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Original Research Paper

Linezolid associated peripheral neuropathy in patients with MDR/XDR tuberculosis

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ABSTRACT:
Background and Objectives: Linezolid is one of the effective anti TB drugs used for the treatment of multi drug resistant/extensively drug resistant tuberculosis (MDR/XDR TB). Peripheral neuropathy is common adverse drug reaction seen with prolonged use of Linezolid. We aimed to study peripheral neuropathy in patients on Linezolid based regime for MDR/XDR TB. **Methods**: We observed all MDR/XDR TB patients over a period of 2 years on Linezolid based regime in our institute in Respiratory Medicine Department. On treatment patients who had signs and symptoms of peripheral neuropathy were enrolled, evaluated and followed. **Results**: Out of all patients observed, approximately 15 % developed peripheral neuropathy more commonly involving lower limbs. Maximum patients were young and without any co morbidity. In majority of patients, we had to stop Linezolid. In spite of adequate timely measures, significant number of patients had only partial improvement after 6 months. **Conclusion**: Significant number of patients developed peripheral neuropathy in our study. Early detection and immediate measures need to be taken to avoid serious permanent neurological consequences. We want to emphasize that a simple screening tool for detection of neuropathy needs to be adopted and incorporated in NTEP itself.

Keywords: Linezolid, MDR-TB, XDR-TB, Peripheral neuropathy

INTRODUCTION:

India has one of the highest TB burdens[1,3]. Disease management has been a challenge especially in MDR/XDR-TB, as treatment options are limited. Although MDR TB is curable, only 54% of patients recover entirely[1,14]. Clinical treatment requires at least 18 months of second-line drug regimes.

Linezolid is one of the effective second-line anti TB drug used for the treatment of multidrug-resistant/extensively drug-resistant tuberculosis[1]. The efficacy and favourable treatment outcomes of Linezolid have been well documented in the treatment of DR-TB in numerous studies[1,4,6]. However, adverse events have also been reported in patients with prolonged use of the drug, peripheral neuropathy being the most frequent [4-7].

A meta-analysis reported development of neuropathy in 30% of patients during MDR-TB treatment[4]. Peripheral neuropathy is one of the key causes of early discontinuation of Linezolid in a regimen. Traditional diagnostic methods for peripheral neuropathy include Nerve Conduction Studies (NCS) and Electromyography (EMG) [4,6]. These are expensive, and have to be performed by specialized personnel. Referrals are usually necessary, as the equipment is not readily available in all clinical settings. It would be beneficial if an easy-to-use screening tool could be adopted to monitor drug toxicity to allow early interventions in optimizing treatment outcome and completion.

MATERIALS AND METHODS:

Patients of Drug Resistant Tuberculosis on Linezolid based regimen in the Respiratory Medicine Department were followed up prospectively in outpatient department for side effects related to treatment for a period of 2 years (2021- 2023).

We prospectively studied these patients from September 1, 2021 to August 31, 2023 who were on a Linezolid-based regimen. An anti-TB regimen was tailored for each patient based on their results of drug-susceptibility testing and after review and approval by the MDR-TB care team in the hospital for compliance with guidelines and recommendations of the WHO and DR-TB committee. Management of peripheral neuropathy was based on recommendations from Neurologist and DR-TB committee physicians. Demographic, clinical, and laboratory data were obtained from medical records for all eligible patients.

Linezolid was a common agent in regimen compositions of all participants in this study. Dosage was set at 600 mg, administered once daily. To screen for the presence of peripheral neuropathy during treatment, NCS was adopted. Patients were assessed by attending physician for peripheral neuropathy on a monthly basis. Referral to a neurologist was arranged when deemed necessary

All patients with neuropathic complaints (tingling and numbness etc.) in limbs on Linezolid based regimen were included in the study after written informed consent. All patients with pre-treatment neuropathy, on high dose Isoniazid/Moxifloxacin and with HIV were excluded.

Statistical Analysis was done with SPSS and chi square test.

