e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(1); 623-635

Original Research Article

Impact of Sensorineural Hearing Loss Due to Injectable Aminoglycoside Drugs in Patients of Multi-Drug Resistant Tuberculosis

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Received: 26-12-2022 / Revised: 18-01-2023 / Accepted: 23-01-2022

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Conflict of interest: Nil

Abstract

Introduction: Multi-drug tuberculosis (MDR-TB) is a serious threat and needs a combination of drugs for its effective treatment. The aminoglycoside group of drugs are widely used for the same. The adverse effect of ototoxicity of these drugs is irreversible and can lead to permanent disability. Aminoglycosides affect the higher frequencies first and it gradually progresses to the lower (speech) frequencies. Regular audiological monitoring can help identify patients developing hearing loss early and can prevent its further progression thus preventing debilitating disability. We discuss this drug induced hearing loss in this study.

Material and Methods: In this prospective observational study, sixty patients with MDR-TB who were to be started on aminoglycosides underwent pure tone audiometry testing before starting the drug and every 3 months further on for a total of three follow up visits. The patients were grouped on the drug received (Amikacin, Kanamycin or Capreomycin). The results were tabulated and presented graphically.

Results: Of the 60 patients, 16 (26.67%) patients developed sensorineural hearing loss in the higher frequencies. Furthermore, 3 patients among these developed hearing loss in the speech frequencies too. Hearing loss was seen in 26.08%, 30% and 25% in the Amikacin, Kanamycin and Capreomycin groups respectively. None of the patients who developed sensorineural hearing loss showed any improvement of hearing thresholds after stoppage of the drugs indicating permanent damage.

Discussion: The current study highlights that hearing loss due to aminoglycosides occurs in the higher frequencies and also the speech frequencies in some patients leading to a permanent disability. Audiological management of these patients should therefore be an essential part of their therapeutic treatment plan, to minimize the disabling effect of hearing loss.

Keywords: Hearing Loss, Multi-Drug Resistant Tuberculosis, Aminoglycosides, Audiology, Otorhinolaryngology, Drug Resistance, Ototoxicity.

Introduction

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* that spreads from person to person via droplet infection [1]. India has been engaged in Tuberculosis control activities for many years, yet TB continues to be India's severe health crisis.

Multidrug-resistant tuberculosis (MDR-TB) is a serious form of the disease. Drug resistance is the temporary or permanent ability of an organism to remain viable or to multiply in the presence of the concentration of a drug which would normally inhibit or destroy its growth [1]. Emergence of resistance to anti-tuberculosis drugs has become an obstacle to effective TB control [2] Multidrug-resistant tuberculosis (MDR-TB) is resistant to both Isoniazid and Rifampicin. Inadequate and incomplete treatment are the main causes leading to development of MDR-TB [3].

MDR-TB is often treated with injectable aminoglycosides group of drugs such as amikacin, kanamycin or capreomycin. The treatment of MDR-TB requires long duration of administration of these drugs [2]. The reason aminoglycosides are still being widely used is because of their lower cost and their broad anti-microbial spectrum [1]. However, the negative effects of long-term administration of the aminoglycosides include nephrotoxicity and ototoxicity [4] which affects adherence to treatment and finally it's outcome. Encouragingly, newer drugs to treat MDR-TB are now accepted. Bedaquiline and delamanid, and repurposed drugs such as linezolid and clofazimine [5] are now recommended and can be used as effective alternatives to aminoglycoside drugs. However, sufficient access to these drugs is a challenge in developing countries.

Drug induced ototoxicity refers to damage to the inner ear and its functions (hearing and balance) following exposure to specific medications [6] leading to sensorineural hearing loss (SNHL) [1]. These drugs pass through the blood-labyrinth barrier and enter the inner ear through the stria vascularis. They further enter the sensory hair cells via mechano-electrical transduction (MET) channels [7] where they form highly reactive free radicals that damage these hair cells, irreversibly [8].

The N-methyl-D-aspartate (NMDA) is a glutamate receptor, which is present at the synaptic site between cochlear hair cells and the dendrites of spiral ganglion afferents. Aminoglycosides mimic the effects of polyamines on these NMDA receptors. The overstimulation of NMDA receptors leads to increase in the formation of nitric oxide (NO), which leads to increased oxidative stress on hair cells leading to cell damage [9].

Furthermore, increased susceptibility to aminoglycoside ototoxicity is now linked to several mutations in mitochondrial DNA. Exposure to aminoglycosides leads to impairment of RNA translation within mitochondria [10].

