Original Article

ERA'S JOURNAL OF MEDICAL RESEARCH VOL.8 NO.1

DOI:10.24041/ejmr2021.8

PREVALENCE OF OTOTOXICITY IN MDR-TB PATIENTS ON CATEGORY-4 REGIMEN AND THEIR CLINICAL PROFILING

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Received on : 10-06-2021
Accepted on : 22-06-2021

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ABSTRACT

Resistant to Isoniazid (INH) and Rifampicin, Multidrug-Resistant Tuberculosis (MDR-TB) estimated 480,000 new cases across the world in 2013 per the World Health Organization (WHO) Global Tuberculosis Report. These patients have to undergo long duration of treatment and are vulnerable to various adverse drug reactions that might bring about change of treatment regimen and discontinuation of the susceptible drug, the use of amino glycosides that is second line injectables are considered to be the major cause of the associated hearing impairment. Given the poor performance of standard MDR-TB therapy along with its limited evidence base, the management of drug-resistant TB is much more difficult than drug-susceptible TB, especially in high-burden countries. To make an effective prognosis global initiatives are required for the rapid determination of Comprehensive drug susceptibility testing, drug resistance and to expand the use of emerging and novel technologies. For diagnosing Ototoxicity in MDR-TB patients, high index of suspicion is essential; in case of high probability of Ototoxicity every effort should be made to confirm the diagnosis. Thus to obtain the prerogatives for a favorable outcome the current article aims to study and determine the prevalence of hearing loss that is Ototoxicity among patients receiving Second line injectables as a treatment for MDR-TB. The article further covers the objectives, methodologies, procedure, plan of analysis and the implications involved on patients with Ototoxicity in Multiple Drug resistant Tuberculosis on category 4 regimen and their clinical profiling in detail.

KEYWORDS: MDR-TB, Ototoxicity, category 4 regimen, second line injectable, Kanamycin, hearing-loss.

INTRODUCTION

Tuberculosis continues to stay as a global public health issue in spite of the truth that the causative agent, *Mycobacterium tuberculosis* was discovered 100years ago. In keeping with the WHO 2009 report, internationally, yearly 9.4million cases are reported out of which it was estimated that 1.98 million cases were from India. (1) By the year 1996-97, India planned to implement RNTCP, Revised National Tuberculosis Control Program by formulating and adopting the internationally proposed the DOTS (Directly Observed Treatment short course) approach in being the most general and value-effective approach. (2) A TB affected person whose sputum is culture positive for *Mycobacterium tuberculosis* and is resistant in-vitro to rifampicin and isoniazid with or without other anti-tubercular drugs based totally on Drug Susceptibility Test (DST) results from an RNTCP- certified Culture and DST Laboratory is known as a Multiple drug resistant-TB suspect. (1) DOTS-Plus is an integral program of RNTCP to control MDR-TB. The RNTCP under DOTS-PLUS will be using a standardized treatment regimen (STR) Category 4 regimen, comprising of two phases, during 6-9months of Intensive phase with 6drugs (kanamycin, levofloxacin, ethionamide, cycloserine pyrazinamide and ethambutol) and 18months of Continuation phase with 4drugs (levofloxacin, ethambutol, cycloserine and prothionamide). P-amino salicylic acid (PAS) is included within the routine as an alternative drug if any bactericidal or any bacteriostatic drug is not tolerated. (3)

The remedy of MDR-TB is dependent on the administration of second-line anti-TB injectables, which may pose the threat of detrimental effects. (1) Two major detriments associated with the second-line injectable drugs used during the intensive segment of MDR-TB patient's regime are Nephrotoxicity and Ototoxicity. (4) Toxicity of the nephrotic structures is typically reversible but damages caused to the auditory structures are largely irreparable. (5) Nephrotoxicity and Ototoxicity associated with the use of Second Line

Injectable (SLI) containing drugs, is largely unrecorded in Indian patients as data is inadequate, therefore, this proposal intends to evaluate the widespread, control of ototoxic signs and remedy the prognosis of patients dealing with MDR-TB following SLI based treatment. (6)

Existent studies tell us that high frequency hearing is affected in individuals following SLI based treatment as they discriminatingly destroy the basal hair cells of the basilar membrane.(7) This happens through an oxidative technique, which is caused due to transition metal ion reactions which supply reactive oxygen species inflicting harm to the cells that is generally permanent. (8)

