RESEARCH ARTICLE

Ocular side effects in tuberculosis patients receiving direct observed therapy containing ethambutol

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ABSTRACT

Background: India is among the largest countries to implement the revised national tuberculosis (TB) control program (RNTCP). Ocular toxicity of ethambutol has been known since 1962. It can be halted with early detection and cessation of the contributing drug. Aims and Objectives: This study aims to detect early ocular toxicity of ethambutol in TB patients under directly observed treatment strategy (DOTS). Materials and Methods: This was a prospective cross-sectional study of 30 patients getting AKT including ethambutol along with isoniazid, rifampicin, and pyrazinamide under RNTCP-DOTS center at a tertiary care hospital. The detailed history, best-corrected visual acuity (BCVA), color vision, fundus examination, visual field, retinal nerve fiber layer (RNFL) thickness, and central subfield macular thickness were carried out in all patients pretreatment and then at the 2nd month of treatment. Results: The mean age of patient was 44.87 years. Reduced visual acuity from the baseline was noted at the second in 23.33% of the right eyes (P = 0.01) and 30% of the left eyes (P < 0.01). Mean temporal RNFL thickness was significantly reduced from baseline after 2 months of treatment (P = 0.046). No significant difference was observed with color vision and visual fields pre- and post-treatment. Conclusion: The assessment of BCVA, color vision, visual field, RNFL, and macular thickness is essential at baseline and thereafter at frequent intervals to detect early ethambutol toxicity and probable reversible visual loss.

KEY WORDS: Ethambutol; Retinal Nerve Fiber Layer; Color Vision; Visual Field

INTRODUCTION

Tuberculosis (TB) is a multisystemic airborne infectious disease of global importance which significantly increases economic and social burden. TB has been found to be accounting of more than 33% of avoidable deaths in majority of developing countries as per the WHO.¹ India is the highest TB burden country in the world having an estimated incidence of 26.9 lakh cases in 2019 (WHO).² Treatment of TB involves combinations of various drug regimens of which the most common regimen followed worldwide includes use of first-line antitubercular drugs comprising isoniazid, ethambutol, rifampicin, and pyrazinamide.³ India frequently encounters drug-resistant TB due to genetic mutation of the bacilli and has been found to be more prevalent since the time, anti-TB drugs were introduced. Directly observed treatment short (DOTS) course strategy with first-line agents was implemented by the WHO as 6 months duration treatment to reduce the prevalence of multidrug-resistant TB. All these therapeutic interventions are associated with unexpected adverse effects.⁴
All drugs used in DOTS are prone to ocular side effects out of which the most common is ethambutol followed by isoniazid. Ocular side effects of ethambutol were first reported by Carr and Henkindin in 1962 which was most prevalent in patients with long-term treatment and were associated with retinobulbar neuritis. Ethambutol-induced optic neuropathy (EON) accounts for 100,000 new cases each year. Patients with EON suffer with thinner peripapillary retinal nerve fiber layer (pRNFL) thickness below 75 μm. Ethambutol-induced optic toxicity belongs to the class of mitochondrial optic neuropathy attributable to the zinc chelating property of ethambutol and its metabolite on mitochondrial enzymes which was found to be reversible on discontinuation of the drug in many patients. Ethambutol at a dose more than 20 mg/kg/day causes injury to the unmyelinated and narrow caliber fibers in the papillomacular bundle responsible for conducting central vision along with presentation of bitemporal hemianopia involving the optic chiasmal region. Administration of isoniazid to adults at a dose of 20 mg/kg develops peripheral neuritis as isoniazid competes with pyridoxine (Vitamin B6) acting as a cofactor for the synthesis of synaptic neurotransmitter showing evidence of a bilateral reduction in visual acuity and bilateral optic disc swelling along with visual fields taking the appearance of bitemporal hemianopic scotomas.

There is a wider prevalence of ocular toxicity among TB patients with DOTS therapy. Onset of visual symptoms such as bilateral and often an unequal decrease in visual acuity, loss of color vision, bitemporal hemianopsia, or centrocecal scotoma on perimetry were observed among many patients from a period of 10–90 days following AKT therapy. Permanent visual damage due to anti-tubercular agents has been reported in several studies. Visual acuity, contrast sensitivity, color vision, and pattern reversal visual evoked potential are some sensitive tests recommended to detect drug induced ocular toxicity in subclinical stages, but still reversibility of toxicity depends on early diagnosis and early cessation of the culprit drug. Hence, other visual parameters such as central subfield macular thickness and peri-papillary RNFL thickness as measured by SD-optical coherence tomography may prove to be an important tool for early detection.

The present study was aimed toward evaluating the role of various modalities for early detection of ocular toxicity in anti-TB patients following DOTS regimen that may affect the effectiveness of treatment and course of TB.