RESULTS:

Total MDR/XDR TB patients treated with Linezolid based regimen were 123. 18 (15%) patients developed peripheral neuropathy which is statistically significant. No gender disparity observed in our study (Figure 1)

Table I: NERVE CONDUCTION STUDY TEST ANALYSIS	
Sensory involvement	3
Motor involvement	2
Both sensory and motor involvement	13
Axonal neuropathy	3
Demyelinating neuropathy	6
Both axonal and demyelinating neuropathy	9

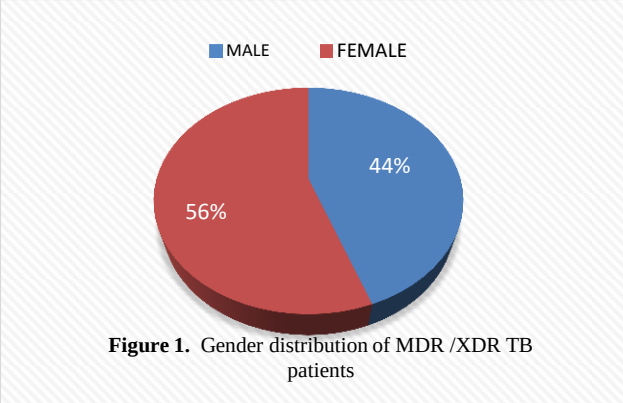

Figure 1. Gender distribution of MDR /XDR TB patients

Peripheral neuropathy was mainly seen in working age group 15–50 years (Figure 2).

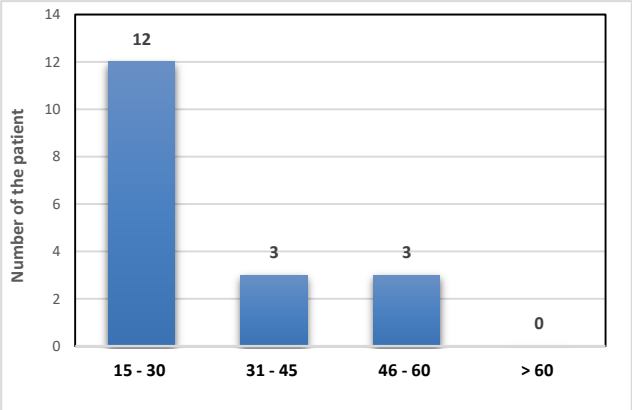

Figure 2. Age groups of MDR /XDR TB patients on linezolid based regimen

Among 123 patients, 14 patients were with diabetes mellitus. Only 1 patient out of 14 had a Linezolid induced peripheral neuropathy, had a controlled DM, showed partial improvement after 6 months of discontinuation of Linezolid. Majority of patients with Linezolid induced peripheral neuropathy were without any co-morbidity.

Almost 72% had both sensory and motor neuropathy, isolated sensory and motor neuropathy seen in 16% and 12% respectively in NCS. 50% had both axonal and demyelinating neuropathy whereas 16% and 34% had only axonal and only demyelinating neuropathy respectively. All patients had lower limb involvement with only 11% having additional upper limb involvement.

Among patients with peripheral neuropathy, 03 patients reported symptoms of peripheral neuropathy within 2 months, 14 patients within 2–6 months, and 01 patient after 6 months of treatment with Linezolid based regimen (Figure 3).

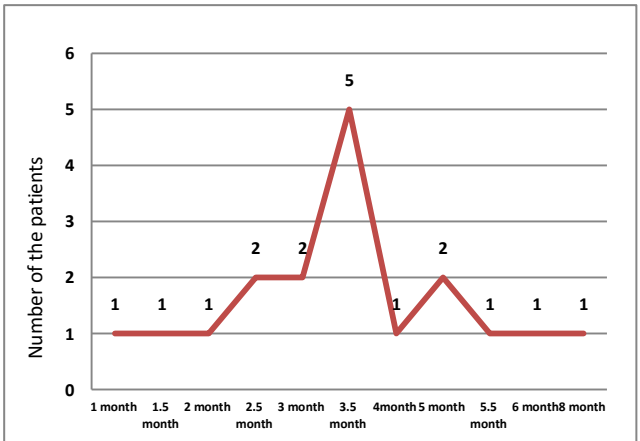

Figure 3. Duration of development of symptoms

As per NTEP guidelines, we initially decreased the dose of the Linezolid but could manage only 2 patients without clinical deterioration. In rest 16 patients, we

had to stop Linezolid. We observed these 18 patients for 6 months after diagnosis of peripheral neuropathy and taking appropriate action. We found that more than 80% improvement in 03 patients, 51-80% in 07 patients, 31- 50% in 07 patients and less than 30% in 01 patient. Only one patient had a significant residual peripheral neuropathy at the end of 6 months. The median duration from Linezolid withdrawal to partial recovery from peripheral neuropathy was approx. 4–6 months.