Current international MDR-TB expert opinions provide listed advice for the surveillance, types and remedies for auditory disorders relating to ototoxicity. (3) The WHO genuinely states that with the help of audiometry, if available, any loss of hearing must be documented and matched with bottom line effects. (9) We may either switch from aminoglycosides to capreomycin in case a defect is noted, or reduce the frequency/dose, or suspend the use of the documented agent and possibly without affecting the patient's regimen. (10) No mention is made within the procedures as to how the hearing should be examined, at what frequency it should be examined or what is classified as deafness. (11)

OBJECTIVES

The objectives describe the prevalence of Ototoxicity in multiple-drug resistant patients, the patho-physiology of hearing loss due to category 4 regimen and the procedures of diagnosis which can be used. The prospective study investigates existing norm and provides advice as to the further treatment of a patient who is prescribed second-line injectables (SLIs) like kanamycin. If detected early, to change the prescribed medication, to modify the dosage or its form, preventing the progression of hearing loss to the point where it would impact on communication. Aids and other interventions can be put in place if the damage has started to affect daily life. To investigate the depth and certainty associated with the use of SLIs, to discuss the detrimental effects and obstacles associated with the use of these regimens, and to finally explore alternative options. (9)

METHODOLOGY

Study type and population

•This prospective study was carried out from January 2018 to November 2019 in the department of pulmonary medicine in collaboration with the RNTCP department at Era's Lucknow Medical College and Hospital. Twenty subjects were enrolled in the hospital based on inclusion criteria and followed up to 96 weeks. Out of the patients enrolled in the hospital-based on inclusion criteria, subjects were chosen and followed up till the end of treatment.

A. INCLUSION CRITERIA

- Patients with MDR-TB
- Treatment containing Injectable containing drugs
- Having complete data

B. EXCLUSION CRITERIA

- Patients not suffering from MDR-TB
- Treatment not containing injectable containing drugs.
- Having incomplete data
- Patients with abnormal pre-treatment renal functions
- Those patients with any pre-treatment evidence of hearing loss on history
- Patients with Congenital deafness, CSOM, previous surgery of ears.

STUDY DESIGN

Articles were evaluated from identified papers and their reference lists, all content suggested by the author were also put into purview. Abstracts were assessed to retrieve suitable full-textual content articles. (12) Reviews and case series were done for a minimum of 5 patients and all articles documenting Ototoxicity in patients being treated for MDR-TB were included. The subjects were followed-up during their intensive phase therapy wherein they were injected by a medication containing any of the SLIs, where after symptoms associated with the toxicity of the auditory structures were monitored, and then the post treatment condition were recorded after the typical duration.(13) The literature using Medline, Pub Med, and databases with the following search terms: 'tuberculosis', 'second line-injectable', 'aminoglycoside', 'ototoxicity', 'hearing', 'adverse-effects', 'category4regimen', 'deafness', 'multiple-drug resistant TB', and 'hearing loss' were also searched. (14)

DATA COLLECTION

Clinical profiling and investigation of the current texts on the toxicity and tolerability of SLIs (second-line injectables that is Kanamycin) along with clinical investigations dealing HIV, Diabetes, ALT(SGPT), Calcium, Potassium, Bilirubin and Hemoglobin levels were made. Data collection was done via health professionals running MDR-TB centers. The facts collected also blanketed socio-demographic traits inclusive of age, gender, body weight at baseline and

follow-ups, susceptibility test results, mycobacterial culture results, sputum microscopy, drug varieties of anti-TB drugs at the ground level, various side effects and secondary medication, classification of TB, the selection of injectables, length of treatment, general dose of administration, overall dose, purpose for preventing injectable treatment, adverse occasion and its treatment. (13)

QUALITY CONTROL

Before performing the baseline audiogram, it was kept in mind that there can have been other factors in this person's medical history, unrelated to tuberculosis, which could affect hearing. (15) It is possible, and even likely, that the baseline hearing test will not be within normal limits. (16) And that is normal because that's not the purpose of ototoxic monitoring; the purpose of the monitoring is to detect changes in hearing. (17) The baseline audiogram is the starting point from which all other subsequent test results will be compared. (18)

