ORIGINAL RESEARCH PAPER

Pulmonary Medicine

INCIDENCE OF KANAMYCIN INDUCED TOXICITY AMONG DRUG RESISTANT TUBERCULOSIS PATIENTS ATTENDING TIRUNELVELI MEDICAL COLLEGE HOSPITAL, DOTS PLUS CENTRE, TAMILNADU

KEY WORDS: Ototoxicity, Nephrotoxicity, Kanamycin, drug resistant tuberculsis

Dr. N. Jayakumar	MD DCH,Department of tuberculosis & Respiratory medicine, Tirunelveli medical college hospital, Tirunelveli, Tamilnadu
Dr. K. Krishnamoorthy*	MD, Department of tuberculosis & Respiratory medicine, Tirunelveli medical college hospital, Tirunelveli, Tamilnadu *Corresponding Author
Dr. E. Mathan	MD, Department of tuberculosis & Respiratory medicine, Tirunelveli medical college hospital, Tirunelveli, Tamilnadu
Dr. G. Sangamithra	MD, Department of tuberculosis & Respiratory medicine, Tirunelveli medical college hospital, Tirunelveli, Tamilnadu
Dr. Rahman Shahul Hameed	MD, Department of tuberculosis & Respiratory medicine, Tirunelveli medical college hospital, Tirunelveli, Tamilnadu

INTRODUCTION

Tuberculosis is one of the most common infectious diseases in the world responsible for more than nine million new cases, two million deaths per year [1]. India is the country with the highest burden of TB. World Health Organization statistics for 2013 gives an estimated new cases of 2.1 million cases of TB for India out of a global incidence of nine million new cases . The estimated TB prevalence in the year 2013 is 2.6 million . It is about 40 % of the Indian population is infected with TB bacilli , most of them have latent TB . In our country TB treatment after defaulters are high about (30%) , which leads to MDR – TB [2].

During intensive phase, injection Kanamycin, Levofloxacin, Ethionamide, Ethambutol, Cycloserine, Pyrazinamide is given for a period of six to nine months. In the continuation phase, Levofloxacin, Ethionamide, Ethambutol, Cycloserine is given for the next 18 months period. In the treatment of drug resistant tuberculosis , above mentioned second line drugs are associated with significant adverse effects which leads to permanent disability. Inj Kanamycin (15 -20 mg/kg) given as an Intramuscular injection daily for six days/week. Inj.kanamycin produces well documented ototoxicity and renal toxicity. Early detection of these adverse effects and their correction will improve the adherence to the treatment, and prevent permanent hearing loss.

Kanamycin induced ototoxicity initially involves higher frequencies then slowly progresses to lower frequencies, later it involves speech frequencies also. Vestibular symptoms like tinnitus, vertigo, giddiness, ataxia, nystagmus may be noticed by the patient taking inj.Kanamycin.

MATERIAL AND METHODS

AIM :

Audiologic monitoring and renal function monitoring for Drug Resistant patients under PMDT(programmatic management of drug resistant tuberculosis reatment) for six to nine months period in Tirunelveli Medical College Hospital DR-TB UNIT, from January 2014 to December 2014.

MATERIALS AND METHODS :

Total of 152 newly diagnosed DR-TB patients those registered in DR-TB centre , Tirunelveli medical college hospital from January 2014 to December 2014 were screened.

INCLUSION CRITERIA

All newly diagnosed DR-TB patients in tirunelveli, tuticorin, kanyakumari, virudhunagar districts in Tamilnadu state with normal baseline audiometry were included in this study

EXCLUSION CRITERIA

1. Pre treatment evidence of hearing loss in newly diagnosed DR-TB patient with baseline audiometry changes more than 25 db
2. Patient with prior history of audiological impairment, presbyacusis, any vestibulo-cochlear symptoms
3. Patients with age less than 10 year
4. Pregnant females
5. Patients not willing for routine follow up
6. Major psychiatric illness

METHODS :

After getting the permission from the institutional ethical committee in Tirunelveli Medical College Hospital study commences, this prospective observational study was conducted from DR-TB unit in tirunelveli medical college . Informed Consent will be obtained from DR-TB patients admitted in DR-TB ward. This study starts after explaining the treatment regimen and probable adverse effects expected in the course of the treatment .