This hair cell loss progresses from the basal to the apical region of the cochlea; starting from the outer hair cells to the inner hair cells and then to the supporting cells and spiral ganglion cells [11]. Thus, aminoglycoside induced hearing loss starts at the higher, often inaudible, frequencies and further progresses to the lower frequencies which are more associated with communication [2]. The hearing loss is reported to be bilaterally symmetrical and gradual in onset [12]. The emergence of ototoxicity in a patient can lead to either discontinuation or change of the regime which may hamper treatment and its outcome [13].

Sequential ototoxicity monitoring can help with the following [14].

1. Comparison of the auditory faculties of the patient during therapy,
2. Early identification of hearing loss,
3. Prevention of debilitating hearing loss,

4. Auditory rehabilitation to reduce the social impact of ototoxicity.

The American Speech-Language-Hearing Association (ASHA)'s [15] "Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy (1994)" says that the baseline audiometric test should be done within 72 hours of administering aminoglycoside antibiotics. There should be a comprehensive case history including any otologic disorders, noise exposure, co-morbid conditions, family history of ear disorders or hearing loss and prior usage of ototoxic medication by the patient. Patient should be then called for follow up testing to identify any change in hearing. Additionally, testing is to be continued for up to 3 or 6 months or even longer after stoppage of therapy [16] As per ASHA [15] Significant ototoxic change must meet one of the following three criteria: ≥20 dB decrease in pure tone thresholds at any test frequency or ≥10 dB decrease at two adjacent frequencies or decreased response at three consecutive test frequencies where responses were previously obtained. These changes in hearing thresholds can be identified on follow up audiograms done during the course of treatment and also after stoppage of the ototoxic drugs.

Since hearing impairments have negative impact on psychosocial wellbeing and communication abilities, it is of extreme importance to implement the various hearing loss monitoring measures [17]. Hence the present study was done at our tertiary care center to study the complication of sensorineural hearing loss in patients receiving injectable Anti-Tuberculosis treatment.

Materials and Methods

This hospital based prospective observational study was done in the outpatient department in a tertiary care government hospital in a major metropolitan centre from June 2021 to December 2022.

It was conducted on a total of 60 adult male and female patients who were diagnosed with MDR -TB and were being started on the injectable aminoglycoside drugs of either amikacin, kanamycin or capreomycin as a part of their MDR-TB regimen. Permission to conduct study and ethical clearance was obtained from the institutional ethical clearance committee. The treatment was along the lines of standard recommended protocols of weight banded dosage of drugs with a daily intramuscular dose. The choice of aminoglycoside to be added to the patient regimen was based on various factors like drug sensitivity, availability of drug in the government setup, cost of the treatment etc.

The patients were called for a total of four visits and pure tone audiometry was conducted at each visit. Baseline (Pre-treatment) pure tone audiometry was performed on Visit 1 before starting the drugs and three follow up visits were done at three-monthly intervals. Written informed consents of all patients were obtained.

Otorhinolaryngologic examination was done at the time of patient enrolment as well as on each follow-up visit. Data was recorded on patient sheets including the baseline and follow-up audiogram outcomes. Patients with any hearing loss prior to starting of the aminoglycosides (based on history, clinical assessment or audiological examination) or those with a past history of exposure to any drugs known to cause hearing loss were excluded from this study.

Furthermore, patients for whom aminoglycosides were prematurely discontinued for any reason other than hearing loss or completion of treatment were also excluded from the study. Pure Tone audiometry was done in a sound treated room and both air-conduction and bone-conduction

hearing thresholds at frequencies between 250Hz and 8000Hz were documented.

All the pure tone threshold shifts were recorded at each frequency tested with reference to the baseline pure tone threshold at the same frequency. ASHA's criteria [15] was utilised for determining ototoxic threshold shift in comparison to the baseline audiogram.

Based on the drug started, the enrolled patients were divided into three groups- Group I consisted of patients receiving Amikacin, Group II were those receiving Kanamycin and finally Group III had those patients receiving Capreomycin. After each audiogram, the findings were considered as follows- 'Normal' (N) defined by patients with pure tone audiograms showing air-conduction thresholds up to 20 ± 5 dB at all the tested frequencies from 250 Hz to 8000 Hz with an air-bone gap of <10 dB. 'High frequency loss' (HFL) defined by ASHA's criteria [15] for ototoxic threshold shift. 'Flat' (FLAT) when along with HFL, ASHA's criteria were also fulfilled in the frequencies below 4000 Hz.

Data was coded and entered in Microsoft Excel 2019 and analysed using appropriate

statistical methods in SPSS version 25.

Any patient on treatment showing hearing loss was immediately referred to the treating physician for any change in regimen. Furthermore, these patients were counselled and advised about hearing care and rehabilitation.

