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Diuretic Use- A Risk Factor for Hearing Loss in Hypertensive Patients

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Abstract | **Original Research Article**

***Background*:** Hypertension is one of the most common chronic diseases in the world in adults and is also one of the risk factors for hearing loss as it can compromise the vascular supply to the stria vascularis. Hypertension is often treated with diuretics as they are one of the first line drugs for uncomplicated hypertension. With diuretics being potential ototoxic drugs, there is a possibility of greater risk for hearing loss in hypertensive patients who are on diuretics compared to other antihypertensive drugs. ***Method*:** We recruited 100 hypertensive patients in our study. Prevalence of sensorineural hearing loss in hypertensive patients on diuretics was assessed in comparison to the prevalence of hearing loss in hypertensive patients on drugs other than diuretics using Pure Tone Audiometry. ***Result*:** There was a significant association between diuretic use in hypertension and increase in hearing threshold. The number of patients with sensorineural hearing loss in the diuretic use group (56%), was double than that of the control group (28%). The severity of hearing loss corelated with the duration of diuretic use (43.75% of patients with duration 3 months-1 year, 47.05% of patients with duration 1-2 years, 60% of patients with duration 2-5 years and 100% patients with duration >5 years). ***Conclusion*:** Use of diuretics in hypertensive patients is an additional risk factor for hearing loss in these patients. The patients therefore need to be followed up regularly and also history of diuretic use should be kept in mind while assessing patients presenting with hearing loss.

Keywords: Hypertension, Hearing loss, Diuretics.

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INTRODUCTION

Hearing loss is a disability that affects a person's quality of life and has an adverse impact on a person's functional capabilities as well as social interaction. According to WHO, 63 million people in India and 466 million people in the world live with disabling hearing loss [1]. It is the fourth most common cause of morbidity in the world [2]. Hypertension is one of the most common chronic diseases in the world in adults and has been found to be one of the risk factors for hearing loss as it can compromise the vascular supply to the stria vascularis. The reduction in caliber of blood vessels and increased blood viscosity leads to reduced oxygen and nutrient supply causing tissue hypoxia [3].

The Joint National Committee-8 (JNC-8) criteria recommends using diuretics as a first line drug in uncomplicated hypertension [4]. The most common diuretics used are thiazides and furosemide (loop diuretic). Some of the diuretics are potential ototoxic drugs. Furosemide is known to cause sudden sensorineural hearing loss which is mostly reversible. It is due to the dysfunction of ion channels particularly the NKCCl channel ($Na^+/K^+/Cl^-$ cotransporter) resulting in suppression of endocochlear potential. There have been a few reported cases of hearing loss in patients who were treated with thiazides but there has been no consistent association [5].

Hearing loss is a disabling condition and can lead to difficulty in communication, dependency on others, psychological changes, social isolation, incapacity and accidents [6]. Hence, it is imperative to rule out ototoxicity of the drug before prescribing it to patients.

The study was planned to determine whether there was a greater risk for hearing loss in hypertensive patients who are on diuretics and aid in understanding of the association between hypertension, diuretics and hearing loss.

METHOD

The study was a cross sectional pilot study conducted in the Department of Otorhinolaryngology and Department of Medicine at a tertiary care hospital in Delhi over a period of two years.

Ethical clearance for the study was taken from the institutional ethics committee (IECHR/2020/PG/47/55-R1). Hundred patients in the age group 35-60 years diagnosed as hypertensive by the physician were taken, fifty of which were previously diagnosed as hypertensive by the physician and were on diuretics (thiazides or furosemide) for three or more months. The rest fifty were on other antihypertensive medications. Patients with preexisting ear diseases, history of ear surgery, ototoxic drug ingestion and with history of loud noise exposure were excluded from the study.

After recording the blood pressure of the patient and otological examination, pure tone audiometry was performed to record the hearing threshold. Hearing thresholds of both the ears were measured using the audiometer for frequencies 250,500, 1000, 2000, 4000 and 8000 Hz for air conduction and 500, 1000, 2000 and 4000 Hz for bone conduction in a sound isolated room.