All newly diagnosed DR-TB patients admitted in DR-TB unit for DOTS PLUS regimen initiation in Tirunelveli Medical College were included in study group.

After using inclusion and exclusion criteria 51 eligible newly dignosed DR-TB patients were enrolled in this study .These patients were started on CATEGORY IV regimen according to weight basis. Pure tone audiometry was done in the ENT department in tirunelveli medical college.

AUDIOMETRY:

1. First Pure tone audiometry was done at the time of initiation of the CATEGORY IV regimen.
2. Second pure tone audiometry was done at third month of the treatment.
3. Third pure tone audiometry was done at sixth month of the treatment.
4. If patients develops tinnitus, vertigo, hard of hearing or any audiological impairement , pure tone audiometry was done in the intensive phase.

DURATION OF THE STUDY :12 months(January 2014 to December 2014)
SAMPLE SIZE : 51
STUDY DESIGN : prospective observational study
SOURCE : MDR-TB Patients registered in DR-TB unit , Tiruneveli medical college hospital

WHO CRITERIA FOR CATEGORISING HEARING LOSS :

- Normal – amplitude less than 25 decibels
- Mild – amplitude 26 to 40 decibels

- Moderate- amplitude 41 to 55 decibels
- Moderately severe- amplitude 56 to70 decibels
- Severe - amplitude 71 to 90 decibels
- Profound - amplitude more than 90 decibels

RESULTS;

Total of 51 newly diagnosed DR-TB patients were included in this study. Pure tone audiometry and renal function monitoring was done and analysed as follows

AGE DIRSTRIBUTION :

- Out of 51 patients , 27 % (n -14) of the patients belongs to the age group of 41 to 50. 24% of the patients (n-12)belongs to the the age group of 31 to 40 years. 18% of the patients (n-9) belongs to the age group of 21to30 years. 18% of the patients (n-9) belongs to the age group of 51to 60 years . 8% of the patients (n-6) belongs to the age group of 61 to70 years 6%of the patients (n-4) belongs to the age group of 11 to 20 years.

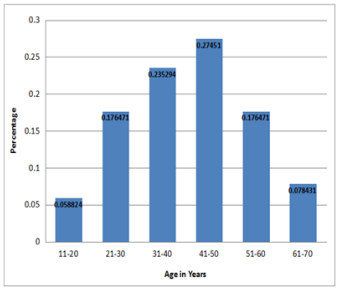

Fig 1. Age Distribution

SEX DIRSTRIBUTION:

Out of 51 MDR-TB patients,82% (n- 42) patients are males,18% (n-5) are females. Out of 51 MDR-TB patients 22 patients developed SNHL, among which 81% (n-18) are males , 18% (n-4) are females .

DEGREE OF HEARING LOSS

UNILATERAL HEARING LOSS: total of 51 DR-TB patients, 8 patients (n-8) developed unilateral hearing loss. Among them 7 patients had mild hearing loss (male-6, female -1), one had moderate hearing loss .

DEGREE	RIGHT	LEFT
MILD	4 (M 4 / F 0)	3 (M 2 / F 1)
MODERATE	1 (M 1 / F 0)	0
MODERATLY SEVERE	0	0
SEVERE	0	0
PROFOUND	0	0

TABLE 1 : Unilateral Hearing Loss

BILATERAL HEARING LOSS : TOTAL 14 (M 11 / F 3)

Out of 51 patients, 14 patients (28ears) developed bilateral hearing loss, among these patients 11 were males, 3 were females. In this group 9 patients developed bilateral mild SNHL, 1 patient had severe hearing loss, one patient had right sided profound hearing loss and left severe hearing loss on 3rd month of follow up