Results

All the patients in this study were in the age group of 18 to 65 years with 36 (60%) male patients and 24 (40%) female patients (Chart 1). Out of the 60 patients, 7 (11.6%) patients were in the age group of 18-25 years, 12 (20%) patients were in the age group of 26-35 years, 26 (43.40%) patients were in the age group of 36-45 years and 15 (25%) patients were in the age group 46-65 years. (Chart 2)

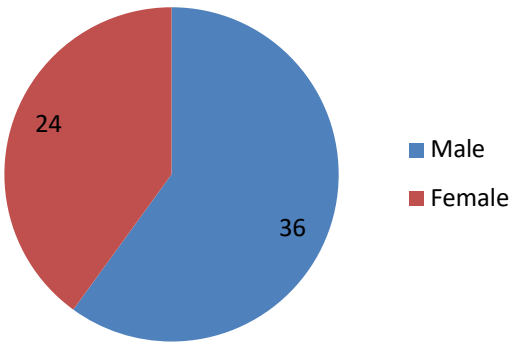

Chart 1: Gender

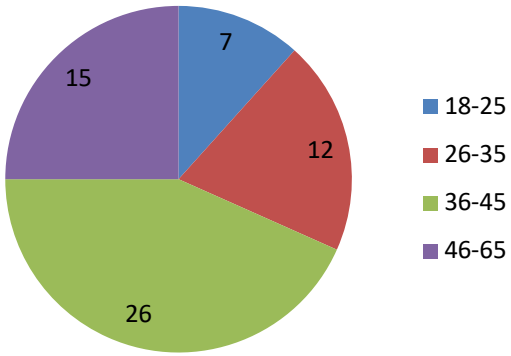

Chart 2: Age group (years)

Of the 60 patients in the study, 46 (76.67%) patients were on Amikacin (Group I), 10 (16.67%) patients were on Kanamycin (Group II) and 4 (6.67%) patients were on Capreomycin (Group III). (Chart 3)

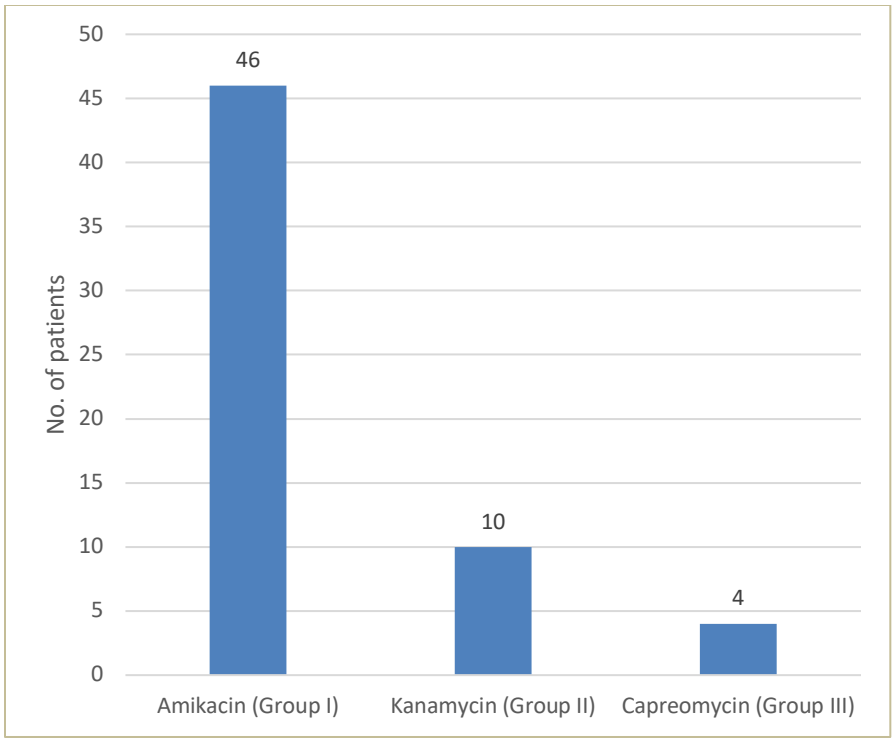

Chart 3: Distribution of patients according to Drug used

Overall sensorineural hearing loss was seen in 16 (26.67%, n=60) patients and all these patients had HFL. FLAT loss was seen in 3 (5%, n=60) of the patients who developed sensorineural hearing loss. The hearing loss was found to be bilateral and symmetrical in involvement. 44 (73.33%, n=60) patients showed normal thresholds (N) during all visits. (Chart 4)

