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Research Article

Assessment of hearing loss in multi-drug resistant tuberculosis (MDR-TB) patients undergoing Aminoglycoside treatment

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ABSTRACT

Background: Incomplete treatments and treatment failures has led to Multi-drug resistant tuberculosis, which has emerged as a significant problem in treating tuberculosis and thus the second line drugs are used with the concomitant increase in the incidence of adverse effects.
Methods: This prospective study was carried out from June 2009 to May 2014 in the department of ENT in collaboration with TB & Chest at Teerthanker Mahaveer Medical College & Research Centre.
Out of 104, only 84 patients were included in our study. Patients were divided into three groups: group I (n=27) patients using Amikacin, group II (n=40) patients using kanamycin and group III (n=17) patients using streptomycin. Baseline pre-treatment pure tone audiometry was performed on all the patients and repeated every three months until completion of therapy.
Results: Patients included were 15 to 55 years age with higher number of males (65%, n=55) than females (35%, n =29). Only 22.7% (n=19) of patients were found to be suffered from Hearing Loss. At the end of the study (at 12 month), Overall incidence of HFL was 58.0% (n=11) while incidence of Dead ear was 31.5% (n=6) and LFL was 10.5% (n=2). Amikacin was found to be more Ototoxic than Kanamycin and streptomycin.
Conclusion: Aminoglycosides in MDR-TB patients may cause irreversible hearing loss involving higher frequencies and can become a hearing handicap as speech frequencies are too implied in more or less of the patients, thus underlining the need for regular audiologic evaluation in patients of MDR-TB during the treatment.

Keywords: Tuberculosis, MDR-TB, Amikacin, Kanamycin, Streptomycin

INTRODUCTION

Tuberculosis is one of the leading infectious diseases in the world and is responsible for more than two million deaths and nine million new cases annually. India is the country with the highest burden of TB with World Health Organization (WHO) statistics for 2013 giving an estimated incidence figure of 2.1 million cases of TB for India out of a global incidence of 9 million. The estimated TB prevalence figure for 2013 is given as 2.6 million.[1] It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB. Also cases of TB defaulters are also higher in India (30%), which leads to MDR-TB. As per the Revised National Tuberculosis Control Programme (RNTCP) incidence of Treatment defaulters are higher in Uttar Pradesh than in comparison to other states of India.[2]

Therefore, the emergence of resistance to anti-tubercular drugs and particularly multi-drug resistant (MDR-TB) has become a hindrance to effective global TB control.

Incomplete and inadequate treatment is the most important factor leading to its development, suggesting that it is often a man-made problem.[3]

The other important causes of treatment failures are related to the length of treatment (especially considering tolerability and compliance), the longer time that is required to treat MDR-TB results in an additional risk of poor treatment adherence and thus of treatment failure.[4] Two other major issues are the increased cost (up to 100 times higher) and higher toxicity of using second-line drugs.[5,6]

In order to treat MDR-TB, residual first-line oral drugs must be appropriately combined with additional second line drugs comprising injectable aminoglycosides (amikacin, kanamycin, capreomycin), fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin), old bacteriostatic second line anti-tuberculosis agents (ethionamide, protionamide, cycloserine, para-amino salicylic acid, thiocetazone) and anti-tuberculosis agents with unclear efficacy (clofazimine, amoxicillin/clavuanate, clarithromycin, linezolid).[7] A major issue related to long-term administration of the Aminoglycosides is toxicity. Ototoxicity and nephrotoxicity are well recognized as dose-related adverse effects of aminoglycosides.[8] Ototoxicity is the major irreversible toxicity of aminoglycosides. Cochlear damage can produce permanent hearing loss, while damage to vestibular apparatus results in dizziness, ataxia and/or nystagmus. Aminoglycosides appear to generate free radicals within the inner ear, with subsequent permanent damage to the sensory cells and neurons resulting in permanent hearing loss.[9]

First row outer hair cells (OHCs) in the basal turn tend to be affected earlier than inner apical cells and type I cells are affected before type II cells. The progression of hair cell loss in cochlea tends to be from basal to apical and from OHCs to inner hair cells (IHCs) to supporting cells to more central neural structures like spiral ganglion cells.[10] This stepwise progression of damage explains the clinical findings of high frequency hearing loss occurring first with ototoxic drugs.

