greater the visual acuity improvement was 12 months after stoppage of EMB (P < 0.001).	The thickness of each retinal layer was measured automatically using the SD-OCT software. The thickness values for the inner locations (inner superior, inner nasal, inner temporal, and inner inferior) were measured in the Early Treatment Diabetic Retinopathy Study (ETDRS) central circular 1000- μ m-diameter area. Thicknesses of the outer areas (outer superior, outer nasal, outer temporal, and outer inferior) were measured in the ETDRS circular 3000- μ m-diameter area.	We described a structure-function relationship between the retinal changes that occur in early EON and vision recovery. Temporal GCIPL could be used to predict vision recovery at 12 months after stoppage of EMB. Careful evaluation for GCIPL damage is required for visual prognosis in early EON.
5	Jin (2019)	Case control study	USA	patients with newly and definitely diagnosed pulmonary and extra-pulmonary tuberculosis. The patients had been diagnosed in the Pulmonology or Infection	84 patients (168 eyes)	45.50 ± 17.17 years	2 years	Ethambutol (14.72 ± 3.07 mg/day/kg)	Increase temporal RNFL thickness	BCVA, color vision, and contrast sensitivity showed no change from the baseline.	Subclinical change or toxicity was defined as the lack of recognizable clinical symptoms or signs, but with any significant changes on ophthalmic examinations including color-vision, contrast sensitivity	Conclusion, mean temporal RNFL thickness showed increases after administration of ethambutol. Contrast sensitivity, BCVA and color vision showed no significant change from the baseline. The VFI, VF pattern, and

				Clinics within the Internal Medicine department and referred to Neuro-ophthalmology Clinics prior to starting anti-tubercular treatment including ethambutol.							testing, fundus photography, RNFL photography, VF testing, or OCT.	quadrant RNFL thickness could prove useful in assessment of subclinical toxicity. Subclinical ethambutol-induced optic neuropathy was found in a total 22 eyes of 14 patients (i.e., 13% of 168 eyes). Medication duration was shown to be a strong risk factor for occurrence of subclinical toxicity.
6	Lee (2018)	Case control study	Korea	patients who complained of visual disturbances during EMB medication use for treating pulmonary and extrapulmonary	25 patients (50 eyes)	61.4±14.5 years	6 years	Ethambutol	The average pRNFL thickness was 97.7±11.2 µm in the EON group and 98.5±8.6 µm in the control group, with no statistical. All of the mGCIPL thickness measurements were thinner in the EON group than in the control group in early EON (p<0.001).	-	All OCT images were obtained using the Cirrus spectral-domain OCT (V.6.0 software; Carl Zeiss Meditec). All scans were acquired by experienced operators using the Optic Disc Cube 200×200 and the Macular Cube 512×128 protocols in the eyes sans pupil dilation.	In challenging cases of EON, the mGCIPL thickness has better diagnostic performance in detecting early-onset EON as compared with using pRNFL thickness. Among the early detection ability of mGCIPL thickness, minimum GCIPL thickness has high diagnostic ability.
7	Taffner (2018)	Clinical trial	Brazil	Tuberculosis patient who used ethambutol	30 patients	43,5 years	1 year	Ethambutol	There was a significant reduction in OCT nerve fiber layer thickness between the pre and post treatment times in ten eyes of the extended group, mean reduction of 7,8 microns and in seven eyes of the standard group, with an average of 5.57 microns. During the study, a significant reduction of retinal thickness was	reduction of visual acuity and / or change in the Ishihara test.	OCT was performed on the CIRRUS HD-OCT (Humphrey-Zeiss, Dublin, CA) macular thickness protocols using 512 x 128 µm and nerve fiber layer (RNFL).	There was a significant reduction in the thickness of the nerve fiber layer by OCT in the patients studied, being more pronounced in those submitted to the extended treatment regimen. This reduction was observed two months after the start of therapy, and was more significant in the cases that presented changes in the Ishihara test.

									observed in both groups at two months of treatment,			
8	Han (2015)	Cohort Study	Korea	Patients with newly diagnosed pulmonary TB who received treatment with EMB	49 patients	46.4±19.4	6 months	Ethambutol (15–20 mg/kg per day)	Thickening of the RNFL and thinning of the GCIPL	At the 6-month follow-up (3 months after cessation of EMB), BCVA was 20/20 in both eyes, but small paracentral scotoma remained in the left eye.	All scans were acquired by the same operator using the optic disc cube 200×200 and macular cube 512×128 protocols in eyes without pupil dilation. One fovea-centered macular cube 512×128 scan and one optic disc cube 200×200 scan were acquired for each of the subject's eyes.	Thickening of the peripapillary RNFL and thinning of the perifoveal GCIPL is an effective quantitative and early marker for diagnosis of EMB-induced optic neuropathy.
9	Vieira (2015)	Cross sectional study	Portugal	all patients with TNON	8 Patients (16 eyes)	66.0 ± 21.1	-	Ethambutol (20 mg/kg on daily regimen and 35 mg/kg on 3 times weekly regimen)	Decreased RGL thickness	-	All participants underwent full ophthalmologic examination, SD-OCT (Heidelberg Engineering, Heidelberg, Germany), and automated static perimetry (ASP) using Octopus 900 (Haag-Streit, Switzerland).	Decreased RGL thickness and volume detected in this study support a mechanism of RGL toxicity. RGL analysis may contribute to the diagnosis and management of toxic and nutritional optic neuropathies.

EMB: Ethambutol ; GCIPL: Ganglion Cell Inner Plexiform Layer ; RNFL: Retinal Nerve Fiber Layer ; BCVA: Best-Corrected Visual Acuity ; OPT: Optical Coherence Tomography ; VER: Visual Evoked Response ; VF: Visual Field