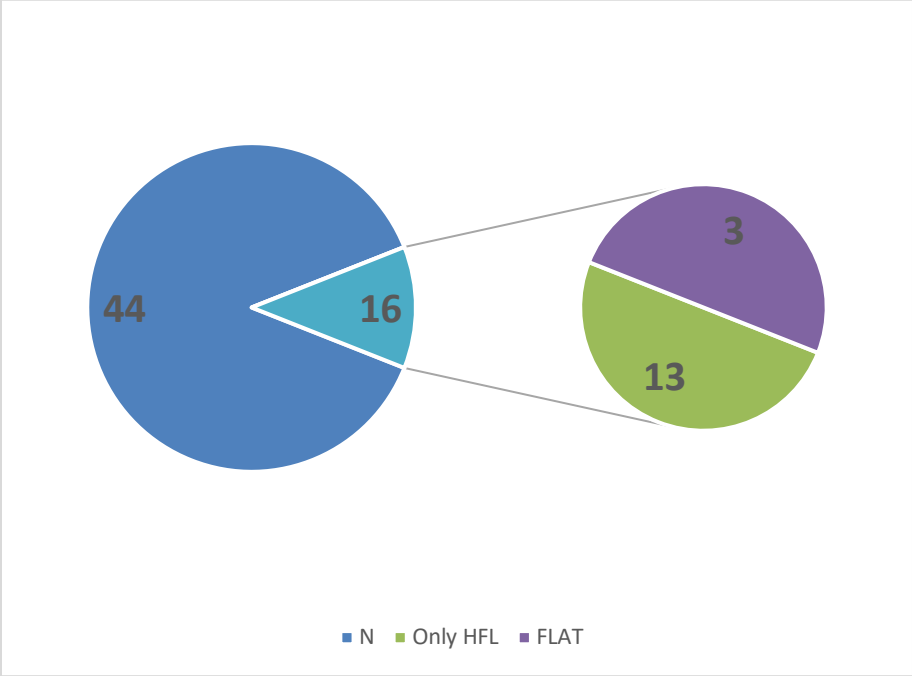

Chart 4: Hearing Loss

Gender wise, 9 male patients (25%, n=36) and 7 female patients (29%, n=24) showed sensorineural hearing loss. (Chart 5)

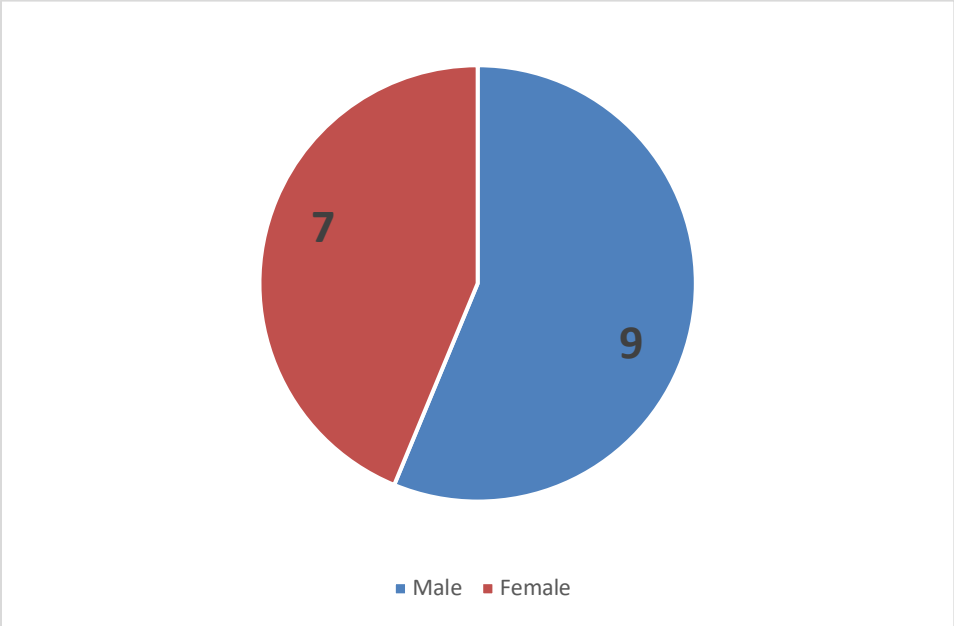

Chart 5: SNHL (Gender wise)

Age wise, the age groups of 18-25 years and 26-35 years each had 3 patients who developed HFL (42.85%, n=7 and 25%, n=12 respectively) with 0 patients showing FLAT. In the age group of 36-45 years, 6 (23.07%, n=26) patients developed HFL and 2 (7.69%, n=26) patients from these had FLAT hearing loss. In the age group of 46-65 years, 4 (26.66%, n=15) patients developed HFL and 1 (6.66%, n=15) patient from these had FLAT hearing loss. (Chart 6)

