

To Study Optic Neuropathy in Multi Drug Resistant Tuberculosis Patients on Linezolid Based Regimen

Authors:

Dr. Saloni S Choksi¹, Dr. Khushnood M Sheikh², Dr. Manisha N Patel³

¹Senior Resident at SMIMER Hospital Surat.

²Professor, Department of Ophthalmology.

³Professor and Head, Department of Ophthalmology Surat.

Corresponding Author:

Dr. Saloni S Choksi

<https://doi.org/10.5281/zenodo.18426552>

Received: 24-December-2025, Revised: 14-January-2026, Accepted: 28-January-2026, Online First: 30-January-2026

ABSTRACT:

Background: Multidrug-resistant tuberculosis (MDR-TB) remains a major global health challenge, necessitating prolonged treatment with second-line anti-tubercular drugs such as linezolid. Although linezolid has demonstrated significant efficacy against MDR-TB, its long-term use is associated with adverse effects, particularly optic neuropathy, which can lead to irreversible visual impairment if not detected early. **Aim and Objectives:** To study the magnitude of linezolid-induced optic neuropathy in MDR-TB patients and to assess the clinical ophthalmological profile of these patients. **Materials and Methods:** A cross-sectional observational study was conducted over a period of 18 months at a tertiary care center. Forty MDR-TB patients receiving linezolid-based regimens for more than three months were included. Comprehensive ophthalmological evaluation was performed, including assessment of visual acuity, colour vision, contrast sensitivity, pupillary reactions, fundus examination, and visual field screening. Data were analyzed using SPSS version 24.0, and associations were evaluated using the chi-square test, with $p < 0.05$ considered statistically significant. **Results:** Among the 40 patients studied, a high proportion demonstrated features suggestive of linezolid-induced optic neuropathy. Decreased visual acuity ($<6/60$) was observed in more than 50% of patients. Fundus abnormalities were noted in 28 patients, including hyperemic disc (13 cases), disc pallor (11 cases), and disc edema (4 cases). A statistically significant association was found between duration of linezolid therapy and fundus changes ($p = 0.0001$). Reduced contrast sensitivity was observed in 16 patients and showed a significant association with duration of therapy ($p = 0.004$). Colour vision defects were identified in 9 patients and were more common with prolonged linezolid use. Relative afferent pupillary defect was present in 8 patients, though this association was not statistically significant. **Conclusion:** Linezolid-induced optic neuropathy is a significant and duration-dependent adverse effect in patients undergoing long-term treatment for MDR-TB. Regular ophthalmological screening, including visual acuity, colour vision, contrast sensitivity, and fundus examination, is essential for early detection and prevention of irreversible visual loss.

Keywords: Multi Drug Resistant Tuberculosis; Linezolid; Optic Neuropathy; Visual Impairment; Colour Vision Defect

INTRODUCTION:

Tuberculosis also known as Phthisis Pulmonalis is a contagious infection caused by bacteria *Mycobacterium*. Tuberculosis is a significant contributor to global morbidity and mortality. It is estimated that 10 million developed active TB, resulting in 1.5 million deaths, making it the second leading cause of death from infectious diseases after COVID -19(1). Anti TB medications have been used for decades and thus strains that are resistant to one or

more medications have been documented in every country surveyed Known as drug resistance.

Multi Drug Resistant Tuberculosis (MDR-TB) is defined as Tuberculosis resistant to both isoniazid and rifampicin is an ongoing threat and accounts for expanding proportion of incident global TB cases (2). The global incidence of MDR- TB is 3.4% in new cases and 18 % in previous treated cases (1) Treatment of these infections requires the use of second line drug. Currently, one of the core second line anti TB drugs

used for the treatment of MDR TB is linezolid (4). Linezolid is a Food and Drug Administration in 2000(3) approved repurposed oxazolidinone bacteriostatic antibiotic active against gram positive *Mycobacterium tuberculosis*. However its side effects limits its long term usage. Linezolid induced optic neuropathy is characterized by bilateral painless progressive visual loss and color vision impairment. Data on the frequency of linezolid - associated optic neuropathy are still relatively limited and rather inconclusive. (3). Although Linezolid has shown promised efficacy its long term use has been associated with optic neuropathy (4), which is of paramount value in highlighting the need to evaluate the patients of MDR TB patients for visual assessment and arrange close follow up sessions who require prolonged therapy. However, as the Global cohorts for DR-Tb are limited it is a need of time to add more to the literature- a significant amount of data to the evidence base. So the main Aim and Objective of the study is to determine the magnitude of linezolid induced optic neuropathy and to assess the clinical profile of MDRTb patients.

