Research Article ISSN 2771-9057

Recent Advances in Clinical Trials

Comparison of Hearing Thresholds among Patients on Treatment for Drug-Resistant Versus Drug-Susceptible Pulmonary Tuberculosis in A Sub-Saharan African Healthcare Setting

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Received: 18 Jan 2023; **Accepted:** 27 Feb 2023; **Published:** 03 Mar 2023

Citation: Nduagu SU, Onyeagwara NC, Ogisi FO, et al. Comparison of Hearing Thresholds among Patients on Treatment for Drug-Resistant Versus Drug-Susceptible Pulmonary Tuberculosis in A Sub-Saharan African Healthcare Setting. Recent Adv Clin Trials. 2023; 3(1); 1-5.

ABSTRACT

Background: *Pulmonary tuberculosis is a debilitating infectious disease that affects all age groups and sadly, a leading cause of death in developing countries particularly in sub-Saharan Africa. One major challenge facing the global efforts against tuberculosis is drug-resistance, which necessitates the use of aminoglycoside-based second line drugs that are known to have ototoxic potentials. Hearing impairment can be a source of social distress, professional disability and in some cases, litigation. This research compared the pure tone audiometric patterns of patients on treatment for drug-resistant versus drug-susceptible pulmonary tuberculosis. The incidence of hearing loss between the groups was assessed.*

Patients and Method: *The research was a prospective comparative study of all eligible newly diagnosed pulmonary tuberculosis patients admitted into the Pulmonology unit of Federal Medical Centre, Owerri, Nigeria. Pre-treatment (baseline) and monthly pure tone audiometry was done for each patient before and during treatment respectively. The patients were followed up and assessed for three months. Data collected was analyzed with Statistical Package for Social Sciences (SPSS) version 20.0 software for Windows. Statistical significance was set at $p< 0.05$.*

Results: *A total of 76 patients (38 in each group) completed the study. The M:F ratio was 1.53:1 and 1.24:1 for the drug resistant and drug susceptible groups respectively while the mean duration of presenting symptoms were 11.7 ± 7.8 and 7.4 ± 5.1 weeks for the groups respectively. The prevalence of baseline hearing impairment was 73.7% among both groups while by the third month it was 89.5% among the dug-resistant group and 78.9% among the drug-susceptible group implying a cumulative incidence of hearing loss of 15.8% and 5.3% respectively over three months. This difference was statistically significant.*

Conclusion: *The incidence of hearing impairment among patients on treatment for drug-resistant pulmonary tuberculosis was approximately three-fold higher than their drug susceptible counterparts after three months of treatment; this was statistically significant.*

Keywords

Drug-resistant, Drug-susceptible, Tuberculosis, Audiometry, Impairment.

Introduction

Pulmonary tuberculosis (PTB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*. The disease is thought

to have been in existence for several centuries as suggested by palaemicrobiological studies on human and animal skeletons, thousands of years old [1]. It is a disease of public health concern and a major cause of death globally. It is also widely associated with low socioeconomic status therefore commoner in developing countries [1,2]. Tuberculosis is the first infectious disease to be declared a global health emergency by the World Health Organization (WHO) [1]. The WHO revealed in 2015 that there were about 10.4 million new tuberculosis cases worldwide and six countries accounted for 60% of this global burden, Nigeria ranking fourth after only India, Indonesia and China [3]. Nigeria, a sub-Saharan African country, has a relatively high tuberculosis burden with 586,000 sufferers in 2015; 29,000 of them being drug-resistant cases [4]. Tuberculosis is said to be drug-resistant when resistance develops to one or more conventional anti-tuberculosis drugs. Multi-drug resistant tuberculosis (MDR-TB) is a form of the disease in which the mycobacterium strain is resistant to at least rifampicin and isoniazid [5] The treatment of drug-resistant tuberculosis requires the use of second-line anti-tuberculosis drugs among which are aminoglycosides such as Kanamycin, Amikacin and Capreomycin that have ototoxic potentials [6,7]. Hearing impairment developed while on treatment with aminoglycosides can be a source of social disability, leading to poor drug compliance and sometimes litigation [8] with the magnitude of this problem it is safe practice for treatment facilities to adopt a policy of pre-treatment and periodic testing with documentation of the hearing status of their patients. This will aid early identification of ototoxic hearing impairment.