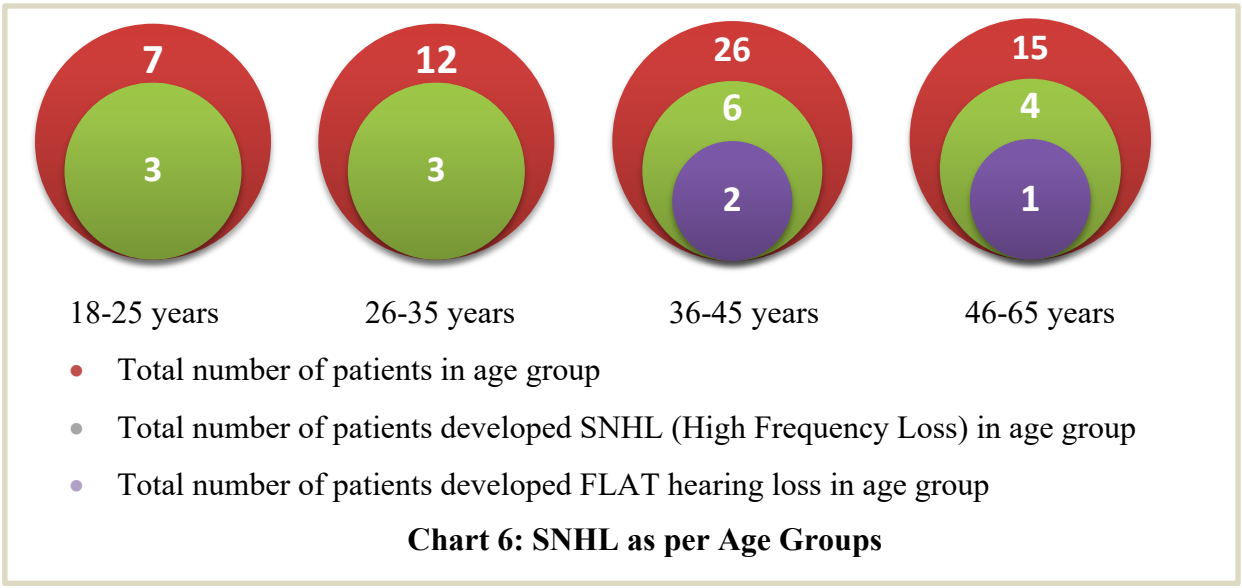

Chart 6: SNHL as per Age Groups

All patients had normal hearing thresholds at Visit 1. Patients were consequently started on the aminoglycoside regimen and were called for follow up after 3 months for Visit 2. At Visit 2, 5 (8.33%) patients showed HFL. Out of these, 4 (6.66%) patients belonged to Group I (Amikacin) and 1 (1.6%) patient belonged to Group II (Kanamycin). None of the patients who developed hearing loss at Visit 2 showed FLAT hearing loss. No patient from Group III (Capreomycin) showed hearing loss at Visit 2.

At Visit 3, 11 (18.33%) patients showed newly developed HFL with 3 patients from these showing FLAT hearing loss. Out of these 11 patients, 8 (13.33%) patients belonged to Group I (with 2 patients having FLAT), 2 (3.33%) patients belonged to Group II (with 1 patient having FLAT) and 1 (1.6%) patient belonged to Group III.

At Visit 4, 0 patients showed any new onset SNHL. Additionally, none of the patients with SHNL showed any improvement or recovery in their hearing thresholds. All patients who showed hearing loss on follow up visits were referred to the treating physician and were put on a new regimen for their MDR-TB treatment with discontinuation of aminoglycosides. None of the patients showed any worsening of hearing thresholds after stoppage of the drugs.

Table 1: Group wise development of hearing loss.

	Visit 2-(3 months)		**Visit 3-(6 months)**		**Visit 4-(9 months)**	
	HFL	FLAT	HFL	FLAT	HFL	FLAT
Group I (Amikacin)	4	0	8	2	0	0
Group II (Kanamycin)	1	0	2	1	0	0
Group III (Capreomycin)	0	0	1	0	0	0

Chart 7 shows the number of patients showing SNHL (HFL & FLAT) on the follow up visits.