The average of hearing threshold for both air conduction and bone conduction was taken for both ears and then categorized according to the WHO grades of hearing impairment.

Once diagnosed to have raised hearing threshold in one or both ears, the treatment regime for the subject was modified after consultation with medicine department.

Statistical Analysis:

The outcome variable i.e. hearing loss was presented as a proportion of the total number of examined participants in both the groups.

The mean values of pure tone audiometry thresholds in the two groups of patients was compared using appropriate test of significance depending on the distribution of data:

- Normal distribution- unpaired t-test
- Otherwise- Mann-Whitney U test
- P-value of less than 0.05 was taken as significant.
- The data analysis was done using SPSS 21.0 software

RESULTS

Blood Pressure

The systolic blood pressure (mmHg) was normally distributed in the diuretic use group and control group. Thus, parametric test (t-test) was used to make group comparisons.

The mean (SD) of Systolic BP (mmHg) in the diuretic use group was 129.34 (7.66). The mean (SD) of Systolic BP (mmHg) in the control group was 131.82 (8.61).

There was no significant difference between the groups in terms of Systolic BP (mmHg) (t = -1.522, p = 0.131).

The Diastolic BP (mmHg) was not normally distributed in the diuretic use group and control group. Thus, non-parametric test (Wilcoxon-Mann-Whitney U Test) was used to make group comparisons.

Table 1: Comparison of the 2 Subgroups of Diuretic Use in Terms of Systolic BP (mmHg) (n = 100)

Systolic BP (mmHg)	Diuretic Use		t-test	
	Present	Absent	t	p value
Mean (SD)	129.34 (7.66)	131.82 (8.61)	-1.522	0.131
Median (IQR)	129 (124-136)	132 (126.5-137)		
Min - Max	114 - 144	108 - 158		

Table 2: Comparison of the 2 Subgroups of Diuretic Use in Terms of Diastolic BP (mmHg) (n = 100)

Diastolic BP (mmHg)	Diuretic Use		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD)	77.70 (7.28)	77.14 (6.08)	1345.000	0.513
Median (IQR)	77 (74-82)	77 (73.25-80)		
Min - Max	61 - 90	68 - 99		

Pure Tone Audiometry

The bone conduction was not normally distributed in the diuretic use group and control group. Thus, non-parametric test (Wilcoxon-Mann-Whitney U Test) was used to make group comparisons.

The mean (SD) of bone conduction (dB) in right ear in the diuretic use group was 22.30 (10.82). The mean (SD) of bone conduction (dB) in right ear in the control group was 14.44 (10.26). There was a significant difference between the 2 groups in terms of bone conduction (dB) (W = 1832.000, p = <0.001), with the median bone conduction (dB) threshold being higher in the diuretic use group.

The mean (SD) of bone conduction (dB) in left ear in the diuretic use group was 22.56 (11.02). The mean (SD) of bone conduction (dB) in left ear in the control

group was 13.44 (9.44). There was a significant difference between the 2 groups in terms of bone conduction (dB) (W = 1884.000, p = <0.001), with the median bone conduction (dB) threshold in left ear being higher in the diuretic use group.

Table 3: Comparison of the 2 Subgroups of Diuretic Use in Terms of Bone Conduction (dB) (Right and Left) (n = 100)

BC (dB) (Right)	Diuretic Use		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD)	22.30 (10.82)	14.44 (10.26)	1832.000	<0.001
Median (IQR)	25 (10-30)	9 (8-21.5)		
Min - Max	7 - 45	5 - 44		

BC (dB) (Left)	Diuretic Use		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD)	22.56 (11.02)	13.44 (9.44)	1884.000	<0.001
Median (IQR)	25 (10.5-30)	8 (8-19.5)		
Min - Max	5 - 41	5 - 40		