Our study set out to assess the hearing patterns of patients on treatment for pulmonary tuberculosis in our sub-Saharan African setting, aiming to ascertain if there are differences between the pure tone audiometric patterns of patients on treatment for drug-resistant and drug-susceptible tuberculosis.

Patients and Method

The research was a prospective comparative study carried out in Federal Medical Centre (FMC) Owerri, Nigeria, sub-Saharan Africa over an eighteen (18) month period (April 2019 to September 2020). All consecutive newly diagnosed pulmonary tuberculosis patients were recruited into the study and classified into drug-resistant and drug-susceptible groups using the GeneXpert test. Excluded patients include those on treatment for other medical conditions with potentially ototoxic drugs as well as those too ill, or unable to comply appropriately with pure tone audiometry and those who declined consent. Two (2) patients in the drug-susceptible group whom in the course of the study became drug-resistant were removed from the study. Thirty-eight (38) patients completed the study in each group making a total of seventy-six (76) participants.

Patients in the drug-resistant group received weight-appropriate doses of Kanamycin (Km) or Capreomycin (Cm). Either was combined with Moxifloxacin (Mfx), Clofazimine (Cfz), Prothionamide (Pto), Pyrazinamide (Z), Ethambutol (E) and high dose Isoniazid (H^h). The seven (7) drugs were given together daily for 4 months (intensive phase) and thereafter only Moxifloxacin, Clofazimine, Ethambutol and Pyrizinamide were given for 16 months (continuation phase). Kanamycin was commenced in patients with normal pure tone audiometric results whereas; Capreomycin was commenced in those who had abnormal audiometry.

Patients in the drug-susceptible group received Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E). These four (4) drugs were given together daily for 2 months (intensive phase) and thereafter only Isoniazid and Rifampicin were given for 4 months (continuation phase).

Baseline pure tone audiometry was performed for each recruited patient before commencement of treatment and repeated monthly for a total of three months while on treatment. The criterion for identification of significant changes in hearing was the ASHA 1994 criteria [9]. Data was analyzed using the IBM Statistical Package for Social Sciences (IBM SPSS) version 20.0 software for Windows. Statistical significance was set at $p < 0.05$.

Patient participation was voluntary and documented ethical approval was obtained from the Ethical Clearance Committee (ECC) of Federal Medical Centre, Owerri, Nigeria.

Results

Table 1: Gender and age distribution of study participants.

Age (years)	Drug resistant group				Drug sensitive group			
	Male	*Female*	*Total (%)*	*p-value*	Male	Female	Total (%)	*p*-value
Nov-20	1	0	1 (2.6)	0.153	0	0	0 (0.0)	0.466
21-30	2	3	5 (13.2)		3	5	8 (21.1)	
31-40	4	1	5 (13.2)		5	6	11 (28.9)	
41-50	9	3	12 (31.6)		7	3	10 (26.3)	
51-60	1	6	7 (18.4)		4	1	5 (13.2)	
61-70	2	1	3 (7.9)		1	1	2 (5.3)	
71-80	3	1	4 (10.5)		0	1	1 (2.6)	
>80	1	0	1 (2.6)		1	0	1 (2.6)	
Total	**23**	**15**	**38 (100.0)**		**21**	**17**	**38 (100.0)**	
	M:F ratio = 1.53:1					**M:F ratio = 1.24:1**		

Table 2: Clinical profile of study participants.

