Evaluation of Extended High-frequency hearing in individuals consuming PDE5i drugs

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Abstract: ***Introduction:*** **The cellular degeneration of inner ear post consumption of a drug is called as ototoxicity. The drugs like phosphodiesterase type 5 inhibitors (PDE5i) are widely used as vasodilators. These drugs are found to have been studied widely as therapeutic agents in treating cardiac ailments, hypertension, and erectile dysfunction. A few case studies and case series have attempted to explore the effect of these drugs on hearing. However, there is a dearth of literature documenting the hearing sensitivity of individuals consuming PDE5i drugs. The current study is an attempt to document the extended high-frequency hearing of patients consuming the drugs.** ***Patients and methods:*** **The participants were recruited using the purposive sampling technique. Eighty participants in the observation group were diagnosed with erectile dysfunction. Forty-five typical individuals were recruited in the control group. Following the routine hearing evaluation comprising of pure-tone audiometry and Immittance Audiometry, extended high-frequency audiometry was performed and the data thus obtained was subjected to statistical analysis.** ***Result:*** **It was observed that the hearing sensitivity of the participants was significantly poorer at 14000Hz and 16000Hz frequencies. However, the hearing and middle ear status was within normal limits for the routine pure-tone audiometry and immittance audiometry.** ***Conclusion:*** **There is a significant reduction in extended high-frequency hearing in individuals consuming phosphodiesterase type 5 inhibitors (PDE5i).**

Keywords: Hearing, Extended High-frequency audiometry, PDE5i.

I.INTRODUCTION

The intake of a particular drug causes the process of cellular degeneration of tissues in the inner ear is called Ototoxicity as defined by Rybak and Ramkumar [1]. The drug causing ototoxicity is the ototoxic drug. A few drugs that are known to be ototoxic are aminoglycosides, macrolides, glycopeptide antibiotics, cisplatin, loop diuretics, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs [2]. The hearing evaluations sensitive to evaluating the effect of otoxicity and widely used in literature to test for ototoxicity are Otoacoustic emissions, extended high-frequency audiometry (EHFA), and a few electrophysiological evaluations like auditory brainstem evoked potentials or late latency potentials. The use of EHFA is popular among researchers for detecting ototoxicity [8].

Fausti, Larson [3]] found that high-frequency audiometry is sensitive to detecting ototoxicity. They tested the routine pure tone audiometry (250 Hz to 8000 Hz) and EHFA (8000 Hz to 20000 Hz) in patients treated with drugs aminoglycoside and chemotherapy agent cisplatin. It was projected that the thresholds on routine PTA were unchanged before and after the consumption of the drugs, however, a significant reduction was observed in EHFA thresholds. The EHFA was also reported to be effective in documenting hearing impairment in children with cystic fibrosis [4]. The researchers have tested the hearing sensitivity with similar two techniques on 70 patients diagnosed with cystic fibrosis. These participants were treated with intravenous aminoglycosides. The authors have observed the same findings as the previous researchers.

The phosphodiesterase type 5 inhibitor (PDE5i) group of drugs are vasodilators. There are medicines like Sildenafil available as Viagra, Tadalafil available as Cialis, and Vardenafil commercially known as Levitra. These drugs were widely used by medical professionals treating pulmonary hypertension, cardiovascular disorders, and benign prostatic hyperplasia [5]. It was also projected to improve the neurogenesis post-stroke [6]. Additionally, McMahon, Smith [7] used PDE5i to treat patients with erectile

dysfunction. Pellar and Pope [8]] have utilized the PDE5i group of drugs in treating Raynaud's phenomenon as the second line of treatment. With this wide use of drugs in treating various disorders, there are limited studies on the probable otoxicity of the drugs. Klotz, Sachse [9] reported a few side effects of 10mg to 20 mg dosage of Vardenafil in 21 patients with erectile dysfunction (ED). The side effects projected by them included headache (6.8%), flushing (10.2%), dyspepsia (0.7%), and rhinitis (4.8%). They also reported that 4.8% of participants dropped out because of the adverse effects. However, no evaluations were made to test the effect of the hearing status of the participants.

Barreto and Bahmad Jr [10] reported two cases with sudden sensorineural hearing loss. They have also reviewed case reports of individuals with hearing impairment after drug consumption. Additionally, the study done by Khan, Sheikh [11] was first interview-based report for probable ototoxic nature of the drug. They found that there were 47 cases out of 57 with a complaint of hearing impairment. They ruled out any other known cause of hearing impairment in the participants like middle ear infections. It was reported that five individuals had known cause, however, hearing impairment in 47 individuals was not explained by any known hearing disorder. Similarly, Maddox, Saunders [12] also had reported sudden hearing impairment caused post consumption of the drug. However, in these studies hearing evaluation was not performed using standard procedure.

The ototoxicity is the permanent and mostly irreversible hearing impairment and hence, it is crucial to study the drug for ototoxicity. The PDE5i drugs are rampantly prescribed to patients with ED and they are sometimes available to individuals over the counter without a physician's prescription. The drug is consumed by population of all the age groups without knowing the side effects of it. Therefore, the current study was taken up to study the extended high-frequency hearing of individuals consuming PDE5i drugs.