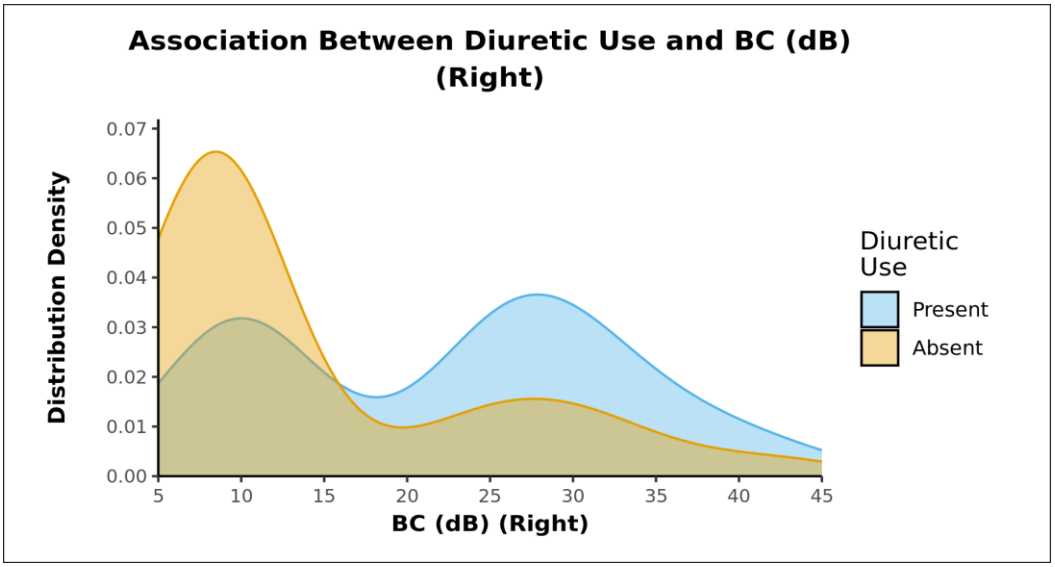

FIG 1: Bone conduction with and without diuretic use in hypertensive patients across both groups for right ear

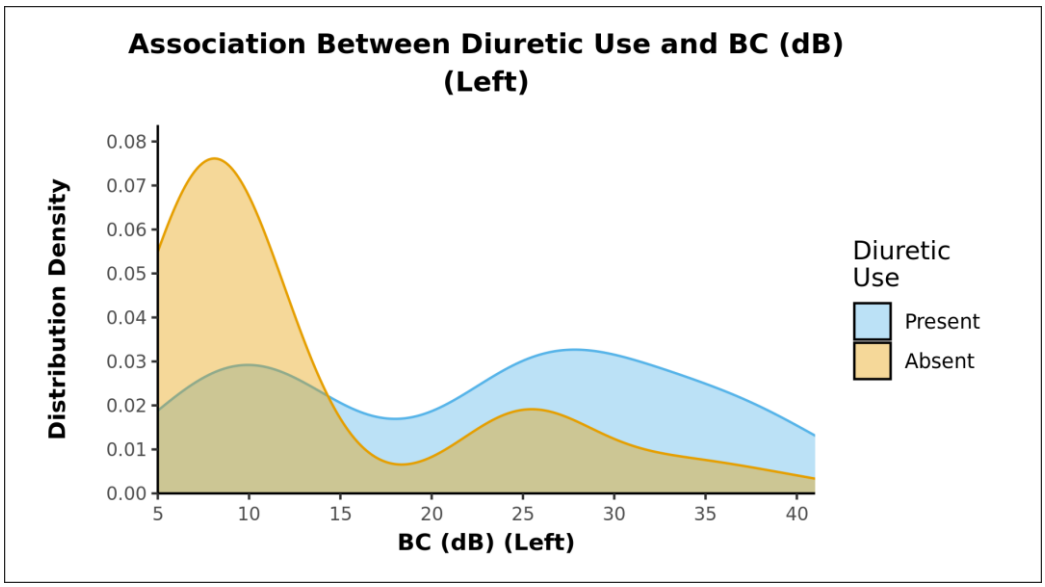

FIG 2: Bone conduction with and without diuretic use in hypertensive patients across both groups for left ear

