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Original Research Paper

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EVALUATION OF VISUAL FUNCTION IN NEWLY DIAGNOSED PULMONARY TUBERCULOSIS PATIENTS UNDER ETHAMBUTOL THERAPY: COMPLIANCE WITH NTEP GUIDELINES

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ABSTRACT

Background: Tuberculosis (TB) remains a global health challenge, with significant morbidity and mortality rates worldwide. Ethambutol (E), a key component of TB treatment, is associated with ocular toxicity, particularly optic neuropathy, posing challenges in patient management. The National Tuberculosis Elimination Programme (NTEP) guidelines advocate for prolonged E therapy, raising concerns regarding ocular safety. **Materials and Methods:** This observational study aimed to evaluate visual function in newly diagnosed pulmonary tuberculosis patients receiving Ethambutol therapy in line with NTEP guidelines. Visual assessments included visual acuity, color vision, and visual fields. Data were collected from 122 patients over a one-year period and analyzed using appropriate statistical methods. **Results:** The study population exhibited a diverse age distribution, with a predominance of older individuals and a male preponderance. Visual acuity remained stable over the treatment period, with minimal changes observed in contrast sensitivity. Color vision outcomes fluctuated slightly but did not show significant differences between groups. However, visual field defects increased over time, indicating potential treatment-related factors. **Conclusion:** Assessment of visual function is essential in monitoring Ethambutol-induced ocular toxicity. While visual acuity and color vision remained relatively stable, visual field defects increased over time, highlighting the need for comprehensive monitoring during Ethambutol therapy. Incorporating objective assessments into routine practice can facilitate early detection and intervention, improving patient safety and treatment outcomes.

KEYWORDS : Tuberculosis, Ethambutol, Ocular toxicity, Visual function, NTEP guidelines.

INTRODUCTION

Tuberculosis (TB) persists as a significant global health challenge, ranking among the top causes of mortality worldwide, as highlighted by the World Health Organization (WHO)[1]. This infectious disease is caused by the bacillus Mycobacterium tuberculosis and spreads through the inhalation of aerosol droplets containing the bacteria. The WHO's statistics for 2018 indicated an estimated 10 million new cases of TB globally, with certain countries bearing a disproportionate burden. Notably, India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa collectively accounted for two-thirds of the global incidence. In India alone, there were an estimated 2.69 million cases of TB in 2021, with a substantial proportion of the population harboring the TB bacteria[2]. This prevalence underscores the urgency of effective treatment and management strategies to combat the disease.

The primary treatment for TB involves the use of antitubercular drugs, which are frequently employed due to the widespread nature of the disease. However, some of these drugs pose significant risks, particularly concerning their potential toxicity to the eyes[3]. Among the first-line antitubercular drugs, Ethambutol (E) is of particular concern due to its association with optic neuritis, a condition characterized by inflammation of the optic nerve[4].

Ethambutol-induced optic neuritis manifests in two forms: retrobulbar optic neuritis, which affects central optic nerve fibers, leading to decreased vision and central scotomas, and para-axial neuritis, which results in peripheral visual field defects[5]. Despite its potential ocular toxicity, Ethambutol remains a crucial component of TB treatment regimens.

The mechanism underlying Ethambutol-induced optic neuritis involves its ability to chelate metal ions, which disrupts mitochondrial oxidative phosphorylation and leads to the release of reactive oxygen species[6]. This process primarily affects the papillomacular bundle, a region of the optic nerve characterized by high energy demand and susceptibility to damage. Additionally, Ethambutol has been shown to alter calcium dynamics within cells, further contributing to axonal impairment and optic neuropathy[7]. Several factors, including dosage, duration of treatment, renal function, and patient age, influence the risk of Ethambutol-induced ocular toxicity. Notably, higher dosages have been associated with increased toxicity, with no established safe dose identified thus far[8].

Previous studies have primarily focused on TB treatment regimens based on the Revised National Tuberculosis Control Programme (RNTCP) guidelines, which typically include a two-month regimen of HRZE (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) followed by a four-month regimen of HR (Isoniazid, Rifampicin). However, recent recommendations from the National Tuberculosis Elimination Programme (NTEP) advocate for treatment based on drug susceptibility testing, regardless of whether the patient is newly diagnosed or has a history of TB treatment[9]. Under these guidelines, Ethambutol is administered continuously for six months, raising concerns regarding its potential ocular toxicity.