MATERIALS AND METHODS:

The present study was cross sectional observational study carried out at a tertiary care centre in a time period of 18 months with due permission from the institutional ethical committee.

Sample Size:

All the patients falling under inclusion criteria, attending the Eye OPD, who gave consent for the study were considered as sample size. The inclusion and exclusion criteria are as follows:

Inclusion criteria:

Only Multi Drug Resistant Tuberculosis patients on linezolid therapy for more than 3 months who gave consent to participate in the study will be considered

Exclusion criteria:

Patient less than 20 years, with any other systemic disease or any Pre-existing Optic Nerve Disease like Optic atrophy, glaucomatous excavation, and chronic papilloedema. Also patients having pre-existing Optic neuropathy due to other causes including ethambutol toxicity were excluded from study.

Study Method:

Standard Protocols were followed to prevent the spread of disease before the procurement of case .All MDR TB patients falling under inclusion criteria attending the eye OPD underwent comprehensive ophthalmological examination that included their detailed demographic

history, Including personal history, Socioeconomic Status, Duration of illness, Duration of therapy , socioeconomic class using BG Prasad scale were classified(17), Visual Acuity for both distant and near vision using Snellens Chart assisted by pinhole and subjective testing to rule out Refractive error. Intra ocular pressure was measured by Non – contact tonometer, Slit lamp bio microscopy ,Pupillary reaction testing for RAPD (Relative Afferent Pupillary Defect) ,Colour Vision (Red – Green deficiency),Contrast Sensitivity tested by Berkeley's Contrast sensitivity testing done by Online free chart. Posterior segment dilated fundoscopic examination to note Optic disc changes. In addition to this. Automated Perimeter and Confrontation test was done for screening of visual field defects.

- To diagnose Optic Neuropathy following criteria taken into consideration as per Standard Guidelines [1][4]
 - A. Visual Acuity- Decreased for distant vision
 - B. Decreased Contrast Sensitivity (Using Online based application)
 - C. Relative Afferent Pupillary Defect (RAPD) in early phase
 - D. Red Green Colour Deficiency
 - E. Fundus Changes – Early – Hyperemic disc, elevated disc
 1. Peripapillary nerve Fibre defects.
 2. Late changes Temporal Disc Pallor, Disc oedema.

Treatment was given to the patients who had positive findings.

STATISTICAL METHODS:

The collected data were analysed with SPSS Statistical system software 24.0 Version and Open Epi. Qualitative analysis for frequency and percentage for RAPD, Colour vision, Contrast sensitivity, Fundus findings were done using chi – square method. In the above statistical tools, the probability value <0.05 is considered as significant level.

OBSERVATION AND DISCUSSION:

It is always a challenging to manage the case of MDR TB due to the drug resistance, its side effects and treatment of spreading disease with the longer duration of therapy. Hence it requires awareness of side effects, monitoring and close follow up to prevent the visual loss.

Among the study participants majority 18 patients belonged to 21-30 years of age group [Figure 1]. According to this data Multi drug Resistant Tuberculosis is a considerable burden among Young adult population. Among 40 patients in the study,14

(35%) patients were on linezolid based regimen therapy for 8-9 months & 7 MDR Tb patients (17.5%) were on linezolid based therapy for more than 9months. Major percentage 93% patients who have been taking linezolid based regimen therapy for MDR-TB for more than 3 months duration, showed Linezolid induced toxic optic neuropathy which explains that it is duration dependent. As an unexpected finding in our study Visual impairment of <6/60 was observed in more than 50% of the study population which is comparable to Sean Wasserman et al (3)., total 148 patients were given linezolid 600mg daily dose. 16 participants out of 148 developed reduction of visual acuity with a cumulative incidence of 12%. Thus early detection can help minimize visual loss. In depth Analysis of this study showed that contrast sensitivity was decreased in 16 patients shows positive association of contrast sensitivity with linezolid treatment p value being 0.004. though it is a one of the diagnostic signs

of Optic neuritis not observed by available literature hence require more indepth studies. Out of 40 patients, more than half of the MDRTB patients consuming linezolid had best corrected vision of <6/60(as minimum requirement for Automated perimetry vision is >6/60(35). and most of the patients belonged to lower and lower middle socioeconomic sections of the society and illiterate hence were not compliant for Automated perimetry. For those who undergone Automated perimetry their results were not reliable even on repeated tests So it is not included in data analysis. Though on Confrontation test they do show some signs of visual field restriction and few patients were complaining of positive scotoma too. However, in Salil et (4) al study the patients having linezolid induced optic neuropathy, Automated perimetry showed generalised reduction of sensitivity bilaterally in three patients.