**MATERIALS AND METHODS**

This was a prospective cross-sectional cohort study of consecutive 30 patients (60 eyes) prescribed with antitubercular therapy of ethambutol (15–20 mg/kg/day) with isoniazid (4–6 mg/kg/day), rifampicin (8–12 mg/kg/day), and pyrazinamide (20–30 mg/kg/day). The study was done in the ophthalmology department of a tertiary eye care center. The duration of the study was 3 months from January 2021 to March 2021. The patients were enrolled from the DOTS center under revised national TB control program of the Government of India. These newly diagnosed patients with TB were sent from the DOTS center to the ophthalmology outpatient department for ophthalmologic evaluation at baseline before starting the treatment and at 2 months follow-up.

The study was approved by the Institutional Ethics Committee, and informed consent was obtained from the patients after explaining the nature of the study. The study protocol was adhered to the tenets of the Declaration of Helsinki on research involving human subjects. All TB patients receiving AKT from DOTS center (including ethambutol) between 20 and 60 years were included in the study.

After taking a detailed clinical history, a complete general and systemic examination was done. Ophthalmological examinations included best-corrected visual acuity, applanation tonometry, slit-lamp biomicroscopy, fundus examination with +90D lens in slit lamp, and indirect ophthalmoscopy. Color vision was assessed with Ishihara pseudoisochromatic plates. The visual field was analyzed by Humphrey field analyzer after full refractive correction. RNFL thickness was measured by (Zeiss optical coherence tomography [OCT], Model 3000°CT-3; Carl Zeiss Meditec, Dublin, California, USA). The first examination was done at baseline before starting the treatment and then at 2 months of therapy. TB patients with other systemic diseases such as renal failure, diabetes, hypertension, and addiction to tobacco and alcohol, patients having other ocular diseases such as diabetic retinopathy, retinitis pigmentosa, glaucoma, sickle cell retinopathy, optic neuropathy, and cataract (>Grade II nuclear sclerosis) were excluded from the study. Patients on drugs causing color vision deficiency such as indomethacin, OC pills and digoxin, and known cases of color blindness were also excluded from the study.

Statistical analysis was performed using Microsoft Excel 13. Student’s paired t-test was done to compare the visual parameters. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

The mean age of patient was 44.87± 13.22 years. Out of total 30 patients, 16 were male and 14 were female. There was no significant difference for either age or gender of the patients in relation to toxicity (\( P > 0.05 \)). Majority of the patient included in the study were suffering from pulmonary TB (83.33%) while other patients were suffering from other types of TB such as tubercular meningitis, abdominal TB, and bone TB [Table 1].
Table 2 indicates difference in visual acuity before starting the therapy (baseline) and at 2 months of the therapy. By applying Chi-square test, it is identified that there is significant differences in $P$ value for both eyes at 2 months of treatment.

It was found that 26 patients (86.7%) had normal vision in the right eye and 25 patients (83.3%) had normal vision in the left eye. The total no. of 4 (13.3%) patient in the right eye and 5 (16.67%) patient in the left eye had blue, red-blue-green, and red-green color defect at 2 months. There was no significant difference in $P$ value for color vision test (Chi-square test). All patients had normal fundus examination except one who had bilateral temporal disc pallor.

The mean deviation, mean sensitivity, and pattern standard deviation were measured for visual field parameters [Table 3]. Out of 30 patients, two patients had central scotoma and one patient had inferotemporal scotoma in the right eye and three patients were suffering from isolated temporal scotoma, incomplete inferior arcuate scotoma, and generalized depression of field respectively in the left eye each.

OCT RNFL-related parameters are reported in Table 4. There is no significant difference in $P$ value for inferior, superior, and nasal thickness in both eyes and temporal thickness in right eye. The mean value for temporal thickness in the left eye was 72.13 ± 8.69 μm at baseline which reduced to 69.73 ± 10.77 μm at 2 months ($P = 0.046$).

### DISCUSSION

Antitubercular treatment with first-line agents is been in clinical practice since the 1960s. Antitubercular drugs with adverse potential for visual impairment were soon identified after the introduction of drugs in treatment regimen. Elderly age male patients were observed to be most affected with significant reduction in RNFL thickness prominently suffering from red color defect. Central and peripheral visual field defects were found in majority of patients with poor macula thickness.

Various literatures have reported dose- and duration-dependent ethambutol-induced ocular toxicity, results of which were found to be consistent with the present study.[12-14] Dose-dependent toxicity of ethambutol was identified by Leibold in which 18% of patients suffered from ocular toxicity consuming a dose of more than 35 mg/kg/day while only 5% of patients suffered from ocular toxicity consuming a dose of 25 mg/kg/day. Around 3% of patients suffered from ocular toxicity consuming a dose of 20 mg/kg/day and negligible toxicity was observed in patients consuming a dose of 15 mg/kg/day, which indicates the importance of dose on adverse effect.[15] The mean age of the patients suffering from TB who received ethambutol was 44.87 years (SD ±13.22) with age ranging from 21 to 63 years. One of the most important factors that increase the risk of experiences of visual disturbance due to ethambutol is the elderly age due to compromised renal function.[16] On the basis of gender, majority of patients consuming ethambutol and suffering from visual disturbance were male (47.1%) compared to females (41.2%) who were comparatively less prone to visual disturbance and this result was in accordance with previously reported studies. Among 30 patients evaluated for visual disturbances, 25 patients (73.5%) suffered from pulmonary TB contributing the majority and were found to be in consistent with the previous studies reported.[17] Color vision was evaluated using Ishihara pseudo-isochromatic color vision test in the present study of 60 eyes of 30 patients. It was observed that a total of 4/30 (6.7%) right eyes had an altered color vision status at 2 months of follow-up. Of these affected eyes, maximum number showed a red-green defect 3/30 (10%). This was consistent with the previous studies.[18] Visual field defects were found to be central, peripheral, or both and they tend to appear with higher dose for long term. In visual field assessment, no significant...