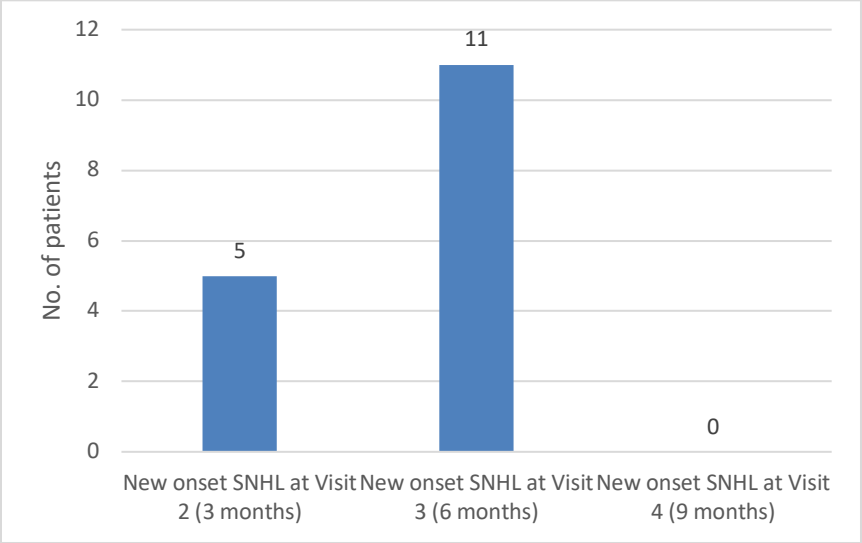

Chart 7: Distribution of cases newly developed SNHL as per Visits

In Group I (Amikacin), 12 (26.08%, n=46) patients developed HFL. 2 patients from this group showed FLAT hearing loss at Visit 3 (6 months). (Chart 8) One patient from these was a 38-year-old male while the other was a 37-year-old female patient. Both patients gave a history of hearing

loss on Visit 3. In Group I (Amikacin), age wise mean hearing loss was found to be 50dB, 55dB, 65dB and 55dB in the age groups of 18-25, 26-35, 36-45 and 45-65 years respectively. (Chart 9)

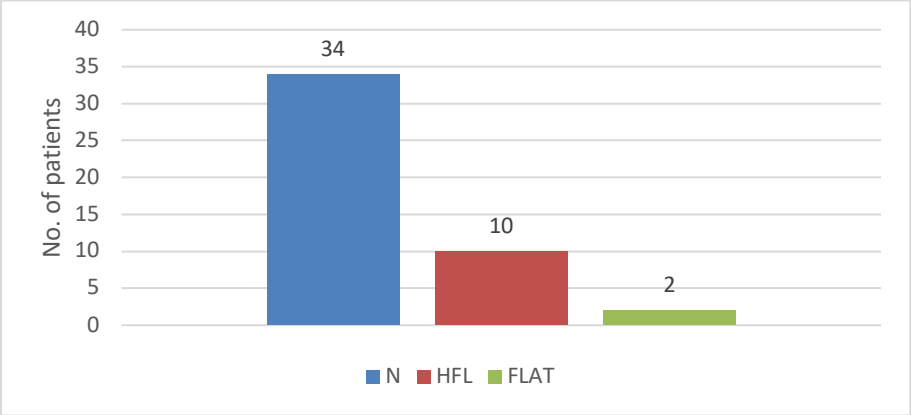

Chart 8: Group I (Amikacin)

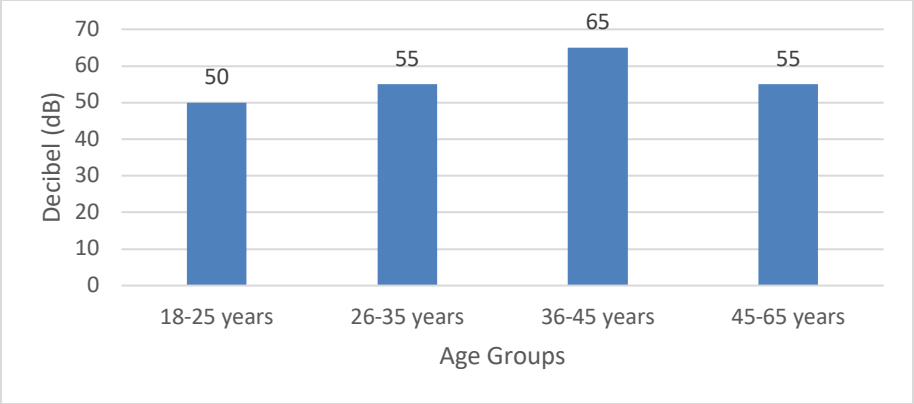

Chart 9: Mean hearing loss in Group I (Amikacin)

In Group II (Kanamycin), 3 (30%, n=10) patients developed HFL. 1 patient (55-year-old, male) from this group showed FLAT (Chart 10). The patient complained of hearing loss at Visit 3 (6 months) with the concurrent audiogram showing a FLAT hearing loss. In Group II (Kanamycin), age wise mean hearing loss was found to be 45dB, 55dB and 65dB in the age groups of 18-25, 36-45 and 45-65 years respectively. None of the patients developed hearing loss in the ages 26-35 years in Group II. (Chart 11)