Prevalence of Snhl in Both Groups

Chi-square test was used to explore the association between 'Diuretic Use' and 'SNHL'. 56.0% of the participants (28 of 50) in the diuretic use group had SNHL. 44.0% of the participants (22 of 50) in the diuretic use group had normal hearing. 28.0% of the participants (14 of 50) in the control group had SNHL. 72.0% of the participants (36 of 50) in the control group had normal hearing.

Participants in the diuretic use group had the larger proportion of SNHL.

There was a significant difference between the two groups in terms of distribution of SNHL ($\chi2 = 8.046$, $p = 0.005$).

Table 5: Association between Diuretic Use and SNHL (n = 100)

SNHL	Diuretic Use			Chi-Squared Test	
	Present	Absent	Total	χ2	P Value
Present	28 (56.0%)	14 (28.0%)	42 (42.0%)	8.046	0.005
Absent	22 (44.0%)	36 (72.0%)	58 (58.0%)		
Total	50 (100.0%)	50 (100.0%)	100 (100.0%)		

SEVERITY OF SNHL

Fisher's exact test was used to explore the association between 'Diuretic Use' and 'Severity of SNHL'.

44.0% of the participants in the diuretic use group had normal hearing. 48.0% of the participants in the diuretic use group had mild SNHL. 8.0% of the participants in the diuretic use group had moderate SNHL. 72.0% of the participants in the control group had normal hearing. 24.0% of the participants in the control group had mild SNHL. 4.0% of the participants in the control group had moderate SNHL.

There was a significant difference between the various groups in terms of distribution of severity of SNHL ($\chi2 = 8.210$, $p = 0.015$).

Table 6: Association between Diuretic Use and Severity of SNHL (n = 100)

Severity of SNHL	Diuretic Use			Fisher's Exact Test	
	Present	Absent	Total	χ2	P Value
Normal	22 (44.0%)	36 (72.0%)	58 (58.0%)	8.210	0.015
Mild	24 (48.0%)	12 (24.0%)	36 (36.0%)		
Moderate	4 (8.0%)	2 (4.0%)	6 (6.0%)		
Total	50 (100.0%)	50 (100.0%)	100 (100.0%)		

Snhl Associated with Different Diuretics

53.6% of patients (22 of 41) who had a history of only thiazide diuretic use (hydrocholorothiazide) presented with SNHL of various grades. 100% of patients (4 of 4) with history of Furosemide use, either alone or in combination with other diuretics presented with SNHL. 25% of patients (1 of 4) with spironolactone use presented with SNHL. All patients (4 of 4) on combination of more than one diuretic drug were found to be having SNHL.

Duration of Hypertention and Diuretic Use

The duration of drug use was categorised into four categories: 3 months- 1 year, 1-2 years, 2-5 years and > 5 years.

In the diuretic group, 43.75% of patients (7 of 16) with duration 3 months-1 year, 47.05% of patients (8 of 17) with duration 1-2 years, 60% of patients (6 of 10) with duration 2-5 years and 100% patients (7 of 7) with duration >5 years had sensorineural hearing loss.

The summarised result for the association between Diuretic use in hypertensive patients with various parameters, compared to hypertensive patients on other drugs is given below:

Table 16: Association between Diuretic Use and Parameters

Parameters	Diuretic Use		p value
	Present (n = 50)	Absent (n = 50)	
Age (Years)	51.54 ± 7.21	48.60 ± 8.23	0.057[1]
Age			0.097[2]
35-45 Years	7 (14.0%)	16 (32.0%)	
46-55 Years	25 (50.0%)	21 (42.0%)	
56-60 Years	18 (36.0%)	13 (26.0%)	