Clinical parameters	Drug resistant group			Drug sensitive group		
	Category	n (%)	*p*-value	Category	n (%)	*p*-value
Prior TB treatment	Yes	15 (39.5)	0.192	Yes	0 (0.0)	<0.001
	No	23 (60.5)		No	38 (100.0)	
Family history of hearing impairment	Yes	8 (21.1)	0.183	Yes	6 (15.8)	0.237
	No	30 (78.9)		No	32 (84.2)	
Presence of co-morbidity	Yes	15 (39.5)	0.957	Yes	10 (26.3)	0.739
	No	23 (60.5)		No	28 (73.7)	
HIV status	Negative	31 (81.6)	0.630	Negative	32 (84.2)	0.570
	Positive	7 (18.4)		Positive	6 (15.8)	
Medication administered	Kanamycin	19 (50.0)	0.319	*PIRE	38 (100.0)	
	Capreomycin	19 (50.0)				
Comparison of Means	Drug-resistant group mean		Drug susceptible group mean			*p*-value
Duration of complaints prior to presentation (weeks)	7.4 ± 5.1		11.7 ± 7.8		0.006	
Age of subjects (years)	43.2 ± 14.1		48.3 ± 16.1		0.146	
*PIRE = Pyrazinamide, Isoniazid, Rifampicin and Ethambutol.						

Table 3: Prevalence of hearing impairments among study participants.

	Drug-resistant group			Drug-susceptible group		
	Normal	Abnormal	Total	Normal	Abnormal	Total
Baseline	10 (26.3)	28 (73.7)	38 (100.0)	10 (26.3)	28 (73.7)	38 (100.0)
Cumulative incidence over 1 month		4 (10.5)			0 (0.0)	
First month	6 (15.8)	32 (84.2)	38 (100.0)	10 (26.3)	28 (73.7)	38 (100.0)
Cumulative incidence over 2 months		4 (10.5)			2 (5.3)	
Second month	6 (15.8)	32 (84.2)	38 (100.0)	8 (21.1)	30 (78.9)	38 (100.0)
Cumulative incidence over 3 months		6 (15.8)			2 (5.3)	
Third month	4 (10.5)	34 (89.5)	38 (100.0)	8 (21.1)	30 (78.9)	38 (100.0)
'Abnormal' denotes number of patients with hearing threshold worse than 25dB in at least one ear. Cumulative incidence ratio (third month): DR/DS = 2.98.						

Table 4: Comparison of mean pure tone threshold averages (PTA) between study groups.

	AIR CONDUCTION						*BONE CONDUCTION*					
	RIGHT			LEFT			RIGHT			LEFT		
BASELINE		Mean	*p-value*		Mean	*p-value*		Mean	*p-value*		Mean	*p-value*
*DR vs DS	DR	32.6 ± 8.4	0.274	DR	32.9 ± 8.0	0.342	DR	25.7 ± 8.2	0.515	DR	27.2 ± 7.8	0.628
	DS	34.7 ± 8.2		DS	34.7 ± 8.4		DS	26.7 ± 7.8		DS	26.2 ± 8.3	
FIRST MONTH												
*DR vs DS	DR	38.3 ± 13.8	0.361	DR	39.4 ± 14.2	0.115	DR	31.2 ± 12.3	0.17	DR	32.1 ± 14.2	0.099
	DS	35.9 ± 8.3		DS	35.1 ± 8.6		DS	27.9 ± 8.0		DS	27.6 ± 8.6	
SECOND MONTH												
*DR vs DS	DR	43.6 ± 15.7	0.025	DR	46.0 ± 17.0	0.003	DR	35.2 ± 14.1	0.023	DR	38.3 ± 14.6	0.002
	DS	36.9 ± 8.8		DS	36.4 ± 9.2		DS	29.0 ± 8.4		DS	29.7 ± 8.5	
THIRD MONTH												
*DR vs DS	DR	49.8 ± 17.9	<0.001	DR	50.8 ± 19.1	<0.001	DR	42.9 ± 16.9	<0.001	DR	43.4 ± 17.2	<0.001
	DS	37.9 ± 9.5		DS	39.1 ± 7.2		DS	30.4 ± 8.6		DS	31,1 ± 8.6	
DR=Drug resistant group. DS=Drug susceptible group.												
*p-*value derived using Student's T test.*												

Table 5: Comparison of mean pure tone averages between study groups.