Figure: 1. Age group wise distribution among study participants

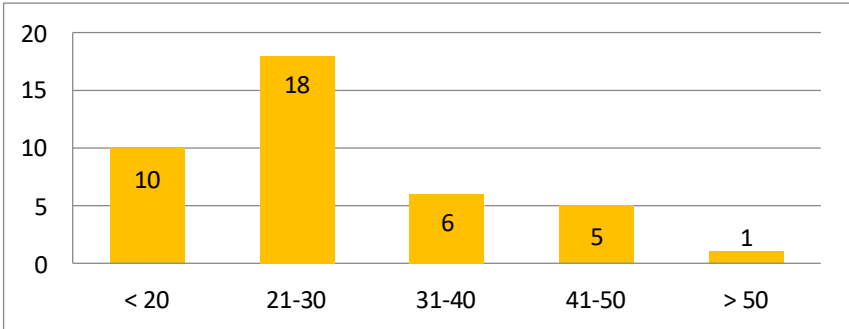


Figure: 2. Bar chart of duration of treatment

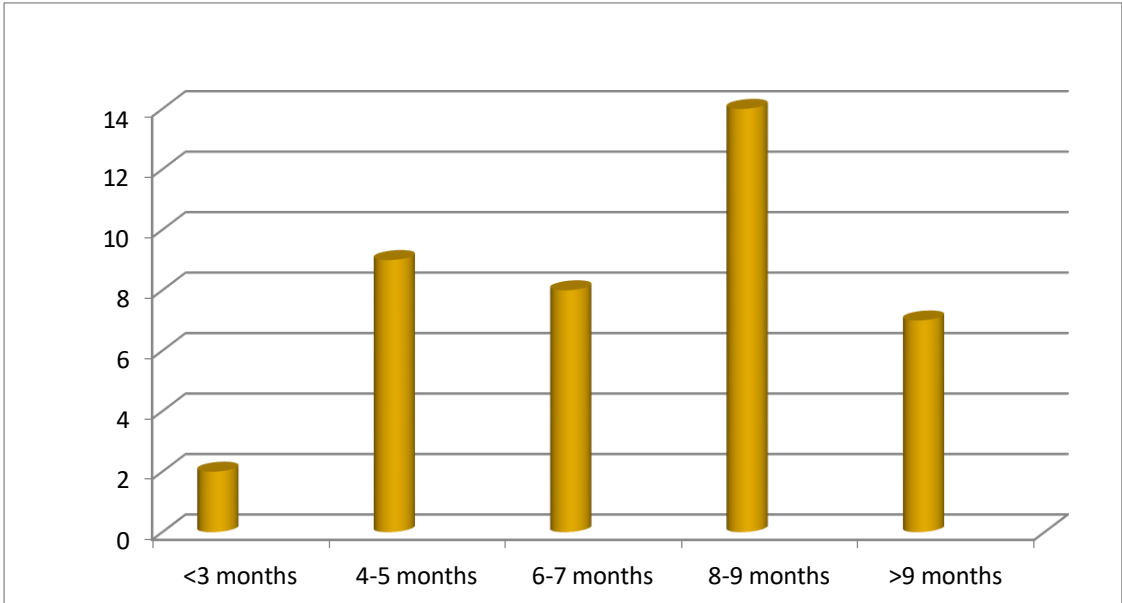


Figure: 3. Association between Contrast Sensitivity and Duration of treatment

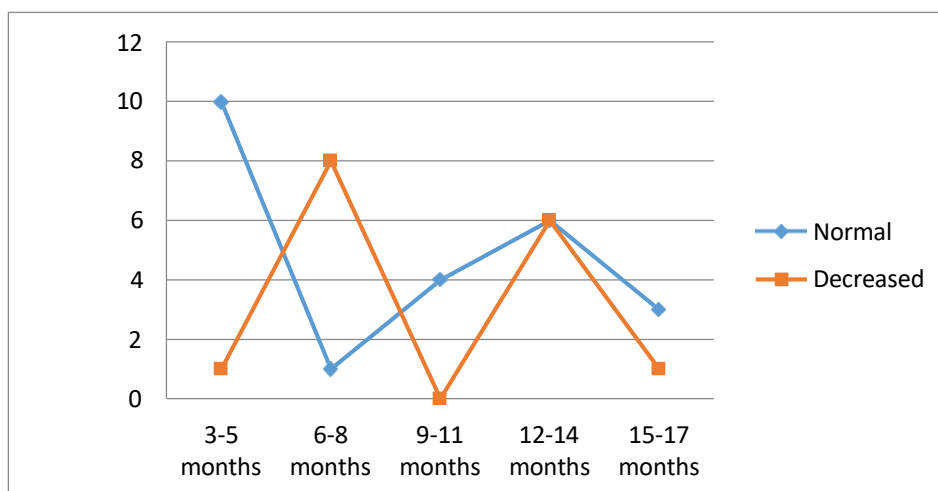


Figure 4: Bar chart of effect of Duration of treatment on Color vision

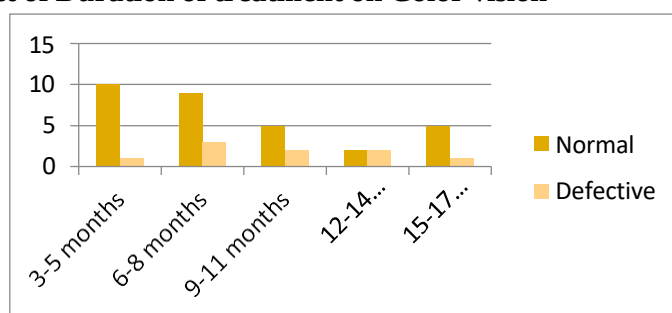


Table 1 Features of Disc at the time of Presentation

Fundus Examination Findings	Duration of treatment		9-11 months	12-14 months	15-17 months	Total patients	p-value
	3-5 months	6-8 months					
Hyperemic disc	2	5	4	2	0	13	0.0001
Disc pallor	3	4	2	1	1	11	
Disc edema	0		0	2	0	04	
Normal	6	4	1	1	0	12	

Further more in the study, 40 Patients consuming linezolid for more than 3 months 28 patients had signs of optic neuritis and fundus changes like, disc edema, hyperemia of disc and disc pallor. With Hyperemia of disc in total 13 patients, Disc Edema in 4 patients and Disc pallor in 11 MDRTb patients. Disc edema, Hyperemic disc and disc pallor are more commonly elicited in patients who were on treatment for more than 3-5 months. Thus there is a significant association

between Duration of linezolid consumption and positive fundus findings which is statistically significant. p value being 0.0001. As per our observation, among 40 patients, RAPD was present in only 8 patients. p value is 0.317 which is not significant. Salil et al (4) in 2016 did systematic review and meta-analysis Study of total 367 MDRTB patients on linezolid based regimen, 23 patients had optic neuritis. This shows strong association of linezolid therapy and disc changes.