DISSCUSSION:

Linezolid, an oxazolidinone antibiotic, is used in the treatment of extensively drug-resistant tuberculosis (XDR-TB). There are many adverse effects attributable to Linezolid use such as myelosuppression, peripheral neuropathy, optic neuritis and gastrointestinal reactions like nausea, vomiting and diarrhea [14]. Peripheral neuropathy is a common toxic effect reported with long-term use of Linezolid. In the existing literature, prescribed daily Linezolid doses range from 300 mg to 1200 mg. All dosages have been proven to be effective and suit patient's specific conditions with precise monitoring. Nonetheless, adverse events have been reported, and they seem to be linearly correlated with dosage. Daily administration of 1,200 mg has been reported to be associated with the presence of peripheral neuropathy in >80% of patients[5]. A lower dose of 300 mg/day is believed to induce less toxicity; however, acquired drug resistance would become another concern with prolonged use. To balance regimen efficacy and safety, a daily dose of 600 mg for 12–18 months is recommended for MDR/XDR-TB [12].

Diagnosis of peripheral neuropathy requires professional expert, diagnostic device and knowledge, which may result in delayed diagnosis. Introduction of a screening tool to identify neuropathy at an early stage to allow effective intervention is must. The incorporation of a systematic assessment tool can assist with early identification of drug toxicity and provide data to assist physicians with close therapeutic monitoring
and treatment management to optimize therapy efficacy and balance the drug's side-effect profile.

In our study, 15% patients on Linezolid based regimen for MDR/XDR-TB developed peripheral neuropathy. It is less compared to other recent studies. 64% of patients discontinued Linezolid permanently due to peripheral neuropathy[14], 30% in one meta-analysis[4] and in one more study it was 32%[25,12]. In our study, peripheral neuropathy was confirmed after median duration of 2 to 4 months after treatment start. Similar results found in a study in China[6].

Peripheral neuropathy is also a common complication of diabetes, but maximum MDR-TB with diabetes mellitus patients in our study did not develop peripheral neuropathy. It seems that Linezolid does not increase the incidence of neuropathy in diabetes patients. Until now, no published studies have described higher incidence of neuropathy or neuropathy deterioration being associated with long-term use of Linezolid in MDR-TB patients with diabetes[25]. As it is difficult to identify whether neuropathy is induced by diabetes itself or by drugs, we suggest closer monitoring of the onset of neuropathy and precise glycemic control in MDR-TB patients with diabetes.

Although peripheral neuropathy is one of the major factors leading to the temporary or permanent withdrawal of Linezolid from treatment regimen of MDR-TB patients, numerous studies have described the relief of neuropathic symptoms after Linezolid has been discontinued[19].Various studies report irreversible peripheral neuropathy[4,11,12,25]. In our study, more than 70% patients had significant partial reversibility in 6 months after withdrawal of Linezolid from treatment regime. Only one patient had significant residual neuropathy.

We also observed that, early detection of peripheral neuropathy has better outcome. This result should encourage close monitoring for neurological symptoms with detail and regular clinical CNS examination. A majority of patients with neuropathy in our study also reported significant relief of symptoms after cessation of Linezolid from treatment regimen. Consistently with other studies, the median time for elimination of peripheral neuropathic symptoms in our study was about 6 months[12].

There are limitations to our study. It was monocentric with a limited number of participants. The number of patients evaluated was small. Follow up Nerve conduction studies could not be undertaken as patients are not affording or still on treatment with modified regimen for multi drug resistant tuberculosis.

To emphasize, a simple and reliable screening tool for peripheral neuropathy needs to be incorporated. Further studies are needed to explore the possible genetic factors associated with Linezolid tolerability and predict the rapid onset of severe adverse effects.

CONCLUSION:

Prolonged use of Linezolid is significantly associated with peripheral neuropathy in MDR/XDR TB patients. Patients may have to live with residual neurological deficits. We want to emphasize on need for close monitoring of these patients for signs and symptoms of peripheral neuropathy, so that we can pick it early to minimize permanent neurological consequences. In our study we observed early detection and early intervention has better outcome. We would like to suggest incorporation of a simple screening tool in a pretreatment evaluation of MDR/XDR TB patients under NTEP.

Further multicentric studies are needed to check risk factors leading to this toxicity and to evaluate the best

treatment duration with Linezolid to decrease the rate of neurological ADR without affecting DR-TB outcome.

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CONFLICT OF INTEREST: There are no conflicts of interest.

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