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A STUDY ON ETHAMBUTOL INDUCED OCULAR TOXICITY IN PATIENTS ON ANTITUBERCULOSIS THERAPY

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Abstract

Background: Ocular Toxicity is one of the most common complication of Ethambutol. It can be in the form of both reversible and irreversible blindness. **Aim and Objective:** To study Ethambutol induced ocular toxicity in patients using anti tuberculosis treatment (ATT). To characterize duration of treatment at which ocular symptoms are starting. To evaluate the dose of ethambutol at which ocular toxicity is evident. To study the reversibility of ocular toxicity in the form of improvement in visual acuity after stopping ethambutol. **Methodology:** Patients on ATT referred to ASRAM Respiratory Medicine department from various ophthalmology hospitals for blurring of vision due to Ethambutol were taken into study from April 2022-2023 after taking consent. **Results:** Most of the patient's symptoms that is blurring of vision started after 3-4 months of ATT [40.15%] and mean dosage is 20.86 mg/kg/day. **Conclusion:** In most patients Ethambutol induced ocular toxicity is observed in continuation phase of treatment and those who are falling at lower end of body-weight band. In few patients with stopping of Ethambutol blurring of vision was reversible.

Key Words: Ethambutol ocular toxicity, Anti tuberculosis treatment.

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Introduction

Ethambutol is one of the first line anti tuberculosis drugs. It is used in both Intensive Phase and Continuation phase of treatment for a duration of 6 months in fixed dose combinations (FDCs). It is a bacteriostatic drug. Its exact mechanism of action is unknown. Ethambutol inhibits arabinosyl transferases involved in cell-wall biosynthesis[1]. It is excreted through kidneys and its plasma half-life is 4 hours. The most important side effect of ethambutol is due to its effect on optic nerve fibers in the form of toxic optic neuropathy causing both reversible and irreversible blindness. Ethambutol can cause other adverse drug reactions such as nausea, fever, rashes and neurological changes which are rare. Optic neuropathy is characterised by painless loss of vision as decreased visual acuity, red–green dyschromatopsia, blurring, central scotomas, and visual field defects. The incidence of ocular toxicity is 0.5 to 35%, as obtained from various studies. Ocular toxicity is thought to be due to the zinc-chelating effect of ethambutol. Increased risk for ethambutol ocular toxicity (EOT) is associated with older age, low body weight, dose and duration of ethambutol treatment, chronic hypertension, renal impairment and chronic smoking.

Aim: To study ethambutol induced ocular toxicity in patients using fixed dose combinations anti tuberculosis treatment (ATT).

Objectives: To characterize the duration of treatment at which ocular symptoms are starting. To evaluate the dose of ethambutol at which ocular toxicity is evident. To study the reversibility of ocular toxicity in the form of improvement in visual acuity after stopping ethambutol.

Methodology

A longitudinal study was conducted on patients referred from various ophthalmology centers to ASRAM hospital respiratory medicine department with diagnosis of ATT induced Optic Neuropathy for changing the treatment regimen. A study was conducted from April 2022-April 2023 in 13 patients after taking consent. Ethambutol induced Optic Neuropathy (EON) was confirmed by ophthalmologists when there was decreased visual acuity, abnormal color vision identified by Ishihara isochromatic test, and central or paracentral scotoma on the Humphrey perimeter. Data is collected in these patients which includes: age, gender, body weight in kilograms (kg), site of tuberculosis infection, daily per kg body weight dose and duration of ethambutol treatment and visual acuity at the time of presentation. In these patients FDCs are stopped and regimen is framed using other antitubercular drugs excluding ethambutol. These patients were followed up monthly and checked for visual acuity improvement after stopping ethambutol. Loss of visual acuity in relation to duration and per-kg body weight dose of ethambutol was analyzed. The outcome in the form of recovery of vision in these patients is measured as the difference between initial visual acuity at first visit when the patient complained of decreased vision and visual acuity after discontinuation of Ethambutol treatment assessed on monthly follow up. An increase in visual acuity of ≥ 2 Snellen lines after stopping ethambutol is taken as positive outcome.

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Inclusion criteria

All patients with ATT induced Optic Neuropathy

Patients who gave consent.

Exclusion criteria

Patients with blurring of vision due to other causes confirmed by ophthalmologist.

Results

Age: Out of 13 cases included in this study, lowest age 23 years and highest age 71 years**.** The mean age of these patients is 48.15 years. The majority of the patients are in the age group of 41-60.

Gender: Males were 7 [53.84%] and females were 6 [46.15%].

Site of TB

Out of 13 cases, Pulmonary Tuberculosis (TB) patients were 9 [69.23%]. Extra pulmonary TB were 4 [30.76%], out of which, 2 patients had lymph node TB [15.38%], 1 patient had spinal TB [7.69%] and 1 had TB pleural effusion [7.69%].

Duration of Ethambutol usage and development of blurring of vision

Patients who developed blurring of vision in first 2 months of ATT were 3[23%], those who developed within 3-4 months of ATT were 6[46.15%] and within 5-7 months were 4[30.76%].