II.PATIENTS AND METHODS

A purposive sampling technique was used to recruit 125 participants in this prospective comparative study. The participants were enrolled in two groups, group 1 was study group and group 2 was the control group. All 80 participants in group 1 have consumed a single dose of minimum 100 mg of the PDE5i drugs as given by the Andrologist during Office Sindenafil Test (OST). The participants were recruited from special andrology outpatient clinic held weekly in a tertiary healthcare hospital in Mumbai, India. The participants were tested post 7 days from the consumption of the first dose of the medicine. The participants in the control group were gender-matched with those in group 1 and were in the same age range. The participants in control groups (n = 45) have never consumed PDE5i group of medications. The mean age of participants in group 1 was 39.3 (10.11) years and that of group 2 was 33 (9.59) years.

The participants with any medical complications like chronic heart diseases, chronic pulmonary diseases, neuro-vascular disorders, and tumors were excluded from the current study. Also, the participants with any history or complaints related to middle ear pathologies were excluded. All the participants underwent regular pure tone audiometry and an immittance audiometry to rule out any known middle ear pathology.

Following this, the participants underwent high-frequency pure tone audiometry. The extended high-frequency audiometry (EHFA) was done using a calibrated two-channel audiometer (GSI Audiostar pro), and the stimuli were delivered via Sennheiser HDA 300 circumaural headphone. The audiometers were calibrated. All the evaluations were done in the sound-treated room with ambient noise levels within the criteria given by ANSI S3.6 (2018) standards.

Statistical Analysis:

The obtained raw data was subjected to statistical analysis using IBM SPSS Statistics for windows (version 21). The descriptive analysis was done to determine the median and quartile deviations. Additionally, a non-parametric set of analyses were employed as the data was found to be skewed on Kolmogorov-Smirnov's test of normality.

Therefore, Wilcoxson signed rank test was administered to study the significance of difference between ears within group on the hearing thresholds obtained in EHFA. The Mann-Whitney U test was done to study the significance of difference between the two groups.

III.RESULT

The descriptive statistics showed that the thresholds obtained by the participants in study group were poorer than those in the control group (median values

given in Table 1). The Wilcoxon signed rank test revealed no significant difference between right and left ears in both groups. The findings of the test are presented in Table 2. Hence the data from the two ears were merged. Therefore, we have 160 ears in the study group (group 1) and 90 ears in the control group (group 2).

This raw data was then subjected to Mann-Whitney U test. The findings revealed significant difference between the two groups. The findings of the test are given in Table 3. Additionally, it was observed that there was no significant difference between the age of the participants in two groups (Mann-Whitney U = 1419.50, $p = 0.05$).

IV.DISCUSSION

In the present study it was observed that the individuals consuming the medicine had hearing sensitivity within normal limits in the routine hearing evaluation. They also never complained of any hearing related difficulty in their day-to-day life. The thresholds on extended high-frequency audiometry were then compared between the two groups. It was observed that the hearing in 14000 Hz and 16000 Hz were affected the most in the participants. This attributed by higher sensitivity of the EHFA to the cochlear pathology [3]. The extended high frequency audiometry is reported to detect subtle loss in the cochlea. Thereby, helps in early detection of the onset of hearing loss [4].

In the study done by [Khan, Sheikh [11]] interviewed the PDE5i drug consumers. They suggested that the impact of the drug is indirect via alteration of the nitrous oxide pathway. This pathway is well documented for its protective property in the hearing mechanism. The drug was reported to interfere with the nitrous oxide pathway in the dieter cell gap protein by causing vasodilation as demonstrated in the guinea pig cochlea.

[Öntepeli, Muluk [13]] has also reported reduction in the Distortion Product Otoacoustic Emission amplitudes in patients consuming PDE5i drugs. They also suggested that it can be an outcome of increased NO concentration in the cochlea. The current study has its limitations as the participants in the observational group were not tested before the administration of the drugs, and therefore the study lacks internal control. Additionally, further studies are required with larger sample size to confirm the ototoxicity caused by the drug.

The current study is one of its kind in evaluating and documenting the status of extended high frequency hearing in patients consuming PDE5i drugs using behavioral audiological evaluation. Additionally, the perception of extended high-frequency sounds are found to help in speech perception in children and adults. They are reported to improve localization by resolving the front and back confusion. The hearing in extended high-frequencies are also noted to contribute in perception of speech in noise. Therefore, the perception of extended high-frequency signals helps in communication [14]. Hence, it is important to evaluate the perception of extended-high frequency in patients prone to developing ototoxicity.

V.CONCLUSION

The status of hearing sensitivity of the individuals using PDE5i drugs was found to be significantly reduced on extended high-frequency hearing as compared to that of the control group. Hence extended high-frequency testing should be done on regular basis to facilitate early audiological rehabilitation.

VI.APPENDIX

Table 1 Mean and Median values of the parameters measured in the groups.