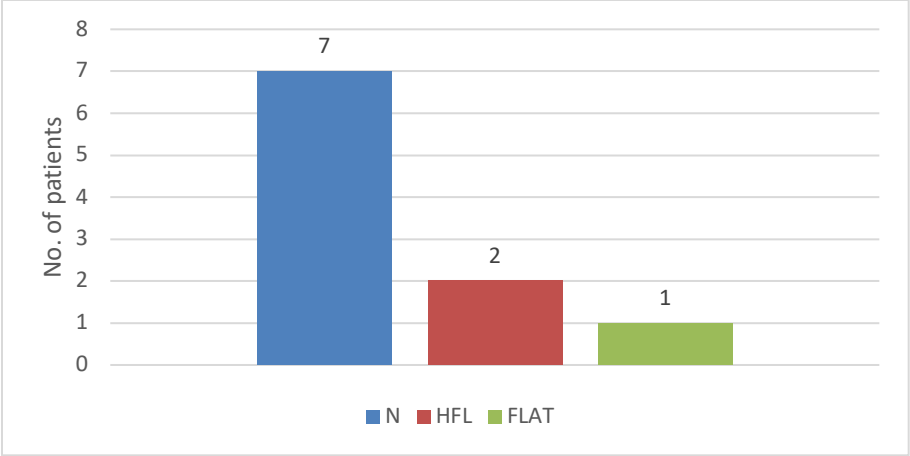

Chart 10: Group II (Kanamycin)

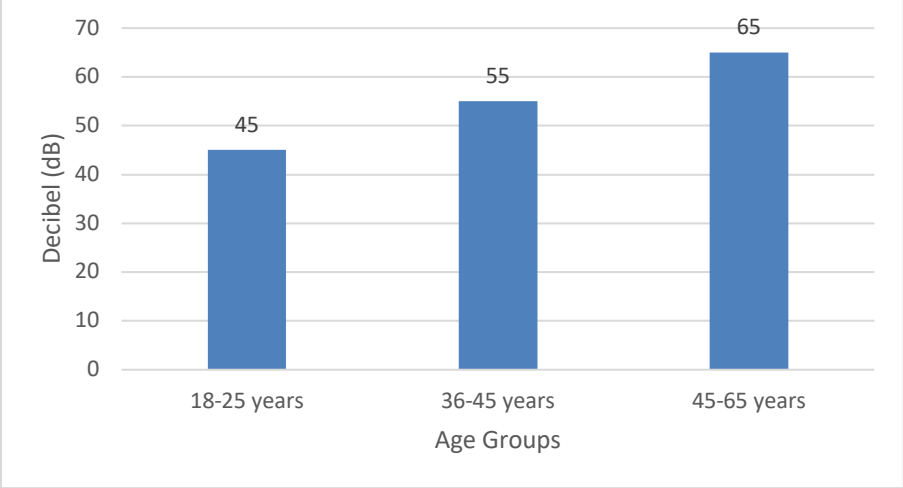

Chart 11: Mean hearing loss in Group II (Kanamycin)

In Group III (Capreomycin), 1 (25%, n=4) patient, a 32-year-old female, developed HFL on visit 3 (6 months). None of the patient on injection Capreomycin developed FLAT hearing loss (Chart 12). The mean hearing loss seen in this group was of 40 dB. The authors recommend studies with larger number of patients receiving Capreomycin. However, the same could not be achieved in the current study due to the higher cost of capreomycin and the limited availability of the same in the current setting of the study.