Therefore the present maiden study in our hospital was conducted to study the effect of second line aminoglycosides (Amikacin, Kanamycin and Streptomycin) on the hearing status in patients of MDR-TB after long term use as a part of multi-drug therapy.

METHODS

This prospective study was carried out from June 2009 to May 2014 in the department of ENT in collaboration with department of TB & Chest at Teerthanker Mahaveer Medical College & Research Centre.

Study duration

Total of 104 patients were enrolled in the study who completed treatment for MDR-TB from June 2009 to May 2014 using second line drugs and were referred to ENT department for audiometric analysis. Out of 104 patients, only 84 patients fulfilled the inclusion and exclusion criteria and were included in our study.

Study Setting

Treatment regimens followed were based on drug susceptibility testing and previous treatment history. All the relevant data were recorded on MDR-TB patient sheets including the baseline and follow-up investigations. Baseline pre-treatment pure tone audiometry was performed on all the patients and repeated every three months until completion of therapy. Other baseline investigations including renal function and liver function tests were also performed on all the patients.

The treatment regimens used were in accordance with the standard recommended protocols with necessary permissions from Institutional Ethics Committee and informed consent of all the patients in the study was obtained just before the commencement of study.

Complete otolaryngologic examination was done as a part of pre-treatment clinical examination in all the patients. Baseline pure tone audiometry (PTA) between 125 Hz and 8000 Hz were performed for all the patients in a sound proof room.

Baseline, in addition to follow-up audiological testing, included both air-and bone-conduction threshold measurements in all the patients.

Inclusion Criteria

Patients 15-55 years aged under MDR-TB treatment in the form of injectable Aminoglycosides were included in our study.

Exclusion Criteria

1. Patients with abnormal pre-treatment renal functions were excluded from the study group.
2. Those patients with any pre-treatment evidence of hearing loss on history, clinical assessment (patients with evidence of infective pathology in ear were excluded) or pure tone audiometry, whether conductive (A-B gap > 10 dB) or sensorineural were excluded.
3. All the patients who had received any ototoxic drug as a part of previous regimen were excluded from the study.
4. Patients of CSOM, Congenital deafness, previous surgery of ears, Presbyacusis were excluded.

Hearing Loss Assessment

The criteria used for determining ototoxic threshold shift from baseline audiogram were: (1) 20 dB or greater decrease at any one test frequency, (2) 10 dB or greater decrease at any two adjacent frequencies, or (3) loss of

response at three consecutive frequencies where responses were previously obtained.[11] All the changes were confirmed by retest on the same day.

Study Groups

These patients were divided into three groups depending upon the ototoxic aminoglycoside used.

Group I (n = 27) patients received Amikacin (15-20 mg/kg per day, intramuscular, single daily dose),

Group II (n = 40) patients received Kanamycin (15 mg/kg per day, intramuscular, single daily dose) and

Group III (n = 17) patients received Streptomycin (15 mg/kg per day, intramuscular, single daily dose) as a part of complete regimen comprising of one injectable (aminoglycoside), one quinolone with a minimum of five drugs depending on the drug sensitivity testing and the costs involved.

Total duration of therapy in all the patients ranged from 18 to 24 months after sputum smear/culture conversion and aminoglycoside was used for six months after sputum conversion.

Audiometric analysis

Audiometry findings were considered under three categories;

'Normal' (N) defined by patients with pure tone audiograms showing air-conduction thresholds up to 20 ± 5 dB HL at all the tested frequencies from 125 Hz to 8000 Hz with air-bone gap of ≤ 10 dB;

'High frequency loss' (HFL) defined by (1) a 20 dB or greater decrease at any of the three frequencies; 4000, 6000 and 8000 Hz, (2) 10 dB or greater decrease at any two adjacent frequencies in above range, (3) loss of response at all the three frequencies (4000, 6000 and 8000 Hz) where responses were previously obtained.

LFL defined as hearing loss at frequency less than 2000 Hz.

Dead Ear The ear is not responding to any frequency at the highest intensity.

