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Original Research Article

# VISUAL FUNCTION CHANGES IN NEWLY DIAGNOSED PULMONARY TUBERCULOSIS PATIENTS ON ETHAMBUTOL THERAPY AS PER NTEP GUIDELINES - A PROSPECTIVE STUDY

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## Abstract

**Background:** Tuberculosis (TB) treatment commonly involves the administration of antitubercular drugs, including Ethambutol, which may lead to ocular toxicity, notably optic neuritis. Detecting ocular toxicity early is crucial for timely intervention and management. This study aimed to assess visual function to detect ocular toxicity associated with Ethambutol use in TB patients. **Materials and Methods:** A total of 244 eyes from 122 subjects were initially included in this observational follow-up study. Patients were assessed every 2 months using subjective methods, including best-corrected visual acuity (BCVA), colour vision, contrast sensitivity, and visual fields. Patients were grouped based on body weight, and various visual parameters were analysed over a six-month period. **Result:** The mean age of the subjects was 43.36 ± 13.3 years, with a higher proportion of males (76.7%). BCVA remained unaltered in Group 1, while Groups 2, 3, and 4 showed varying degrees of decreased visual acuity over the study period. Colour vision abnormalities, predominantly blue-yellow defects, were observed in Groups 3 and 4 from the 2nd month of follow-up. Contrast sensitivity decreased in Groups 2, 3, and 4, with significant changes observed in Group 4. Visual field abnormalities, primarily peripheral field defects, were detected in Groups 3 and 4 during the 4th and 6th month of follow-up. **Conclusion:** Our study suggests that visual function assessment, including BCVA, colour vision, contrast sensitivity, and visual fields, can aid in the early detection of Ethambutol-induced ocular toxicity. Regular monitoring of visual function in TB patients undergoing Ethambutol therapy is essential for timely intervention and minimizing ocular toxicity-related complications.

## INTRODUCTION

Tuberculosis (TB) remains a significant global health challenge, with India bearing a substantial burden.[1] Given the increasing prevalence of tuberculosis, the primary treatment modalities for TB involves the use of antitubercular drugs, among which Ethambutol, Isoniazid, Rifampicin, and Pyrazinamide constitute the first-line regimen, typically administered over a six-month period. However, the therapeutic efficacy of these drugs is overshadowed by their potential ocular toxicity, with Ethambutol emerging as a major concern. Ethambutol-induced optic neuritis manifests in two distinct forms: retrobulbar optic neuritis, characterized by central vision impairment and dyschromatopsia, and paraxial neuritis, leading to peripheral visual field defects.[2-6]

The mechanisms underlying this toxicity involve mitochondrial dysfunction induced by Ethambutol's metal-chelating properties and subsequent release of reactive oxygen species. The papillomacular bundle is particularly susceptible to damage due to its high energy demand and narrow calibre.[5]

The risk factors associated with Ethambutol induced optic toxicity include dosing, duration, renal disease and age. Studies have reported varying incidences of toxicity across different dosage ranges, with no established safe dose. It has been reported in 45% of those taking 60mg/kg/day to100mg/kg/day, 18.6% of those taking more than 53mg/kg/day, 1.3% to 15% of those taking 25mg/kg/day, 2% of those taking 15mg/kg/day.[6]

Previous investigations predominantly focused on traditional TB treatment regimens outlined by the Revised National Tuberculosis Control Programme


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(RNTCP), involving two months of HRZE followed by four months of HR. However, recent recommendations from the National Tuberculosis Elimination Programme (NTEP) advocate for treatment based on drug susceptibility testing, necessitating a longer duration of Ethambutol administration, extending to six months. In view of these evolving treatment paradigms and the imperative to address Ethambutol-induced optic neuropathy, the present study aimed to detect the ocular toxicity associated with Ethambutol by assessing visual functional tests.

**Aim:** The study aimed to assess visual function to detect ocular toxicity associated with Ethambutol use in tuberculosis (TB) patients

**Objectives:**

- To evaluate the visual function by administering the visual function tests tests (visual Acuity, colour vision and visual fields) in tuberculosis patients on Ethambutol therapy as per National Tuberculosis Elimination Programme (NTEP) guidelines.
- To determine the incidence of ocular toxicity in relation to dose and duration of Ethambutol.

## MATERIALS AND METHODS

A hospital based observational follow up study was done in newly diagnosed primary tuberculosis patients on Ethambutol therapy as per NTEP guidelines who fulfilled the inclusion criteria and attended outpatient department of Ophthalmology, SVRRGGH, Tirupati, Over a period of One year from the date of approval of institutional ethical committee (IEC -11/2021)

**Source of Data:** Data was collected from the outpatient departments of Ophthalmology and Pulmonology at SVRRGGH, Tirupati.