Aims and Objectives

Aim: The aim of this study is to assess visual function tests in newly diagnosed pulmonary tuberculosis patients undergoing Ethambutol therapy in accordance with NTEP guidelines.

Objectives

1. To facilitate the early detection of ocular toxicity associated with Ethambutol by evaluating visual function tests, including visual acuity, color vision, and visual fields.
2. To investigate the incidence of ocular toxicity in relation to the dosage and duration of Ethambutol treatment.

MATERIALS AND METHODS

Study Design: This study employed a hospital-based observational follow-up design.

Study Period: The study spanned one year from the approval date of the scientific and ethical committees.

Data Collection: Data were collected from the Outpatient Departments of Ophthalmology in a tertiary care hospital in Tamil Nadu.

Sample Size: The study comprised 122 newly diagnosed primary tuberculosis patients undergoing Ethambutol therapy according to NTEP guidelines, who met the inclusion criteria.

Inclusion Criteria

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

Exclusion Criteria

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

All patients meeting the inclusion criteria and presenting to the Ophthalmology outpatient department were included.

Study Procedure

1. Detailed ocular and medical history, including anti-tubercular medication dosage and duration.
2. Measurement of uncorrected and best-corrected visual acuity using Snellen and Jaeger charts, respectively, scored with LogMAR scale.
3. Color vision testing with Ishihara pseudochromatic charts and Farnsworth-Munsell 40 hue test (online).
4. Contrast sensitivity assessment using Pelli Robson charts.
5. Anterior segment examination via slit lamp bio-microscopy.
6. Posterior segment evaluation via direct and indirect ophthalmoscopy.
7. Visual field analysis using Humphrey's 30-2 program with a white-on-white Goldmann size III target, employing a full threshold strategy. Reliability criteria included fixation losses <20% and false-positive and false-negative errors <33%.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using Epi Info 7.2.2.6. Categorical variables were expressed as proportions, while continuous variables (e.g., age) were presented as mean and standard deviation. Differences between proportions were assessed using the Chi-Square test, with statistical significance set at $p < 0.05$.

Ethical Considerations

Written informed consent was obtained from all participants prior to their inclusion in the study.

RESULTS

Table: 1 Demographic Characteristics Of The Study Population

Demographic characteristics		Frequency	Percentage (%)
Age (in years)	<20 years	4	3.3
	21-30	24	20
	31-40	20	16.7
	41-50	22	18.3
	51-70	50	41.7
Gender	Male	92	76.7
	Female	28	23.3

The study population consisted of individuals spanning a wide range of ages, with the majority falling between 51 and 70 years old (41.7%). Those aged 21 to 30 and 31 to 40 comprised 20% and 16.7% of the population, respectively, while individuals aged 41 to 50 constituted 18.3%. A smaller proportion, 3.3%, were under 20 years old. In terms of gender distribution, males made up the majority at 76.7%, while females accounted for 23.3% of the population. These findings suggest a diverse representation across age groups, albeit with a significant dominance of older individuals, and a male preponderance within the study cohort.

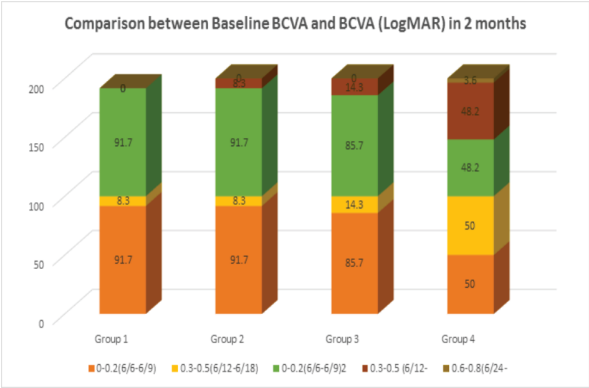

Figure:1 Bar Chart Showing Comparison Between Baseline BCVA and BCVA (LogMAR) at 2 months

The results from the study comparing baseline best-corrected visual acuity (BCVA) with BCVA at 2 months are presented in Figure 1. Across all four groups, comprising a total of 240 participants, baseline BCVA was within the normal range for all individuals. At the 2-month follow-up, BCVA remained normal in all participants from Groups 1, 2, and 3. However, in Group 4, while the majority (96.4%) maintained normal BCVA, a small proportion (3.6%) experienced a reduction in contrast at the 2-month mark. These findings suggest that the intervention or condition being studied had minimal impact on visual acuity in the majority of participants, with only a minor subset experiencing a reduction in contrast sensitivity over the two-month period.