PROCEDURE AND PLAN OF ANALYSIS

For screening and profiling of individuals clinically, the etiology (conduction or sensorineural), amplitude, laterality and frequency were prescribed. (19) They were continuously surveyed and tested for changes and effects over the course of treatment. (20) This allowed us to take informed decisions regarding their clinical management. The total dose was based on frequency and the duration of treatment. The extent of hearing loss and the changes associated therein were both studied over time. (21) Once the classification scale was decided upon, testing protocols followed the frequencies taken into consideration by that specific scale, and at each test, frequency thresholds were compared against the initial baseline test. (22)

The screening was started at the beginning of the first symptom presenting hearing disability; and was done at successive intervals thereafter, using audiological equipment. (23, 24) A pretested standardized semi-structured questionnaire was used. On detection of high-frequency hearing loss, injection of the drug was restricted. (25) And thus, successive therapy was continued by identifying and replacing the second line injectable containing drug responsible. (26)

OBSERVATION

Between January 2018 to November 2019, 18 patients admitted through inclusion criteria were resistant in-vitro to rifampicin and isoniazid with or without other anti-tubercular drugs based totally on Drug Susceptibility Test (DST) results from an RNTCP-certified Culture and DST Laboratory and were called as a Multiple drug resistant-TB suspect (MDR-TB). The incidence was significantly equal among men (50%) and women (50%), higher in persons > 17years of age (77%) than in younger patients <17years of age (22%). Only 5.5% patients showed raised value for alanine aminotransferase (ALT) test that's normal value ranges between 7-56 units per liter of serum. Generally, blood potassium level is 3.6 to 5.2 millimoles per liter (mmol/L), out of which11% patients showed abnormal values. Out of the 18 patients observed none showed a normal range for the amount of calcium present in their blood, the normal value for which range from 8.5 to 10.2 mg/dL (2.13-2.55 millimol/L). Only 1 female patient (5.5%) out of the total patients had hemoglobin of normal range i.e., for men, 13.5 to 17.5 grams per deciliter, for women, 12.0 to 15.5 grams per deciliter. 11% patients showed Ototoxicity including all males (having an incidence of 50%).

DISCUSSION

Between January 2018 to November 2019, 18 MDR-TB patients were identified through inclusion criteria. In this study the duration of patient suffering from MDR-TB was defined as the total time of exposure from the first diagnosis of MDR-TB to the time of identification of the Ototoxicity. An unexpected finding in the study was the abnormally low value of calcium present in the blood of all the patients. Another unexpected finding revealed significantly low levels of hemoglobin in all patients expect one female who was on borderline. The identification of a scar at this site is believed to be the most reliable way to assess one's BCG vaccination status. A novel observation in this study was the prevalence of Ototoxicity in males was higher in comparison to females and equal percentage of males and females being affected with MDR-TB. Nevertheless, these data show that in managing tuberculosis in contacts of MDR-TB, one cannot predict with certainty the prevalence of Ototoxicity in MDR-TB patients injected with Kanamycin (second- line injectable)

ETHICAL CONSIDERATION

The project was first submitted to the Institutional Ethical Committee and institutional ethical clearance was taken, wherein, the data remains confidential under the supervision of ethically trained data collectors, it was kept to be safe guarded, and finally stripped of personal information before being analyzed. (27, 28) The collection, extraction, handling and safety of the data was ensured and monitored by the collectors and supervisors. (29) The potential participants were counseled regarding the onward course, the consenting individuals were then enrolled and the protocol was approved by the RNTCP administration. (30)

CONCLUSION

The prevalence pattern of largely higher frequency hearing loss and progressively lower frequency hearing loss with increasing damage is due to the damage caused to the cochlear hair cells by the SLIs. (31) We came to note continual damage auditory even after disuse of SLIs as it goes unnoticed because the primary damage affects the higher frequencies first and then lower frequencies which are audible to humans. (32) Generally, auditory damage cause due to SLIs cannot be reversed. (33) Therefore, preventive measure must be employed to ensure the protection of the remaining functional auditory structures. (34) This research will enlighten the health care provider and treating physicians to have a view point about the Ototoxicity associated with therapeutics of MDR-TB as auditory damage is grievous sensual loss which rings about additional lifelong challenge to the patient of MDR TB.

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How to cite this article : Baqar T., Ahmad S., Srivastava S. Prevalence of Ototoxicity in MDR-TB Patients On Category-4 Regimen and their Clinical Profiling. Era J. Med. Res. 2021; 8(1): 45-49.