**Inclusion Criteria**

1. Newly diagnosed pulmonary tuberculosis patients receiving Ethambutol therapy as per NTEP guidelines.
2. Patients aged between 18 to 70 years and providing informed and valid consent.

**Exclusion Criteria**

1. Multidrug-resistant (MDR) TB.
2. Extreme drug-resistant (XDR) TB.
3. Extra-pulmonary TB.
4. Patients with systemic diseases such as diabetes mellitus, hypertension, or renal failure.
5. Patients with significant ocular media opacities that hinder the assessment of visual function.
6. Patients with retinal, macular, choroidal, or optic nerve diseases.
7. Patients taking oral contraceptives, digoxin, amiodarone, linezolid, or other medications that can interfere with Ethambutol metabolism

**Study Method**

All participants underwent a comprehensive baseline ophthalmic assessment, encompassing the following procedures:

Detailed ocular and medical history, including information on the dosage and duration of anti-tubercular medication usage.

Measurement of uncorrected and best-corrected visual acuity using Snellen charts for distant vision and Jaeger charts for near vision, scored with the LogMAR scale.

Assessment of colour vision using Ishihara pseudoisochromatic charts and the Farnsworth-Munsell 40 Hue Test (administered online).

Evaluation of contrast sensitivity using Pelli-Robson charts.

Anterior segment examination via slit-lamp bio microscopy (Carl Zeiss Meditec AG, Jena, Germany).

Posterior segment evaluation through direct and indirect ophthalmoscopy with a 90D lens.

Visual field analysis employing Humphrey's 8.1 standard automated perimetry. Visual field examinations were conducted using the 30-2 program on the Humphrey Field Analyzer with a white-on-white Goldmann size III target. All patients underwent a full-threshold strategy for visual field assessment, ensuring reliability with fixation losses <20% and false-positive and false-negative errors <33%. Only reliably performed fields were included in the analysis. All the included patients were categorized into groups according to their body weight and followed up with comprehensive analysis of various visual parameters including BCVA, Colour vision, contrast sensitivity and visual fields at baseline and for every two months over a period of six months of drug usage.

**Data Recording:** All pertinent details were recorded in a standardized study proforma.

**Statistical Analysis:** The collected data was entered into a Microsoft Excel worksheet (MS 2017 version) and analyzed using Epi Info 7.2.2.6 software. provided by the Centres for Disease Control and Prevention (CDC), Atlanta, Georgia, United States. Categorical variables were expressed as proportions, while continuous variables (such as age) were presented as mean and standard deviation. Differences between proportions was assessed using the Chi-square test, with a significance level set at $p < 0.05$.

## RESULTS

120 patients were enrolled in the study, and so the results were analyzed and tabulated in 240 eyes of 120 patients. the mean age of study population was 43.36 years with Majority of patients were in age group of 51-70 years. Among 120 patients, majority being males92 (76.7%) and 28 (23.3%) were females. The study subjects were divided into 4 groups according to body weight and daily dose of ethambutol drug and details were outlined in [Table 1].

The comparison of baseline best-corrected visual acuity (BCVA) among groups yielded a statistically


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significant result, with a chi-square value of 44.658 and a p-value of <0.001. Similarly, the BCVA at the 2nd, 4th, and 6th month follow-ups also demonstrated statistically significant differences among the groups, with chi-square values of 48.658, 43.151, and 84.519 respectively, all with p-values being <0.001. [Table 2] provides comparison of BCVA at follow up intervals of 2months after drug usage in different groups.

Baseline colour vision tested using Ishihara charts and Farnsworth 40 hue test was found to be normal in all groups. However, the analysis of colour vision among groups showed statistically significant differences at the 2nd, 4th, and 6th month follow-ups. At the 2nd month follow-up, the chi-square value was 12.575 with a p-value of 0.05. Similarly, at the 4th month follow-up, the chi-square value was 21.716 with a p-value of 0.01, and at the 6th month follow-up, it was 26.084 with a p-value of 0.02. These findings indicate significant variations in colour vision among the groups across the different time points. [Table 3] shows comparison of Colour Vision at 2-Month Intervals following Drug usage in different Groups

The comparison of contrast sensitivity among groups at the 2nd, 4th, and 6th month follow-ups did not yield statistically significant differences. At the 2nd month follow-up, the chi-square value was 4.649 with a p-value of 0.59, at the 4th month follow-up it was 9.031 with a p-value of 0.172, and at the 6th month follow-up, it was 6.752 with a p-value of 0.344. These results suggest that there were no notable differences in contrast sensitivity among the groups across the specified time points. Nonetheless, significant changes in contrast sensitivity were observed within different groups at 2-month follow-up intervals of drug usage [Table 4].