TABLE 1: ONSET OF OPTIC NEUROPATHY AFTER USING ETHAMBUTOL

SITE OF TUBERCULOSIS	<2 MONTHS	3-4 MONTHS	5-7 MONTHS	TOTAL
Extra pulmonary TB	1	1	2	4
Pulmonary TB	2	5	2	9
TOTAL	3	6	4	13

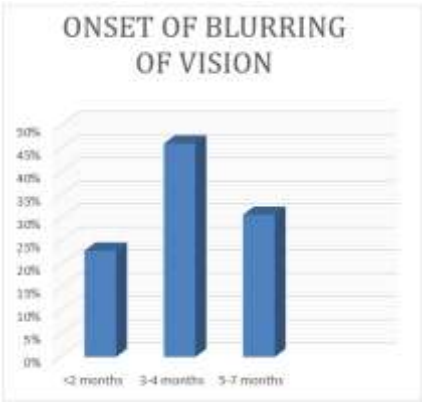

FIGURE 1: DURATION OF ETHAMBUTOL IN RELATION TO ONSET OF BLURRING OF VISION

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Dosage of ethambutol in relation to blurring of vision

Patients falling in the per kg body weight dose range of 15-20mg/kg/day were 1[7.69%] and 20-25mg/kg/day were 12[92.30%]. Mean per kg body weight dosage in these patients was 20.86mg/kg/day.

TABLE 2: DOSAGE USED BY PATIENTS

15-20 mg/kg	1	7.69%
20-25 mg/kg	12	92.30%

All patients had decreased visual acuity. Red-green dyschromatopsia is seen in 2 patients [15.38%].

Follow Up

Among 13 patients 9 patients were followed up for more than 6 months. Of these 9 patients 5 patients [38.46%] showed improvement in visual acuity after stopping ethambutol for 4-5 months. Out of these 5 patients who showed improvement in visual acuity, 3 patients had symptoms in first 2 months of ATT. 2 had symptoms in 3 and 4 months of starting ATT.

Out of 2 patients with Red green blindness, improvement in colour vision is seen after 4 months of stopping ethambutol. In 8 patients blurring of vision is still persistent till date.

Discussion

Gender: In our study most of the patients with ethambutol induced ocular toxicity were of male gender, which is in coordination with Archana Bhargava.*et al.*[2] study.

Age: Most of the patients in this study were in the age group of 41-60 years with a mean age of 48.15. Archana Bhargava.*et al.*[2] study shows mean age of the patients was 50.1 ± 13.5 years.

Type of TB: In our study most of the patients are pulmonary TB patients. V Menon *et al.*[3]. study shows Pulmonary tuberculosis was present in 75% of patients.

Dosage of ethambutol in relation to blurring of vision: The majority of the patients were in the per kg body weight dose range of 20-25 mg/kg body weight. Patients who fall in the lower end of the body weight band of FDCs had higher per kg body weight dose.

Daily dose schedule of FDCs for adults as per the weight bands:

WEIGHT CATEGORY	**No. of FDC tablets per day IP phase HRZE[75/150/400/275mg] CP phase HRE [75/150/275]**	**Cumulative dose of Ethambutol in mg**	**Range of dose in mg/kg/day**
25-34 kg	2	550	22 - 16.17 mg/kg
35-49 kg	3	825	23.57-16.83 mg/kg
50-64 kg	4	1100	22 – 17.18 mg/kg
65-75 kg	5	1375	21.15–18.33mg/kg
>75 kg	6	1650	**22** g/kg

According to Rohit Saxena *et al.*[4]., the reported incidence of ethambutol-related ocular toxicity varies widely in different studies, ranging from 1%–2.5% for dosage of 15 mg/kg per

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day and increasing to 5%–6% for dosage of 25 mg/kg/day and reaches as high as 18% for dosage of 35 mg/kg/day.

Duration of Ethambutol Treatment: The mean duration of Ethambutol usage for development of EOT is 3-4 months i.e these patients are in continuation phase of ATT. According to Chan and Kwok[5] the toxicity typically occurs between 3–5 months of usage, though it may present as early as within 1 month and as late as 12 months of use.

Time to improvement in visual acuity: In our study improvement in visual acuity is seen in all the patients presenting in the intensive phase of treatment and in few patients in continuation phase also, after stopping ethambutol for 4-5 months. Most of the patients with persistent decrease in visual acuity had longer duration of treatment before initial presentation with blurring of vision. Improvement in visual acuity at 5.38 ± 1.71 months after discontinuation of ethambutol is seen in Eun Ji Lee *et al.* study[6].

Conclusion

Ocular toxicity due to ethambutol is more in patients with longer duration of ethambutol usage before presentation and in those with higher per kg body weight dose**.** Reversibility in ocular toxicity is duration dependent and patients with shorter duration of treatment before initial presentation had positive outcome as improvement in visual acuity. All patients on Ethambutol should undergo regular screening by an ophthalmologist to enable early detection of Ethambutol induced Optic Neuropathy [EON], and if it is found medication should be discontinued to prevent visual loss. In patients with persistent visual loss after stopping ethambutol other drugs like isoniazid should be checked.

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