Study group		AIR CONDUCTION			BONE CONDUCTION		
		Means to compare	Mean PTA* values	*p*-value	Means to compare	Mean PTA* values	*p*-value
Drug resistant	Right	Baseline PTA	32.6 ± 8.4	<0.001	Baseline PTA	25.7 ± 8.2	<0.001
		Third month PTA	49.8 ± 17.9		Third month PTA	42.9 ± 16.9	
	Left	Baseline PTA	32.9 ± 8.0	<0.001	Baseline PTA	27.2 ± 7.8	<0.001
		Third month PTA	50.8 ± 19.1		Third month PTA	43.4 ± 17.2	
Drug sensitive	Right	Baseline PTA	34.7 ± 8.2	0.120	Baseline PTA	26.7 ± 7.8	0.084
		Third month PTA	37.9 ± 9.5		Third month PTA	30.4 ± 8.6	
	Left	Baseline PTA	34.7 ± 8.4	0.347	Baseline PTA	26.2 ± 8.3	0.139
		Third month PTA	39.1 ± 7.2		Third month PTA	31.1 ± 8.6	
PTA* = Pure tone average.							

Table 6: Comparison of hearing levels between 'drug resistant' versus 'drug susceptible' groups.

	AIR CONDUCTION						BONE CONDUCTION					
	BASELINE			THIRD MONTH			BASELINE			THIRD MONTH		
RIGHT	DR	DS	*p*-value	DR	DS	*p*-value	DR	DS	*p*-value	DR	DS	*p*-value
NORMAL	10	10	>0.999	4	7	0.005	20	16	0.269	9	11	0.003
MILD	22	22		12	17		17	19		12	23	
MODERATE	6	6		11	14		1	3		13	4	
SEVERE	0	0		8	0		0	0		4	0	
PROFOUND	0	0		3	0		0	0		0	0	
LEFT												
NORMAL	10	9	0.791	4	8	0.003	19	15	0.277	8	13	0.002
MILD	21	20		11	17		18	20		10	21	
MODERATE	7	9		10	13		1	3		13	4	
SEVERE	0	0		11	0		0	0		7	0	
PROFOUND	0	0		0	0		0	0		0	0	

Key: DR=Drug resistant group. DS=Drug sensitive group

Discussion

The male-to-female (M:F) ratios in this study were 1.53:1 and 1.24:1 for the drug resistant and drug susceptible groups respectively. There was no statistically significant difference in gender between the two groups. These ratios are similar to those of similar studies by Sogebi et al. [10], Ibekwe et al. [11], Ramma and Ibekwe [12] and Vasconcelos et al. [13].

The mean duration of presenting complaints of the subjects was 11.7 ± 7.8 and 7.4 ± 5.1 weeks for the drug-resistant and drug-susceptible groups respectively. The difference in duration of presenting clinical symptoms between both groups was statistically significant ($p = 0.03$). The relatively longer mean duration for the drug-resistant group is presumably due to the apparently more chronic nature of this variant of the disease, as well as possibility of failed initial therapy before drug resistance was confirmed. Noteworthy, 39.5% of patients in the drug-resistant group had some form of prior first line treatment before presentation and enrollment at our centre to commence second line treatment. This figure was as high as 94.7% in the study by Sogebi et al. [10].

The prevalence of HIV positivity in this study was 18.4% among the drug-resistant group and 15.8% among the drug-susceptible group ($p = 0.113$). These proportions are relatively comparable to that found by Sogebi et al. [10] in Southwest Nigeria (13.6%) and by Akpaka et al. [14] in Jamaica (11.6%) but much lower than the proportion noted by Sagwa et al. [15] in Namibia (46.9%). These differences may be due to the variation in HIV prevalence among the different populations.