RESULTS

All the patients included in our study were in the age group of 15 to 55 years (mean age = 39.9 ± 13.5 years) with males constituting 65% (n=55) and females constituting 29% (n =29) [Table 1]. Majority of the patients were from rural background (79.5%) while 20.5% were from urban areas. Out of 84 patients, only 22.7% (n=19) of patients were found to be suffered from Hearing Loss. At the end of the study (at 12 month), Overall incidence of HFL was 58.0% (n=11) while incidence of Dead ear was 31.5% (n=6) and LFL was 10.5% (n=2). The mean duration of therapy was 20.3 ± 0.25 months after smear/culture conversion (range was 18–24 months) while aminoglycosides were continued for 6 months (180 days) post conversion in the initial phase. Total duration of aminoglycoside use was 180 days while duration of audiologic follow-up after discontinuation of aminoglycoside use was 180 days.

Table 1: Demographic detail of study population

Age Group (Years)	Male (%)	Female (%)	Number of Patients (%)
15 – 24	06	02	08 (9.5%)
25 – 34	15	09	24 (28.5%)
35 – 44	22	10	32(38.1%)
45 – 55	12	08	20 (23.8%)
TOTAL	55 (65%)	29 (35%)	84 (100%)

Out of 27 patients in Group I (Amikacin), only Nine patients (33.3%) showed sensorineural hearing loss (SNHL) involving the higher frequencies (HFL), LFL (Low Frequency Loss) and Dead ear. Follow-up audiogram showed development of HFL in five cases (55.5%) Dead Ear in three cases (33.3%) and development of LFL (Low Frequency Loss) in one patient (11.1%) [Table 2]. HFL was found in (Patient # 1) at 12 month, (Patient # 3) at 9 months, (Patient # 5) at 3 months, (Patient # 7) & (Patient # 8) at 6 months (pure tone audiogram at 6 months, PTA6). (Patient # 2), (Patient # 4) and (Patient # 9) first developed HFL at 3 months, later converted to dead ear at 6 months (Patient #2 &9), 9 months (Patient#4). Dead ear was found in (Patient # 2) and (Patient # 9) at six months (pure tone audiogram at 6 months, PTA6) and (Patient # 4) at 9 months (pure tone audiogram at 9 months, PTA9), whereas LFL was found in (Patient # 6) at 3 months (pure tone audiogram at 3 months, PTA3) [Table 2].

Out of 40 patients in Group II (Kanamycin), only seven patients (17.5%) showed sensorineural hearing loss (SNHL) involving the higher frequencies (HFL), LFL (Low Frequency Loss) and Dead ear. Follow-up audiogram showed development of HFL in four cases (57.1%) Dead Ear in two cases (28.5%) and development of LFL (Low Frequency Loss) in one patient (14.2%) [Table 3]. Conversion from HFL to Dead ear was seen in two cases (Patient # 1&2) at 9 months and 12 months respectively. HFL was found in (Patient # 3) at 6 month, (Patient # 5&6) at 9 months, (Patient # 7) at 12 months. Dead ear was found in (Patient # 1) at 9 month and (Patient # 2) at 12 month (pure tone audiogram at 12 months, PTA12), whereas LFL was found in only in one (Patient # 4) at 6 month (pure tone audiogram at 6 month, PTA6) [Table 3].

Out of 17 patients in Group III (Streptomycin), only three patients (15.8%) showed sensorineural hearing loss (SNHL) involving the higher frequencies (HFL) and

Dead ear. Follow-up audiogram showed development of HFL in two cases (66.6%) Dead Ear in only one case (33.3%) [Table 4]. Conversion from HFL to Dead ear was seen in one case (Patient # 1) at 6 months. HFL was found in (Patient # 2&3) at 6 month. Dead ear was found in (Patient # 1) at 6 month (pure tone audiogram at 6 month, PTA6) [Table 4].

Table 2: Audiometry findings and length of aminoglycoside use in Amikacin group I (n = 9) patients showing audiological evidence of hearing loss.

(Group)	Length of treatment (Days)	PTA0	PTA3	PTA6	PTA9	PTA12
1	180	N	N	N	N	HFL
2	180	N	HFL	DEAD EAR	DEAD EAR	DEAD EAR
3	180	N	N	N	HFL	HFL
4	180	N	HFL	HFL	DEAD EAR	DEAD EAR
5	180	N	HFL	HFL	HFL	HFL
6	180	N	LFL	LFL	LFL	LFL
7	180	N	N	HFL	HFL	HFL
8	180	N	N	HFL	HFL	HFL
9	180	N	HFL	DEAD EAR	DEAD EAR	DEAD EAR

Days = days of aminoglycoside use in present regimen, PTA0 = baseline pure tone audiogram, PTA3 = pure tone audiogram after 3 months of aminoglycoside use, PTA6 = pure tone audiogram after 6 months of aminoglycoside use, PTA9 = pure tone audiogram after 9 months of aminoglycoside use, PTA12 = pure tone audiogram after 12 months of aminoglycoside use , N = Normal, HFL = High frequency loss, LFL = Low frequency loss.