At baseline and the 2-month follow-up, no visual field defects were detected across all groups. However, by the 4-month follow-up, Group 1 maintained its absence of visual field defects. Group 2 exhibited peripheral constriction in 4.2% of eyes, while Group 3 showed paracentral scotomas and peripheral constriction in 3.6% of eyes each. Group 4 presented with various defects: Centro caecal scotomas (3.6%), paracentral scotomas (5.4%), hemianopia (3.6%), peripheral constriction (5.4%), and superior altitudinal defects (1.8%). The chi-square value was 13.702 with a p-value of 0.005, indicating significance.

At the 6-month follow-up, Group 1 remained free of visual field defects. In Group 3, Centrocaecal scotomas were observed in 3.6% of eyes, while paracentral scotomas were present in 5.4%. Group 4 displayed hemianopia (3.6%) and superior altitudinal defects (3.6%). Peripheral constriction was noted in Group 2 (4.2%), Group 3 (10.7%), and Group 4 (8.9%). The chi-square value was 23.398 with a p-value of 0.006, indicating significance.

**Table 1: Distribution of subjects according to body weight and drug dosage.**

| Group | Weight(kgs) | No of patients (n) (%) | Daily dose of Ethambutol |
|---|---|---|---|
| I | 25-39 | 12 (10% | 550mg |
| II | 40-54 | 24(20%) | 825mg |
| III | 55-69 | 28(23.3%) | 1100mg |
| IV | ≥70 | 56(46.6%) | 1375mg |

**Table 2: Comparison of best corrected visual acuity (BCVA) in different groups at follow up intervals of 2months**

| Group | Mean BCVA (Log MAR units) | | | | |
|---|---|---|---|---|---|
| | Base line | 2months | 4 months | 6 months | P value ≠ |
| I (n = 24 | 0.08 ± 0.12 | 0.08 ± 0.12 | 0.08 ± 0.12 | 0.08 ± 0.12 | 0.82 |
| II (n = 48 | 0.16 ± 0.10 | 0.16 ± 0.10 | 0.18 ± 0.12 | 0.21 ± 0.12 | 0.003 |
| III (n=56) | 0.18 ± 0.11 | 0.18 ± 0.11 | 0.23 ± 0.13 | 0.23 ± 0.13 | 0.029 |
| IV (n=112) | 0.25±0.14 | 0.27 ± 0.17 | 0.30 ±0.15 | 0.37 ± 0.12 | < 0.001 |

≠ unpaired t- test

**Table 3: comparison of colour vision in different groups at the 2nd, 4th, and 6th month follow-ups**

| Group | Colour vision | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2months follow up | | | 4 months follow up | | | | 6 months follow up | | | | X2 | P value ≠ |
| | Normal | B-Y defect | R-G defect | Normal | B-Y defect | R-G defect | Mixed | Normal | B-Y defect | R-G defect | Mixed | | |
| I (n = 24 | 24 (100%) | 0 | 0 | 24 (100%) | 0 | 0 | 0 | 20 (83.3%) | 4 | 0 | 0 | 12.52 | 0.006 |
| II (n = 48 | 36 (75.0%) | 12 (25%) | 0 | 32 (66.7%) | 16 | 0 | 0 | 26 (54.2%) | 22 | 0 | 0 | 28.01 | <0.001 |
| III (n=56) | 40 (71.4%) | 12 (21.4%) | 4 (7.1%) | 36 (64.3%) | 12 (21.4% | 4 (7.1%) | 4 (7.1%) | 32 57.1%) | 12 (21.4%) | 6 (10.7%) | 6 (10.7%) | 30.23 | <0.001 |
| IV (n=112) | 88 (78.6%) | 20 (17.9%) | 4 (3.6%) | 76 (67.9%) | 24 (21.4%) | 8 (7.1%) | 4 (3.6%) | 72 (64.3%) | 28 (25.0%) | 8 (7.1%) | 4 (3.6%) | 50.05 | <0.001 |

**Table 4: comparison of contrast sensitivity in different groups at the 2nd, 4th, and 6th month follow-ups**

| Group | Contrast sensitivity | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2months follow up | | 4 months follow up | | 6 months follow up | | X2 | P value≠ |
| | Normal | Reduced | Normal | Reduced | Normal | Reduced | | |
| I (n = 24 | 24 | 0 | 24 | 0 | 24 | 0 | | |
| II (n = 48 | 48 | 0 | 48 | 0 | 42 (87.5%) | 6 (12.5 %) | 18.58 | <0.01 |