The baseline prevalence of hearing impairment was 73.7% in both groups. This relatively high figure represented patients with conductive pure tone audiometric thresholds above 25dB in at least one ear (using the WHO classification of hearing of 2008) [16]. This did not necessarily translate to disabling hearing impairment as only eight (8) subjects (21.1%) in the drug-resistant group and six (6) subjects (15.8%) self-reported hearing difficulty at the start of the study. By the third month of follow up, the prevalence were 89.5% and 78.9% for the drug-resistant and drug-susceptible groups respectively, which was statistically significant. These figures imply cumulative incidence of hearing impairment of 15.8% and 5.3% respectively over three months. In effect, the cumulative incidence ratio between the drug-resistant and drug-susceptible groups was 2.98 implying a 3-fold difference, which was statistically significant. Sogebi et al., also working in sub-Saharan setting, found comparable prevalence (78.8%) of abnormal hearing among the 132 drug-resistant patients, albeit within 2 weeks of commencement of second line drugs for tuberculosis [10]. In contrast, slightly lower prevalence (61%) was found by Ibekwe and Nwosu in Port Harcourt, Nigeria after 3 months of treatment with second line drugs although majority of their patients (94%) had bilateral sensorineural hearing loss [11]. They also reported a significantly higher cumulative incidence of hearing impairment (43.0%) after 3 months. Vasconcelos et al. in Brazil also noted statistically significant difference in hearing patterns of patients treated for drug-resistant versus drug-susceptible tuberculosis [13]. Similarly, a relatively large study in Namibia by Sagwa and colleagues assessing the hearing levels of 353 patients on treatment for drug-resistant tuberculosis who all had normal baseline hearing found cumulative incidence of hearing loss of 58% at the end of intensive phase of treatment [15]. Their South-African counterparts, Appana et al. also found that whereas by the first month of treatment with second line drugs, 52% of their patients had hearing impairment, this proportion was 100% by the fifth month of treatment [17]. These findings compellingly suggest that continued treatment with second line anti-tuberculosis medications carry a significant risk of development of hearing impairment.

It is not exactly clear how much ototoxic medication is required to cause hearing impairment among patients on treatment for drug resistant tuberculosis [18]. Findings in our study suggest that consistent administration of second line anti-tuberculosis drugs for two to three months can significantly impair hearing. A study by Peloquin and colleagues found the median onset of hearing loss to be nine (9) weeks during treatment with daily injectable aminoglycosides for drug-resistant tuberculosis [19]. While there are not many studies on ototoxicity among patients on treatment

for drug sensitive tuberculosis, it is noteworthy that Gulbay et al. found ototoxicity in 1.7% of 1,149 patients on first line anti-tuberculosis treatment [20]. Our study found cumulative incidence of 5.3% after 3 months, which was insignificant statistically. Some literatures have suggested ototoxicity by first line anti-tuberculosis drugs like Isoniazid and Rifampicin but the evidence available appear to be weak and non-compelling [21,22].

When the mean hearing thresholds at each frequency (125Hz to 8,000Hz) were analyzed, only the drug-resistant group met the ASHA criteria for threshold shift between baseline audiometry and third month audiometry [9]. There was greater than 10dB shift at adjacent frequencies between 500Hz and 2,000Hz and greater than 20dB shift at the higher frequencies (4,000Hz, 6,000Hz and 8,000Hz) and these patterns were bilateral. In the drug-resistant group, seventeen (17) participants (44.7%) met the criteria for threshold shift after three (3) months whereas only one (1) participant (2.6%) met these criteria in the drug-susceptible group. Jain et al. found similar threshold shifts in their study of patients on treatment for drug-resistant tuberculosis as majority of their patients (85.7%) had bilateral threshold shifts at the higher frequencies [23]. Threshold shift appears to be a consistent audiometric finding among patients treated for drug-resistant tuberculosis for a prolonged duration.

Conclusion

This research concludes that:

1. Patients treated for drug-resistant pulmonary tuberculosis developed hearing loss far more than their counterparts treated for drug-susceptible form of the disease.
2. Hearing loss associated with treatment with second line anti-tuberculosis medications tend to worsen between the second and third months of treatment. Patient surveillance is imperative.

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