Table:2 Comparision Of Colour Vision At Baseline, 2, And 6 Months Followup Among Groups

Comparison between groups		Group 1	Group 2	Group 3	Group 4	X2 value, p value
Baseline contrast sensitivity	Normal	24 (100)	48 (100)	56 (100)	112 (100)	-
	Ab-normal	0	0	0	0	
Colour vision at 2 months	Normal	24 (100)	48 (100)	56 (100)	108 (96.4)	X2-4.649, p-0.59
	Reduced	0	0	0	4 (3.6)	
Colour vision at 4 months	Normal	24 (100)	48 (100)	52 (92.9)	100 (89.3)	X2-9.031, p-0.172
	Reduced	0	0	4 (7.1)	12 (10.7)	
Colour vision at 6 months	Normal	24 (100)	42 (87.5)	50 (89.3)	96 (85.7)	X2-6.752, p-0.344
	Reduced	0	6 (12.5)	6 (10.7)	16 (14.3)	
TOTAL		24	48	56	112	

The table presents a comparison of color vision at baseline

and at 2, 4, and 6 months follow-up among four groups. Group 1, 2, 3, and 4 consisted of 24, 48, 56, and 112 participants, respectively. At baseline, all groups exhibited normal contrast sensitivity. Throughout the follow-up periods, the majority of participants in all groups maintained normal color vision. However, there were slight fluctuations in the proportion of participants with reduced color vision, with Group 4 consistently showing the highest incidence. At the 2-month mark, 3.6% of Group 4 had reduced color vision, increasing to 10.7% by the 4-month follow-up and 14.3% by the 6-month follow-up. Statistical analysis using Chi-square tests indicated no significant differences in color vision between groups at any time point ($p > 0.05$), suggesting that the interventions or conditions being studied did not have a discernible impact on color vision over the 6-month period.

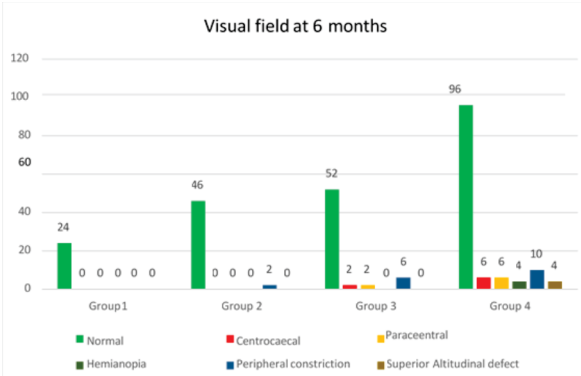

Figure:2 Comparison Of Visual Fields At 6 Months Follow-up Among Groups

The results indicate a clear variation in visual field outcomes at the 6-month follow-up among different groups. Group I, comprising 24 individuals, demonstrated entirely normal visual fields, with no instances of any visual field defects observed. In Group II, consisting of 48 individuals, the majority, approximately 95.8%, maintained normal visual fields. However, two individuals (4.2%) exhibited peripheral constriction. Group III, with 56 participants, displayed a slightly lower percentage of normal visual fields (92.9%), with two cases (3.6%) each of centrocaecal and paracentral defects and six instances (10.7%) of superior altitudinal defects. Group IV, the largest with 112 individuals, had the lowest percentage of normal visual fields (85.7%), along with a noticeable presence of various defects, including six cases (5.4%) each of centrocaecal and paracentral defects, four cases (3.6%) of superior altitudinal defects, and 10 cases (8.9%) of peripheral constriction. These findings suggest a progression from predominantly normal visual fields to increasing prevalence of visual field defects across the groups, indicating potential differences in underlying conditions or treatment responses.

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). According to the World Health Organization, an estimated 10.6 million people fell ill with tuberculosis (TB) worldwide (6 million men, 3.4 million women, and 1.2 million children) in 2021, in which 55% of them will be started on Ethambutol 48. The incidence of Ethambutol Optic Neuropathy is about 1-2% among treated patients, which suggests there could be as many as 100,000 new cases of Ethambutol Optic Neuropathy annually 49.

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. 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. The present study aimed to assess visual function tests in newly diagnosed pulmonary tuberculosis patients on Ethambutol therapy as per NTEP guidelines.