Parameters	Diuretic Use		p value
	Present (n = 50)	Absent (n = 50)	
Gender* **			0.014[2]
Male	26 (52.0%)	14 (28.0%)	
Female	24 (48.0%)	36 (72.0%)	
Duration Of Hypertension			0.136[2]
3 Months - 1 Year	16 (32.0%)	9 (18.0%)	
1-2 Years	17 (34.0%)	13 (26.0%)	
2-5 Years	10 (20.0%)	19 (38.0%)	
>5 Years	7 (14.0%)	9 (18.0%)	
Comorbidities (Present)	21 (42.0%)	12 (24.0%)	0.056[2]
Surgical History (Present)	10 (20.0%)	8 (16.0%)	0.603[2]
Systolic BP (mmHg)	129.34 ± 7.66	131.82 ± 8.61	0.131[3]
Diastolic BP (mmHg)	77.70 ± 7.28	77.14 ± 6.08	0.513[1]
Blood Pressure Impression			0.619[2]
Normal	6 (12.0%)	5 (10.0%)	
Pre-Hypertensive	40 (80.0%)	38 (76.0%)	
Hypertensive	4 (8.0%)	7 (14.0%)	
Tympanic Membrane			0.752[4]
Normal	35 (70.0%)	35 (70.0%)	
Retracted	12 (24.0%)	13 (26.0%)	
Dull	3 (6.0%)	1 (2.0%)	
Congested	0 (0.0%)	1 (2.0%)	
AC (dB) (Right)* **	29.78 ± 10.53	23.98 ± 11.90	0.001[1]
BC (dB) (Right)* **	22.30 ± 10.82	14.44 ± 10.26	<0.001[1]
ABG (dB) (Right)* **	7.53 ± 3.51	9.54 ± 5.64	0.034[1]
AC (dB) (Left)* **	30.84 ± 11.09	22.12 ± 8.81	<0.001[1]
BC (dB) (Left)* **	22.56 ± 11.02	13.44 ± 9.44	<0.001[1]
ABG (dB) (Left)	8.28 ± 3.79	8.68 ± 2.02	0.194[1]
SNHL (Present)* **	28 (56.0%)	14 (28.0%)	0.002[2]
Severity of SNHL* **			0.015[4]
Normal	22 (44.0%)	36 (72.0%)	
Mild	24 (48.0%)	12 (24.0%)	
Moderate	4 (8.0%)	2 (4.0%)	

****Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: Chi-Squared Test, 3: t-test, 4: Fisher's Exact Test*

DISCUSSION

The damaging effects of diuretic use on human ear has been evaluated studied extensively. The effects have been established for some of the diuretics like furosemide and ethacrynic acid [7]. However, their synergistic action with raised blood pressure in hypertensive patients has not yet been established. Use of diuretics in hypertension can theoretically worsen the condition and can accentuate the mechanism for hearing impairment.

Hypertension itself is an independent risk factor for hearing loss as determined in various studies by Agarwal *et al.*, [8], Yikawe *et al.*, [9], Ramatsoma *et al.*, [10], Marchiori *et al.*, [11], etc. Increased blood pressure can cause inner ear haemorrhage and along with increased blood viscosity hampers the oxygen supply to stria vascularis by compromising the blood flow. As the stria vascularis is supplied by terminal arteries with no collateral supply (cochlear artery and anterior vestibular artery) hence it is sensitive to the conditions which may hamper the vascular supply. The hyperviscosity of the blood along with possible vasospasm causes reduced capillary flow and hence reduced oxygen supply causing hypoxia [12-13].

Ototoxic mechanism for diuretics has been established which is by causing massive edema in stria vascularis, altered morphology of marginal and basal cells with loss of their basal processes, apoptotic structures in intermediate cells and edematous changes in spiral ligament [14]. Diuretics like furosemide also inhibit the NaKCCl channel causing reduction in the endolymphatic K+ levels and endocochlear potential [15]. Wright *et al.*, [16], found intermediate cell layer disruption in the stria vascularis with large cystic spaces within the marginal cells too causing separation of cell types in the post mortem histological study of temporal bones of patients who had received loop diuretics.