Table 3: Audiometry findings and length of aminoglycoside use in Kanamycin group II (n = 7) patients showing audiological evidence of hearing loss.

(Group)	Length of treatment (Days)	PTA0	PTA3	PTA6	PTA9	PTA12
1	180	N	HFL	HFL	DEAD EAR	DEAD EAR
2	180	N	HFL	HFL	HFL	DEAD EAR
3	180	N	N	HFL	HFL	HFL
4	180	N	N	LFL	LFL	LFL
5	180	N	N	N	HFL	HFL
6	180	N	N	N	HFL	HFL
7	180	N	N	N	N	HFL

Days = days of aminoglycoside use in present regimen, PTA0 = baseline pure tone audiogram, PTA3 = pure tone audiogram after 3 months of aminoglycoside use, PTA6 = pure tone audiogram after 6 months of aminoglycoside use, PTA9 = pure tone audiogram after 9 months of aminoglycoside use, PTA12 = pure tone audiogram after 12 months of aminoglycoside use, N = Normal, HFL = High frequency loss, LFL = Low frequency loss.

Table 4: Audiometry findings and length of aminoglycoside use in Streptomycin group III (n = 3) patients showing audiological evidence of hearing loss.

(Group)	Length of treatment (Days)	PTA0	PTA3	PTA6	PTA9	PTA12
1	180	N	HFL	DEAD EAR	DEAD EAR	DEAD EAR
2	180	N	N	HFL	HFL	HFL
3	180	N	N	HFL	HFL	HFL

Days = days of aminoglycoside use in present regimen, PTA0 = baseline pure tone audiogram, PTA3 = pure tone audiogram after 3 months of aminoglycoside use, PTA6 = pure tone audiogram after 6 months of aminoglycoside use, PTA9 = pure tone audiogram after 9 months of aminoglycoside use, PTA12 = pure tone audiogram after 12 months of aminoglycoside use, N = Normal, HFL = High frequency loss, LFL = Low frequency loss.

Amikacin (47.36%, nine cases out of total 19 cases) was found to be more Ototoxic than Kanamycin (36.84%, seven cases out of total 19 cases) and streptomycin (15.78%, three cases out of total 19 cases) [Table 5, Figure 1].

Table 5: Prevalence of ototoxicity in patients using Aminoglycosides.

Groups	Patients reported Ototoxicity (n=19)	Patients not reported Ototoxicity (n=65)	Total (n=84)
Amikacin	9	18	27
Kanamycin	7	33	40
Streptomycin	3	14	17

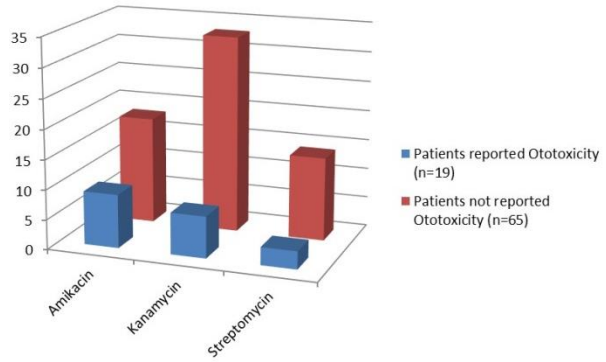

Figure 1: Prevalence of ototoxicity in Aminoglycosides.

DISCUSSION

Due to prescription errors and also non-compliance of the patients regarding their Tuberculosis treatment, emergence of MDR-TB is inevitable. MDR-TB is a growing problem throughout the world and is itself can lead to other problems in the form of patient's disabilities.[12] As we know that in MDR-TB treatment second line drugs such as Aminoglycosides are given to the patients. Using Aminoglycosides in these patients is itself a problem because they can cause irreversible hearing loss in the patients. Therefore this study was carried out to compare the ototoxicity in different aminoglycosides. Another reason for choosing this study was that this region is an epidemic area for Tuberculosis.

