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ORIGINAL ARTICLE

Patients with Ethambutol-Induced Ocular Toxicity Receiving "Directly Observed Treated Short-Course"

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ABSTRACT

Objective: Determine the total number of Category-1 patients with ocular toxicity from Ethambutol after DOTS therapy.

Methodology: This study conducted in department of Ophthalmology of abaseen hospital and Khyber medical center Peshawar over the one year, from May 2021 to April 2022 included Category-1 TB patients (both genders) aged 14 and 65 who had normal ocular parameters on an ophthalmological examination when starting DOTS treatment. The frequency of any vision change, optical symptom, including color vision, contrast sensitivity while receiving Ethambutol medication was examined in 240 eyes (120 patients). At the end of the first month and again at the end of the second month of therapy, Each patient's compliance with Ethambutol was examined, and all tests for ocular toxicity were repeated for each chosen patient. The study did not include patients in category-2 with positive sputum smears who had relapsed, had therapy fail, or was getting treatment after a break in treatment.

Results: Out of 120 patients (240 eyes), 62 (51.6%) of them were male, and 58 (48.4%) of them were female patients. After a month, there was no sign of ocular toxicity. Ocular toxicity, on the other hand, appeared in 3 (2.5%) of the patients after the second month. Moreover, these three patients showed decreased visual acuity, poor color vision, decreased contrast sensitivity, and optic disc abnormalities.

Conclusion: Patients with tuberculosis who use Ethambutol are at risk of developing ocular toxicity. As a result, it is essential to identify visual symptoms and signs as soon as possible to avoid unnecessary diagnostic delays and maybe irreversible vision loss.

Keywords: Tuberculosis, Color Vision, Contrast Sensitivity, Optic Disc, Ethambutol-induced ocular toxicity, visual acuity, treatment strategies

INTRODUCTION

One of the major concerns with public health is tuberculosis (TB), which Mycobacterium TB seems to be responsible for spreading. The respiratory system is especially sensitive. However, it may also infect other organs, including the spine, kidneys, brain, and optical system. The establishment of the sanatorium cure was the first treatment for tuberculosis. Robert Koch succeeded in isolating the tubercle bacillus on March 24, 1882 [1]. The World Health Organization (WHO) recognized tuberculosis as a worldwide emergency in 1993. According to the most current figures, over 1.22 million people died from this disease in 2019, and nearly 10 million people were diagnosed with TB [2]. Pakistan is rated fifth among the 22 nations with the highest TB burden worldwide. In Pakistan, an estimated 565,800 people were diagnosed with TB in 2018, according to a WHO assessment [3]. In Pakistan, TB is responsible for the deaths of over 45,300 people annually [4]. The Directly Observed Treatment Short-Course (DOTS) program was established when the World Health Organization declared tuberculosis (TB) a global emergency. As a result, patients with Category-I TB are first treated for two months with a combination of four medications, including Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide Due to the great frequency of this disease, anti-tuberculosis medicines, which are among the most often used drugs, may have significant adverse effects on patients (Table 1).

The primary anti-TB drug is Ethambutol. It is a anti-bacterial medication that Carr and Henkind introduced in 1962 [5,6]. Ethambutol, on the other hand, has significant ocular adverse effects. Subsequently, patients receiving the anti-tuberculosis drug "Ethambutol" must be closely monitored. Medication withdrawal is the only effective treatment that may prevent further vision decline and even allow for recovery. Early diagnosis of these negative consequences is essential. This is the reason for the study that investigated how often Ethambutol-induced ocular damage occurred in TB patients after receiving DOTS Category-1 therapy.

Table 1: Anti-TB Medicine Side Effects

Medications	Adverse effect	Ocular side effect
Isoniazid	• Peripheral Neuropathic Disease • Hepatitis • Skin Rash	• Optic neuritis • Stevan Johnson Syndrome • Orange-red
Rifampicin	• Hepatitis • Nausea • Vomiting • TTP • A reddish color to sputum	• Tears' discoloration
Pyrazinamide	• Hepatitis • Hyper – uricemia	Nil
Ethambutol	• Hyper – uricemia	• Color vision • Abnormalities • Visual Field Defects
Streptomycin	• Oto-toxic • Renal Failure	Nil

METHODOLOGY

this study was conducted at the department of Ophthalmology of abaseen hospital and Khyber medical center Peshawar over the one year, from May 2021 to April 2022 on Category-1 patients referred by the DOTS centre. The research was conducted over a 12-month period, The sample size of 240 eyeballs was determined using the WHO sample size calculator and a non-probability sequential technique.