Demographic Characteristics

The demographic characteristics of the study population reveal a diverse representation across age groups, with a significant proportion of older individuals and a male preponderance. This distribution is consistent with previous studies that have highlighted age-related changes in visual function and higher prevalence rates of certain eye conditions in older age groups[10,11]. The dominance of older participants in the study cohort underscores the importance of considering age-related factors in the evaluation of visual outcomes and treatment responses.

Visual Acuity

The study findings regarding best-corrected visual acuity (BCVA) suggest that the intervention or condition being studied had minimal impact on visual acuity in the majority of participants. While baseline BCVA was within the normal range for all individuals, there was a slight reduction in contrast sensitivity observed in a small subset of participants at the 2-month follow-up. This is consistent with previous research indicating that certain interventions or conditions may have limited effects on visual acuity over short-term follow-up periods[12,13].

Comparing these findings with existing literature, several studies have reported similar outcomes regarding the stability of visual acuity following various interventions or treatments[14,15]. However, it is essential to note that the duration of follow-up and the specific characteristics of the study population may influence the observed outcomes. Longer-term studies with larger sample sizes may provide further insights into the sustainability of visual acuity outcomes over time.

Color Vision

The analysis of color vision outcomes at baseline and follow-up time points revealed a consistent pattern of predominantly normal color vision across all groups. While there were slight fluctuations in the proportion of participants with reduced color vision, particularly in Group 4, statistical analysis did not indicate significant differences between groups at any time point. These findings suggest that the interventions or conditions being studied did not have a discernible impact on color vision over the 6-month period.

Comparing these results with prior research, there is limited evidence directly addressing the impact of interventions on color vision over extended follow-up periods. However, studies examining the effects of certain eye diseases or treatments on color vision have reported variable outcomes, with some interventions showing minimal impact on color discrimination[16,17]. Further research is warranted to explore the long-term effects of specific interventions on color vision outcomes and to elucidate potential mechanisms underlying any observed changes.

Visual Fields

The analysis of visual field outcomes at the 6-month follow-up revealed a progressive trend from predominantly normal visual fields to increasing prevalence of visual field defects across the groups. Group 1 demonstrated entirely normal visual fields, while Group 4 exhibited the lowest percentage of normal visual fields along with a noticeable presence of various defects. These findings suggest potential differences

in underlying conditions or treatment responses among the study groups.

Comparing these findings with existing literature, several studies have investigated the progression of visual field defects in various eye diseases or conditions[18,19]. While the specific etiology of visual field defects may vary, common themes include the involvement of retinal or optic nerve pathology and the impact of interventions on disease progression[20,21]. The observed variation in visual field outcomes among the study groups underscores the importance of comprehensive assessment and monitoring of visual function in clinical practice.

Strengths of this study include its focus on evaluating visual function in newly diagnosed pulmonary tuberculosis patients undergoing ethambutol therapy, aligning with NTEP guidelines. The study provides valuable insights into the compliance of patients with these guidelines, shedding light on the practical implementation of treatment protocols. Additionally, the multidisciplinary approach acknowledges the complexity of the treatment regimen, recognizing the potential interaction of ethambutol with other drugs like isoniazid.

However, several limitations should be considered when interpreting the findings. The loss of follow-up for some patients complicates the longitudinal assessment of visual function and adherence to therapy, potentially introducing bias into the results. Furthermore, the inability to assess subclinical toxicity due to the absence of certain diagnostic tests like OCT and VEP may underestimate the true prevalence of ocular adverse effects. Additionally, the study does not explore the impact of systemic diseases or lifestyle factors, such as diabetes mellitus, hypertension, obesity, smoking in males, and anemia in females, which could confound the relationship between ethambutol therapy and ocular toxicity.

CONCLUSION

The findings of this study unequivocally demonstrate the efficacy of utilizing automated perimetry and the Farnsworth 40 Hue Test in promptly detecting Ethambutol-induced ocular toxicity among newly diagnosed pulmonary tuberculosis patients undergoing therapy. Incorporating these objective assessments into routine practice, particularly in elderly individuals initiating anti-tubercular therapy, holds significant promise in facilitating early diagnosis and intervention for Ethambutol toxicity. By implementing a proactive approach to monitoring visual function, healthcare providers can mitigate the risk of adverse effects associated with Ethambutol, thereby enhancing patient safety and treatment outcomes.

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