The main constraint to the administration of aminoglycosides are risks of nephrotoxicity and ototoxicity.[13]

The present study evaluates the effect of parenteral second line aminoglycosides namely Amikacin, kanamycin and Streptomycin on hearing status of MDR-TB patients. We had included 15 to 55 years (mean age = 39.9 ± 13.5 years) patients in our study to rule out other causes of hearing loss [Table 1]. As our hospital surrounded by villages, therefore majority of the patients were constituted from rural areas (79.5%) than urban areas (20.5%). Our findings are in accordance with the similar study conducted by Duggal P and Sarkar M that majority of the patients were from rural area than urban area.[14]

We reported a hearing loss documented by pure tone audiometry in 22.7% patients of MDR-TB using a single parenteral second line aminoglycoside involving higher frequencies (4000 to 8000 Hz) to start with and progressing to involve lower frequencies (500, 1000, 2000 and 3000 Hz) in 10.5% and to dead ear in 31.5%, thus affecting the speech comprehension of the patient. The loss once developed has been found to be irreversible and none of the patients in the present study showed any improvement after stopping the therapy.

Incidence of HFL, Dead ear was found to be higher in our study as compared to study conducted by Duggal P and Sarkar M i.e., 18.75% and 6.25% respectively.[14] This can be explained by the fact that the burden of Tuberculosis is higher in our place as this area is endemic for Tuberculosis. But our findings are in accordance with the similar studies conducted and reported on the incidence of hearing loss after aminoglycoside treatment range from 0% (Powell, Thompson, & Luthe, 1983) to 63% (Tablan, Reyes, Rintelmann, & Lerner).[15,16] In our study Incidence HFL is higher 58% (n=11, out of Nineteen patients) and also developed first than LFL, well supported by Dreschler, et al., and Fausti et al., that Aminoglycosides have been known to affect hearing exclusively or initially in higher frequencies (9–20 kHz) prior to presentation of hearing loss in lower frequencies.[17,18]

Ototoxicity is determined by comparing baseline data, ideally obtained prior to ototoxic drug administration, to the results of subsequent monitoring tests. Detecting changes in pure tone thresholds directly using serial audiograms is considered the most effective indicator of ototoxic hearing loss, particularly when ultra-high frequency thresholds are included.[19,20]

In the present study, pure tone audiometry was performed on 3 months interval for each patient until the completion of therapy. Because aminoglycoside ototoxicity can progress after discontinuation of the drug,[21] we also performed audiometric follow-up in all the patients for 6 months after drug discontinuation. This long term follow-up confirmed that all aminoglycoside-induced hearing loss in this patient population was permanent and not reversible.

Twice weekly audiograms as recommended were not performed in the present study because of cost involved and the inability of the patients from far distant places to

report twice weekly at our center where facilities for conventional assessment of hearing are available.

Conventional frequency range (250–8000 Hz) was used in the present study as only conventional audiometers with frequency range between 125 and 8000 Hz are available with us owing to low cost compared to high frequency equipment.

Different studies have reported hearing loss as an adverse drug reaction in patients of MDR-TB ranging from 6–18%.[22,23] The finding that higher frequencies are involved before the lower frequencies may be used as a monitoring procedure for the detection of ototoxicity and has the potential for minimizing irreversible communication deficits in patients receiving aminoglycoside therapy.[24] In our study, all the patients showing hearing loss, the aminoglycoside was neither stopped nor changed to another second line drug done. Incidence of hearing loss may have been reduced if the aminoglycoside was stopped immediately at the outset of ototoxicity and substituted with another second line drug showing less ototoxicity.

A number of otoprotective agents should be investigated for protection against hearing loss induced by aminoglycosides or other ototoxic drugs. These agents delivered either before or in combination with ototoxic drugs may help to prevent ototoxicity. As, D-methionine has been reported as an otoprotective agent has shown protection against Amikacin induced ototoxicity.[25]

CONCLUSION

Audiologic changes have been reported in patients of MDR-TB using second line aminoglycosides which can potentially affect the communication ability of the patient. But careful audiologic monitoring and shifting to less ototoxic aminoglycoside may help in limiting this damage which once developed is permanent. As showed in our study that streptomycin is less ototoxic than Amikacin and Kanamycin. Thus otologists and audiologists can have an important role in the management of MDR-TB in preventing the treatment related morbidity.

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