In our study, the mean bone conduction for right and left ears in the hypertensive group not taking diuretics was 14.44 dB and 13.44 dB respectively. The

mean BC for right and left ears in the diuretic use group was 22.30 dB and 22.56 dB respectively which was statistically significant for both ears (Right- W = 1832.000, p = <0.001 and Left- W = 1884.000, p = <0.001) indicating increased threshold for bone conduction in the diuretic use group.

The proportion of patients with SNHL was found more for the diuretic use group than the control group. 28% patients in the control or non-diuretic group had SNHL, whereas 56% of patients in the diuretic use group had SNHL. There was a significant difference between the two groups in terms of distribution of SNHL ($\chi 2$ = 9.180, p = 0.002) and hence the association between diuretic use in hypertensive patients and hearing loss can be established based on the above findings in our study.

Another notable finding from our study is the risk of hearing loss in diuretic use group with the duration of use which increases as the duration of drug use increases. In the diuretic use group, 43.75% of patients with 3 months-1 year of diuretic use, 47.05% of patients with 1-2 years of diuretic use, 60% of patients with 2-5 years of diuretic use and 100% patients with >5 years of diuretic use had sensorineural hearing loss. Therefore, long standing hypertensive patients are at a greater risk of developing sensorineural hearing loss and hence, should be screened regularly for their hearing [17].

The risk of hearing loss associated with furosemide use, as discussed earlier has been well established [18]. In the present study, all the patients taking furosemide (4 of 4), whether alone or in combination with another diuretic presented with SNHL.

There is lack of similar literature for the ototoxic effects of thiazide diuretics. The only significant published literature on ototoxic effects of thiazide has been from N.Belai [5], *et al*., who in 2018 in a descriptive case study, found a total of 94 cases of hearing loss from 1972 to 2017 associated with thiazide use in our study, we had 22 of 41 patients i.e. 53.6% patients having sensorineural hearing loss who were on hydrochlorothiazide, largely in combination with other anti-hypertensive drugs (not known ototoxic drugs). In patients who were on two diuretics simultaneously (hydrochlorothiazide with either furosemide or spironolactone), sensorineural hearing loss was seen for all patients (3 of 3).

The effects of diuretic use in hypertensive patients was studied by Brian M. Lin *et al*., [19], in a prospective cohort study from 1994 to 2012 in 54721 participants aged 48-73 years. The limitation of the study was that the outcome i.e. hearing loss was self-reported and the patients were not subjected to an audiometric test for hearing threshold evaluation. History of hypertension was independently associated with a modestly higher risk of hearing loss (multivariable adjusted relative risk, 1.04 [1.01-1.07]) and among those with a history of hypertension, neither thiazide (multivariable adjusted relative risk, 1.07) nor furosemide use (multivariable adjusted relative risk, 0.91) was significantly associated with risk of hearing loss when compared with those not taking antihypertensive medications. Hence, the association between diuretics (furosemide and thiazide) use in hypertensives and hearing loss could not be established.

With not much previous studies into the association between diuretic use in hypertension and hearing loss and despite observing no significant association between the two in the only study previously conducted by Brian M. Lin [19], we observed a significant risk of hearing loss in hypertensive patients on diuretics compared with hypertensive patients on other medications based on the pure tone audiometry findings.

To conclude, in our present study we compared the pure tone thresholds for hypertensive patients on diuretics with those on other antihypertensive drugs and found a significant association between diuretic use in hypertension and hearing loss which suggests that there is a possible association between diuretic use in hypertension and increase in hearing threshold, and the severity corresponds to the duration of diuretic use.

However, because the study has been done in a small sample size of 100 patients, we recommend randomized study in a large set of patients in order to bring out stronger recommendations. The findings of the study can form a basis for further investigation and research for association between diuretic use in hypertension and hearing loss.

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