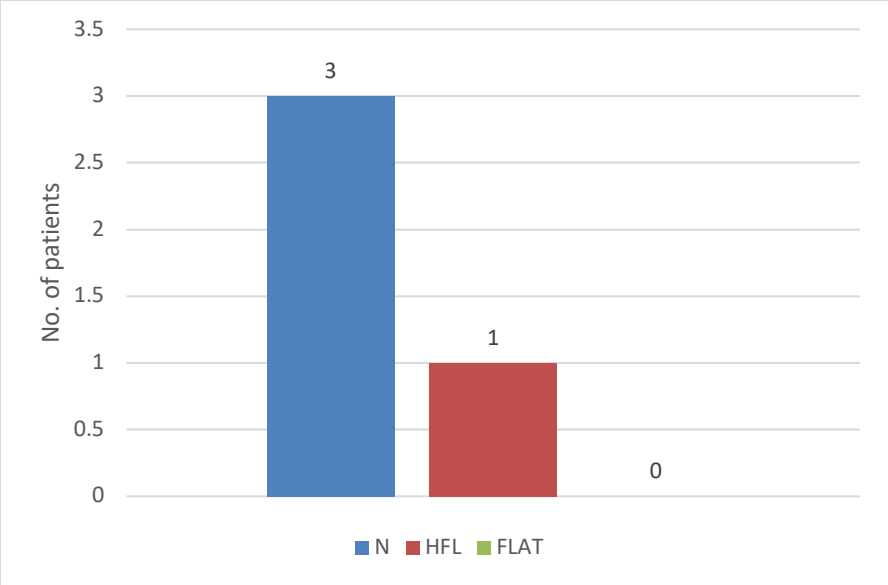

Chart 12: Group III (Capreomycin)

Table 2: Simplified group wise distribution of hearing loss.

Drug	Total patients in group	Patients in group developed SNHL	Percentage of patients in group that developed SNHL
Group I (Amikacin)	46	12	26.08%
Group II (Kanamycin)	10	3	30%
Group III (Capreomycin)	4	1	25%

Discussion

Multi-drug resistant tuberculosis is a major burden in the world [1] owing to its morbidity and the need for long term treatment which raises the importance of adherence to treatment [2]. The need for combination chemotherapy arises in tuberculosis due to the high chances of development of drug resistance on mono-therapy [2]. Aminoglycosides thus come into the picture due to their broad antimicrobial spectrum and low cost [1]. However, the adverse effect of ototoxicity and nephrotoxicity due to aminoglycoside use becomes a major concern [18]. The present observational study was done at our tertiary care centre on 60 patients to study the ototoxic complication of sensorineural hearing loss in MDR-TB patients receiving injectable Anti-Tuberculosis treatment.

Adult patients to be started on injectable aminoglycosides (amikacin, kanamycin or capreomycin) were enrolled in the study. None of the patients had any hearing loss at the time of enrolment (evidenced by Baseline pure tone audiogram) and the patients were called for three more follow up audiograms after every 3 months.

Sensorineural hearing loss was seen in 26.67% of patients. Out of these around 21.66% patients developed high frequency hearing loss (HFL) involving the frequencies of 4,000 Hz and above. 5% patients also developed both high and low frequency hearing loss (FLAT) which included the frequencies of speech and communication causing these patients to concurrently have the subjective complaint of difficulty in hearing. The patients having hearing loss

documented by audiogram were referred to the treating physician and as per protocol their treatment regimen was changed and aminoglycosides were discontinued [2].

On follow up audiograms, none of the patients had any recovery in their hearing thresholds which signifies the permanent and irreversible damage caused by aminoglycosides to the hair cells. No patients showed any sensorineural hearing loss on stoppage of aminoglycoside on follow up audiograms. These findings were concurred by other similar studies [2-19].

Among the patients receiving injectable Amikacin, 26.08% developed hearing loss while 30% of patients receiving injection Kanamycin developed hearing loss. Our study included four patients receiving injection Capreomycin as a part of their MDR-TB regimen out of which only one patient (25%) developed hearing loss. Similar findings were seen in other studies that were done in MDR-TB patients [20,21].

The current observational study shows that the ototoxic effect of aminoglycosides first occurs in the higher frequencies. Ultra-high frequency audiometric tests can therefore be of great value in the ototoxic monitoring of these patients. The same could not be done in this study in our government setup due to the cost of testing. Similarly sequential serum aminoglycoside monitoring [2] and dose titration can play an important role in preventing the ototoxic as well as nephrotoxic effect of these drugs; however, this increases the cost of treatment in these patients.

The current study shows the ototoxic effect of aminoglycosides used in treatment of MDR-TB which highlights that hearing loss not only occurs in the higher frequencies but can also affect the speech frequencies in some patients leading to a permanent disability. This varies from individual to individual but early intervention is important if hearing loss is detected.

Hearing impairment imposes negative impact on psychosocial and communication wellbeing of a person; various actions such as audiological monitoring and early intervention is crucial.

Audiological management of these patients should therefore be an essential part of their therapeutic treatment plan, to minimize the psychosocial disabling effect of hearing loss that they suffer just because of their willingness to get treated.

Once SNHL had developed, there was no recovery of hearing loss on follow up visits. This highlights the role of an otologist and audiologist in the treatment of MDR-TB. It also emphasizes the need for ramping up the availability of alternative drugs like bedaquiline and delamanid or for the use of otoprotective agents for the treatment of MDR-TB.

Acknowledgements

We gratefully acknowledge the audiology department of our institute for their assistance during this study. We extend our thanks to all the enrolled patients without whom this prospective study would not have been possible. The authors of this study declare no conflict of interest.

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