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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| III (n=56) | 56 | 0 | 52 (92.9%) | 4 (7.1%) | 50(89.3%) | 6 (10.7%) | 11.3 | 0.01 |
| IV (n=112) | 108 (96.4%) | 4 (3.6%) | 100 (89.3%) | 12 (10.7%) | 96 (85.7%) | 16 (14.3%) | 21.53 | <0.001 |

## DISCUSSION

Ethambutol is a bacteriostatic antibiotic used in the treatment of Mycobacterium species. Although it is effective in treating Mycobacterium spp. in combination with other medications, one of the most common and devastating side effects is ethambutol-induced optic neuropathy (EON). Unlike other toxic optic neuropathies, EON can occur within a very short period following the initiation of therapy. Symptoms may develop anywhere from 1 to 36 months after starting the drug. It can manifest in around 1% of patients receiving ethambutol at the WHO recommended doses. advised by the World Health Organization (WHO)The risk of Ethambutol Optic Neuropathy is highly dose-dependent. The toxic effect of this extensively used Ethambutol drug can be studied by various modalities including evaluation of BCVA, colour vision, Contrast sensitivity, and Visual field analysis.[7] The study conducted at the Department of Ophthalmology in Sri Venkateswara Ramnarayan Ruia Government General Hospital aimed to evaluate visual function tests in newly diagnosed pulmonary tuberculosis (TB) patients undergoing Ethambutol therapy following National Tuberculosis Elimination Programme (NTEP) guidelines.

In our study, the mean age of patients was found to be 43.36 years, consistent with similar studies by Dave et al,[8] and Mandal et al,[9] which reported mean ages of 44.9 years and 36.5 years, respectively. However, Mohammed et al,[10] noted a higher proportion of patients in the 10-25 age group.

The study assessed the impact of Ethambutol therapy on visual function among newly diagnosed pulmonary tuberculosis (TB) patients, categorized by weight bands. At baseline, all visual parameters were normal, However, a statistically significant decrease in BCVA was observed at the 2$^{nd}$ month, 4$^{th}$ months and 6 months follow up of Ethambutol therapy, aligns with previous studies by Kandel et al,[11] and Dave et al,[8] This trend persisted throughout the treatment duration, with group 4 consistently showing the significant distribution across different levels of best-corrected visual acuity (BCVA), indicative of a dose-dependent effect of Ethambutol on visual function.

Comparative analysis between colour vision and weight bands showed a significant association. Prior to treatment, all cases had normal colour vision. However, by the 2nd month, abnormalities were predominantly observed in group IV, with 20 eyes showing B-Y abnormalities and 4 eyes exhibiting R-G abnormalities. This trend continued at the 4th and 6th months, with group IV consistently showing the highest number of abnormalities.

Our findings corroborate those of previous studies. Bandyopadhyay et al,[12] reported acquired colour vision abnormalities in 8.6% of eyes after 2 months of ethambutol therapy, with blue defects being the most common. Similarly, Konnakkodan et al,[13] noted colour vision disturbances as early symptoms of optic nerve toxicity in patients treated with Ethambutol. In our study, comparative analysis between visual fields and weight categories showed a significant association. Prior to treatment, all weight groups had normal visual fields. Similarly, at the 2nd month, all groups maintained normal visual fields, whereas by the 4th and 6th months, continued to exhibit predominantly normal visual fields, with defective visual fields predominantly noted in the group IV as well. Defects varied, including centro caecal, paracentral, hemianopia, peripheral constriction, and superior altitudinal defects. Our findings are consistent with previous research. Bandyopadhyay et al,[12] reported central and peripheral visual field defects in ethambutol toxicity cases, with some persisting even after therapy cessation. Goyal et al,[14] found a portion of patients experiencing visual field defects, with varying degrees of recovery post-ethambutol cessation.

Limitations of our study include the inability to assess Ethambutol toxicity individually due to its inclusion in multidrug regimens and the lack of assessment for subclinical toxicity using methods such as optical coherence tomography (OCT) or visual evoked potentials (VEP).

## CONCLUSION

In conclusion, our study highlights the efficacy of visual function tests in detecting Ethambutol-induced ocular toxicity early. These findings underscore the importance of regular monitoring of visual function in patients undergoing anti-tubercular therapy (ATT) with Ethambutol regimen, especially in elderly individuals and those with higher body weight. Proactive monitoring can facilitate timely intervention and minimize adverse effects associated with Ethambutol therapy.

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