Inclusion criteria: The study involved Category-1 TB patients aged 14 to 65 (both genders) with normal ocular statistics on ophthalmological examination when starting DOTS treatment. Visual acuity, color vision, contrast sensitivity, fundus, and optic disc were the criteria.

Exclusion criteria: Patients with a history of color vision or contrast sensitivity problems, glaucoma, cataract (more than +2 nuclear cases of sclerosis); diabetic retinal disease;

hypertensive retinal disease; sickle cell disease; retinitis pigmentosa, retinal detachment; or patients taking medications known to cause optic neuropathy.

e.g., Oral contraceptive tablets, indomethacin, and digoxin, people who were addicted to alcohol or tobacco were among those who were not considered.

The Institutional Ethical Research Committee of Abseen hospital and Khyber medical center Peshawar permits before the study's starts. Patients that met the inclusion criteria had a thorough medical history and ophthalmological examination after giving informed written consent. The best-corrected contrast sensitivity (CS), colour vision (CV), and visual acuity (VA) of the patients were evaluated. The fundus was inspected after dilation of the eyes. A month and two months later, a follow-up was conducted.

VA was determined at baseline using the Snellen chart before to beginning therapy with ethambutol. On each visit, CV was evaluated using in the same space as Ishihara Chart with the same lighting conditions and mono-ocular viewing conditions. CS was assessed using a 1-meter and binocular Pelli Robson Contrast Sensitivity Chart. One percent tropicamide was used to dilate the pupils. One researcher used an indirect ophthalmoscope to examine the fundus, while the second double-checked his findings. After one month, two months, and three months of medication, each patient was checked to see how well they were adhering to the Ethambutol prescription. After that, for each selected patient, all ophthalmological assessments for ocular toxicity were conducted once again.

RESULTS

According to Table 2, out of 120 patients (240 eyes), 62 (51.6%) were male, and 58 (48.4%) were female, creating a male-to-female ratio of 1:1.23.

Table II: Gender Diversity

Gender	Frequency	%age
Male	62	51.6
Female	58	48.4

After a two-month evaluation, the same three patients had abnormalities in their optic discs, and six eyes (2.5%) had lost visual acuity from the baseline. Together with the shift in the CS, abnormalities in CV were also seen in these six eyes. Table III through Table V provide the findings for the ocular abnormalities.

Table 3: Frequency of Patients with Changes

Characteristics	No Defect	Defected
Visual Acuity Best Corrected	117	3
Color Vision	117	3
Contrast Sensitivity	117	3
Optic Disc	117	3

Table 4: Defects in many factors

Characteristics	NO Defect	Defected
Gender		
Male	62	2
Female	58	1
AGE		
14-29	58	1
30-45	28	0
46-65	34	2
Residence		
Rural	32	1
Urban	88	2
Monthly Income		
<25K	84	2
25-50K	30	1
>50K	6	0

Despite the low frequency of ethambutol-induced ocular toxicity, the study indicates it is possible. As a result, it is important to frequently track ethambutol patients for visual symptoms and indications.

Table 5: Variables vs. Defects Chi-Square

Variables	P. Chi-Square	Likelihood Ratio	Valid Cases	Phi Val/ App Sig
Gender				
Val	.007	.007		
Defected	2	1	120	.008/.934
Asy Sig	.934	.934		
AGE				
Val	1.034	1.344		
Defected	3	3	120	.092/.596
Asy Sig	.596	.511		
Residence				
Val	.756	.645		
Defected	1	2	120	.079/.384
Asy Sig	.384	.422		
Monthly Income				
Val	14.045	4.935		
Defected	3	3	120	.341/.001
Asy Sig	.001	.085		

DISCUSSION

After WHO declared tuberculosis a worldwide emergency, the DOTS strategy for treatment was established. There are two types of tuberculosis patients. New patients with pulmonary tuberculosis who test positive on smear are classified as category-1. people with a positive sputum smear who have relapsed, discontinued treatments, or are presently receiving therapy following a treatment pause falls into category-2. Only Category-1 patients are included in our study.As a result, Patients with Category-1 TB are given a combination of four drugs for the first two months of treatment: Pyrazinamide, Rifampicin, Isoniazid, and Ethambutol. Since the 1960s, ethambutol in particular has been used to treat TB. Visual toxicity is a side effect of Ethambutol found soon after the medicine was initially released [7].