Further ahead in the study, Colour vision was found to be defective in 9 patients out of total 40. Figure 5 shows that there is a significant association between Duration of the treatment and Colour vision. Colour Vision impairment is seen in patients who have consumed Linezolid for longer period of time. This shows Association of colour Vision with Duration of Treatment which is statistically Significant p value being 0.06. In Karuppannasamy et al study (8). medical history and ophthalmic examinations of a 45year old male revealed defective colour vision along with diminution of vision. This shows positive association between Linezolid therapy and defective colour vision. In J.lee et al (28) study on Linezolid associated Optic Neuropathy in patient with Drug resistant tuberculosis in 41year old woman referred for visual assessment had normal pupillary reaction but colour vision was reduced bilaterally. Lastly, it was observed that Based on Online screening app Contrast Sensitivity was decreased in 16 patients whereas contrast sensitivity was normal in 24 patients. This shows positive association of contrasts sensitivity with linezolid treatment p value being 0.004.

CONCLUSION:

With increase in incidence of multi drug resistant tuberculosis since past few years and forced use of a repurposed second line antitubercular drug Linezolid, The treatment duration of linezolid has led to an increase in number of patients with adverse effects such as optic neuropathy.

Therefore it is of paramount value to create a multidisciplinary approach follow up for patients on long term regimens and particularly in those with visual alterations. Thus extensive ophthalmological examinations including visual assessment, Colour vision testing, contrast sensitivity testing, visual field analysis and fundus examination should be done for early detection and timely withdrawal of the drug for the prevention of blindness

LIMITATIONS:

The use of linezolid has quickly accelerated in recent years and will continue to do. However the clinical data in proportion remain limited. Thus more data would contribute significant amount to evidence database.

Conflict of Interest: None

Funding: None

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