### Table 1: Type of tuberculosis and its association with ocular toxicity

<table>
<thead>
<tr>
<th>Type of tuberculosis</th>
<th>n (No. of patients) (%)</th>
<th>No. of patients with toxicity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary tuberculosis</td>
<td>25 (83.33)</td>
<td>3</td>
<td>Not significant</td>
</tr>
<tr>
<td>Tubercular meningitis</td>
<td>2 (6.66)</td>
<td>2</td>
<td>Significant</td>
</tr>
<tr>
<td>Bone tuberculosis</td>
<td>1 (3.33)</td>
<td>1</td>
<td>Significant</td>
</tr>
<tr>
<td>Lymph node tuberculosis</td>
<td>1 (3.33)</td>
<td>0</td>
<td>Not significant</td>
</tr>
<tr>
<td>Abdominal tuberculosis</td>
<td>1 (3.33)</td>
<td>1</td>
<td>Significant</td>
</tr>
</tbody>
</table>

### Table 2: Visual acuity in studied eyes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline OD n (%)</th>
<th>2 months OD n (%)</th>
<th>P value</th>
<th>Baseline OS n (%)</th>
<th>2 months OS n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6</td>
<td>30 (100)</td>
<td>23 (76.66)</td>
<td>0.01 (significant)</td>
<td>30 (100)</td>
<td>21 (70)</td>
<td>&lt;0.01 (significant)</td>
</tr>
<tr>
<td>6/9–6/12</td>
<td>0</td>
<td>2 (6.66)</td>
<td></td>
<td>0</td>
<td>5 (23.33)</td>
<td></td>
</tr>
<tr>
<td>6/18–6/24</td>
<td>0</td>
<td>3 (10)</td>
<td></td>
<td>0</td>
<td>1 (3.33)</td>
<td></td>
</tr>
<tr>
<td>6/36–6/60</td>
<td>0</td>
<td>1 (3.33)</td>
<td></td>
<td>0</td>
<td>1 (3.33)</td>
<td></td>
</tr>
<tr>
<td>1 m FC</td>
<td>0</td>
<td>1</td>
<td></td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3 m FC</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>1</td>
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</tr>
</tbody>
</table>
changes observed in visual field parameters at 2 months which supports the result obtained in the previous study. OCT was performed on both eyes of each patient using the RNFL analysis protocol. It was observed that the RNFL value was found to be decreasing in inferior, temporal, and superior quadrants in the right eye whereas it was found to be decreasing in all three quadrants for the left eye except the superior quadrant. A trend toward decrease in RNFL value for all patients was observed with greatest decrease in RNFL(T) in the temporal quadrant was observed which was found to be consistent with results of prior studies. Furthermore, in the present study, the average macular thickness significantly decreases in all patients as compared to the baseline as the retinal ganglion cells are most dense in the macula which results in disturbances and higher sensitivity to impairment of optic nerve. This was earlier demonstrated by Lee et al., where he observed a 10 μm thickness loss in inner temporal GCIPL in the initial OCT associated with a 0.5 decrease in the amount of logMAR visual acuity recovery at 12 months. Significant reduction in thickness of RFNL and macula was the most prominent observations among patients with EON. SD-OCT is an important tool for obtaining objective, quantitative measurements to monitor the effects of ethambutol on the optic nerve. Nonetheless, more studies are needed to more clearly evaluate the long-term effect of ethambutol treatment on the optic nerve fiber layer.

This prospective study provides a detailed insight into various risk factors associated with optical neuropathy. Unlike the previous studies, which investigated for a short period of time, the present study involved a follow-up period of 2 months as symptoms of ocular toxicity develops after 2 months of treatment duration. However, there were few limitations pertaining to the study as we were unable to evaluate the patients for a sufficient span of time after stoppage of drug administration. Further implication of subclinical toxicity of anti-TB drugs needs clinical examination of a large population for a longer period of time during treatment and post-treatment. Results of the study can be improved with more frequent assessment and longer duration of follow-up.

CONCLUSION

Intake of anti-TB drugs for a longer duration may damage papillomacular bundle resulting in visual field defects. In addition to visual acuity, color vision, and visual fields, RNFL and macular thickness examination act as an important tool for early detection of ocular toxicity. Periodic examination of eye functions before and during the course of treatment would play a strategic role in modifying the therapeutic regimen and preservation of visual acuity.

REFERENCES

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