		Group 1 (Study group)		Group 2 (Control group)	
		Mean	Median	Mean	Median
Age		39.3	40.5	35.5	33
Extended High-Frequency Thresholds (dB HL)	8000 Hz	20	20	12	10
	9000 Hz	25	25	13	10
	10000 Hz	35	35	19.11	15
	11200 Hz	45	45	22.5	20
	12500 Hz	55	55	26.83	25
	14000 Hz	70	70	39.5	35
	16000 Hz	75	75	46.66	45

Table 2 Wilcoxson signed rank test findings to study the significance of the difference between the ears within the same group.

Groups \ Frequencies (Hz)		8000	9000	10000	11200	14000	16000
Study Group1	Z	-1.723[b]	-1.479[b]	-.965[c]	-1.236[c]	-.992[c]	-1.234[b]
	Asymp. Sig. (2-tailed)	0.085	0.139	0.335	0.216	0.321	0.217
Control Group2	Z	-.579b	-.096b	-.282c	-1.882c	-1.356c	-1.128b
	Asymp. Sig. (2-tailed)	.562	.924	.778	.060	.175	.259
a. Wilcoxon Signed Ranks Test							
b. Based on negative ranks.							
c. Based on positive r							

Table 3 Mann-Whitney U test findings for EHFA thresholds between groups.

Hertz	8000	9000	10000	11200	12500	14000	16000
Mann-Whitney U	5678.00	3568.50	4125.00	3758.50	3132.50	3356.00	3495.50
Z	-2.776	-6.667	-5.626	-6.290	-7.426	-7.015	-6.767
Asymp. Sig. (2-tailed)	0.006	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001

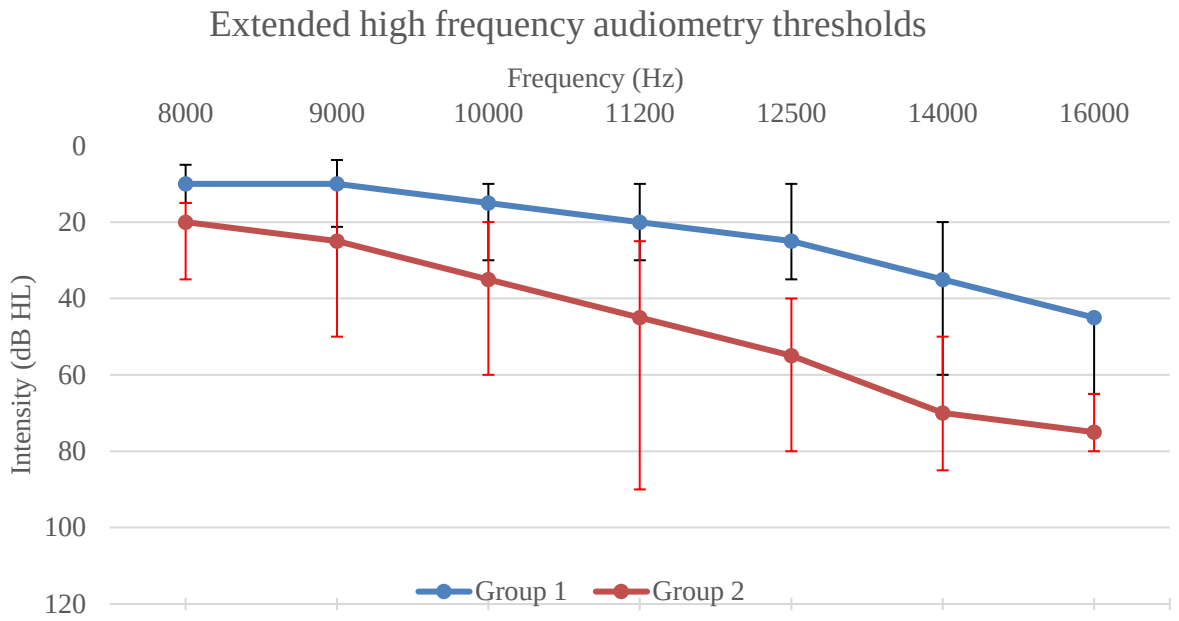

Figure 1 Extended high-frequency thresholds for the control (group 1) and observational groups (group 2), respectively.

Note: The bullets are the median values for the hearing thresholds obtained by the respective group for that particular frequency and the error bars indicate the 25th and 75th percentile values, respectively.

Conflict of interest

Authors declare no conflict of interest.

Authors' Contributions

CU collected, analyzed, and interpreted the data. RR interpreted the data, and assisted in writing the manuscript. All authors read and approved the final manuscript.

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The authors of the study have not received funding for the current research.

Ethical Committee Approval

The ethics approval was obtained from the Ethics Committee for Academic Research Projects, the ethics committee board of A.Y.J.N.I.H.H, Mumbai. The reference number was PRN: 2710100048. Additionally, written informed consent was taken from the participants. All the procedures were non-invasive and follow Helsinki's declaration (2014).

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