DEGREE	RIGHT	LEFT
MILD	1	-
MODERTE	1	1
MODERATLY SEVERE	1	3
SEVERE	1	1
PROFOUND	1	0

TABLE 2 : BILATERAL SNHL

NUMBER OF PATIENTS DEVELOPED B/L MILD SNHL: 9

PERCENTAGE OF HEARING LOSS FOR USING WHO CLASSIFICATION :

Out of 22 patients who developed SNHL (44 ears) , 75% (33 ears) patients developed mild hearing loss, 9.1% (4 ears) patients developed moderate hearing loss, 9.1%(4 ears) patients developed moderately severe hearing loss, 4.5 % (2 ears) developed severe hearing loss, 2.3% (1ear) developed profound hearing loss.

CATEGORY	NO OF EARS	PERCENTAGE
MILD	33	75%
MODERATE	4	9.1%
MODERATLY SEVERE	4	9.1%
SEVERE	2	4.5%
PROFOUND	1	2.3%

TABLE; 3

FOLLOW UP OF HEARING LOSS :

During the follow up period in a 51 DR-TB patients, 3rd month follow up 27% (n-14) DR-TB patients had developed right sided SNHL, 20%(n-10) DR-TB patients had developed left sided SNHL .

In the 6th month follow up period DR-TB, 39% (n-20) patients had developed right sided SNHL, 27% (n-14)) DR-TB patients had developed left sided SNHL

FOLLOW UP VISITS	SIDE	NO OF PATIENTS	PERCENTAGE
1	RIGHT	0	0
	LEFT	0	0
2	RIGHT	14	27%
	LEFT	10	20%
3	RIGHT	20	39%
	LEFT	14	27%

Table 4: NO OF PATIENTS DEVELOPED HEARING LOSS DURING FOLLOW UP

RELATIONSHIP BETWEEN ONSET OF OTOTOXICITY AND DURATION OF THE TREATMENT :

Out of 51 DR-TB patients in this study, 22 DR-TB patients developed hearing loss. Of these 77.27% (n-17) patients had developed hearing loss during the first three month of the intensive period , 22.72% (n-5) DR-TB patients developed SNHL during the sixth month of the DOTS PLUS regimen.

Onest of Ototoxicity	3rd month	4th month	5th month	6th month
No of patients (n=22)	17 (77.27%)	0	0	5(22.72%)

Table 5. Onset Of Ototoxicity in MDR TB

STATISTICAL SIGNIFICANCE OF OTOTOXICITY :

During the follow up period of 51 DR-TB patients audiometry results were analysed by using ANNOVA TEST (analysis of variance) and Overall **p value is 0.002.** This p value is statistically SIGNIFICANT. Hence injection kanamycin produce definite ototoxicity among the DR-TB patients receiving the CATEGORY 4 regimen .

	Follow up	P Value
PTA	All	0.002
Right Ear	1 and 2	0.24
	1 and 3	0.003
	2 and 3	1
Left Ear	All	0.003
	1 and 2	0.039
	1 and 3	0.003
	2 and 3	1

TABLE : 6

SYMPTOMS ANALYSIS FOR OTOTOXICITY :

During the follow up 22 patients developed hearing loss , 36%(n-8) patients had vestibulo cochlear- symptoms like tinnitus , vertigo, hard of hearing, fullness of ear . Most common symptom noticed in this study is tinnitus (75%)

64% (n-14) patients NOT aware of the symptoms associated with hearing loss .

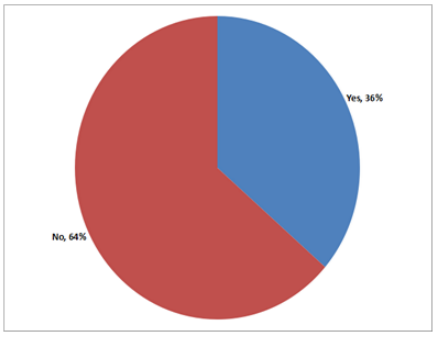

Fig 2. Symptoms Analysis For Ototoxicity

DISCUSSION:

Kanamycin induced ototoxicity is usually irreversible, because it destroys both inner and outer hair cells in the cochlea. kanamycin induced ototoxicity is dose dependent manner, initially it affects the higher frequencies, later it affects lower frequencies and also involves the speech frequencies and interfere with speech communication .