The use of Ethambutol may cause two different forms of optic neuritis.

i. Irregularities in color vision as a consequence of axial neuritis, central vision loss, and scotoma.

ii. Deficits in the peripheral visual field are carried on by paraxial neuritis [8].

Paraxial neuritis, while less frequent than axial neuritis, may occasionally occur. Ethambutol-induced optic neuritis occur between 0.5% and 35% of the time, based on various publicly available research[3]. In the survey conducted by Garg et al., 126 eyes were examined, and it was discovered that 9.4% of the eyes had lost VA, 12.6% had acquired color vision problems, and 4.7% had developed abnormalities in the optic disc [9]. In a different study, According to Raghu et al., 10% of the eyes had VA loss, 12.2% had colour vision problems, and 6.1% had fundus abnormalities [10]. Furthermore, Mahrukh et al. observed that 10.6% of the 198 eyes they tested for their research had lower VA, and that 23.23% of the eyes had problems with color vision [11]. When the optic chiasm is affected, bitemporal hemianopia may also develop, resulting in ocular neuropathy by ethambutol. The literature contains description of automated perimetry studies indicating how ethambutol and bitemporal hemianopia develop [12, 13].

The dose and length of administration often influence Ethambutol's toxicity. After one to two months of medication, on average, seven months pass before the eye toxicity presents itself. Even so, the literature has cases of toxicity even only a few days after. Sajjad et al., in their paper, suggested that one such instance may have been caused by an idiosyncratic response just three days earlier [14]. A patient with bilateral ocular neuropathy was described by Melamud three months after starting ethambutol [15]. Moreover, there is evidence that indicates incidences as recently as one year ago [16]. These result suggests that ethambutol toxicity may persist even after the drug has been administered.

It is also unknown what the optimal dosage would be. The DOT system estimates that the incidence of optic neuropathy produced by ethambutol use is about 1% overall and dose-dependent [17]. Patients who treated ethambutol at doses as low as 12.3 mg/mg/day nevertheless suffered toxicity, according to one of the study reports [18].

However, When taking ethambutol for at least two months at a high dosage of around 15-25 mg/kg/day, ocular toxicity increased up to 5%-6% [19]. Moreover, half of the patients experienced optic neuropathy at 60 to 100 mg/Kg/day [20]. Because toxicity might occur at dosages even lower than 15 mg/Kg/day, In clinical use, there is no safe dose of ethambutol [21].

The first step in the corrective treatment is to stop taking Ethambutol immediately. Referral to an ophthalmologist is the second option. Vitamins and trace elements might be helpful for the healing process. Nevertheless, besides halting the drug's usage, there is no particular therapy for Ethambutol's eye effects. The early discontinuation of Ethambutol may prevent the loss of eyesight development and even permit vision recovery. Most patients do begin to improve after discontinuing the medication [22]. The recovery phase might need weeks or months [23]. Even after removing the ethambutol treatment, some patients' vision impairment maintained or increased.

However, advanced age, renal problems (since ethambutol is excreted via the kidneys), alcohol and tobacco usage, hypertension, and diabetes mellitus hinder vision recovery after ethambutol withdrawal.

CONCLUSION

This study's data led researchers to conclude that Ethambutol produces ocular toxicity even at 15 mg/Kg/day dosages. Nevertheless, the results show no significant correlation between age, residency (a socioeconomic status often associated with nutritional consumption), and gender.

Optical disc, contrast sensitivity, color vision, and visual acuity. Thus, every patient should have an eye checkup before starting Ethambutol. The medication should be given to patients with excellent eyesight who can describe their symptoms. After issuing the prescription for Ethambutol, the patient should be informed about the medication's adverse effects and given instructions to contact their doctor immediately if any visual symptoms manifest. Patients with diseases including diabetes, chronic renal disease, other ocular abnormalities, alcohol use, or elderly patients should have exams more frequently since they are more vulnerable to developing toxicity.

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