In our study incidence of injection kanamycin induced ototoxicity among the DR-TB patients was 43.13%. Prahlad duggal et al reported prevalence of aminoglycoside induced ototoxicity of 47%, out of which 18.75% SNHL involving higher frequencies and 6.25% involving lower frequencies.

In our study of 51 DR-TB patients 22 patients developed hearing loss. During the 3rd month follow up period out of 22 patients, 77.27% (n-16) patients developed SNHL, 22.72 % (n-6) patients developed SNHL at the 6th month follow up period. **Aasishkumar et al** conducted a study in govt surat medical college, overall incidence of ototoxicity is 35%, of which during the 1st month follow up 62.85%, 2nd month follow up 11.4% , 3rd month follow up 2.8%, 4th 5th and 6th month results are 8.57%,8.57%,5.71% respetively developed SNHL .

In our study majority 64% (n-14) of patients were unable to recognised the symptoms of hearing loss, 36% (n-8) patients noticed symptoms of hearing loss like tinnitus, hard of hearing, fullness of the ear and vertigo. In a symptomatic patients most common symptom noticed is tinnitus (75%) , then hard of hearing (16%), least symptoms noticed were fullness of the ear and vertigo.

CONCLUSION :

1. In this prospective observational study, during the intensive phase of CATEGORY IV regimen 43.3% patients developed statistically significant OTOTOXICITY
2. **OTOTOXICITY-** 63.63% patients developed bilateral hearing loss and 36.36% patients developed unilateral hearing loss. among the patients with ototoxicity 75% patients had mild hearing loss, and mostly during first three months period of the intensive phase.
3. In our study 64% patients with hearing loss are asymptomatic and 36% patients noticed symptoms associated with hearing loss and the most common symptom being tinnitus (75%) .
4. In our study 64 % of asymptomatic hearing loss cases were picked up by using pure tone audiometry. Early detection of the hearing loss among these patients shall improve adherence to the treatment. hence pure tone audiometry to be done as a pre treatment evaluation for all MDR-TB patients at the initiation of the treatment, every month for the first six months, then every three month till completion of the treatment.

Kanamycin induced ototoxicity initially involve higher frequencies. At that time most of the patients are not aware of the symptoms of ototoxicity, at this time if the patients was not diagnosed . Later it will involve lower and speech frequencies , patient may land up with audiological symptoms,at this time hearing loss will be permanent. Detection of the hearing loss in the later stages may not be beneficial to the patient by stopping the inj. kanamycin. Hence strict audiogical evaluation is mandatory in DR-TB patients at the time of initiation of CATEGORY IV regimen, also every month follow up period till completion of inj.kanamycin, thereafter every three months till end of the treatment for early detection and prevention of ototoxicity .

REFERENCES:

1) Global Tuberculosis control 2014,WHO, Geneva, 2014 www.who.int/tb/publications/ global report.
2) TB India 2012, Revised national TB control programme annual status report,New Delhi2012.www.tbcindia.nic.in/documents.html
3) Lambregts-van Wezenbeek CSB, Veen J. Control of drug-resistant tuberculosis. Tubercle and lung disease1995:76;455-458.
4) Ramachandran R, Nalini S, Chandrasekar V, Dave PV, Sanghvi AS, Wares F, Paramasivan CN, Narayanan PR, Sahu S, ParmarM, Chadha S, Dewan P, Chauhan LS. Surveillance of drug-resistant tuberculosis in the state of Gujarat, India. Int J Tuberc Lung Dis 2009: 13(9); 1154-1160.