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Original Article* / *Çalışma - Araştırma

Are thiazides effective on hypertensive vertigo? A preliminary study

Tiazidler hipertansif vertigo tedavisinde etkili olabilir mi? Ön çalışma

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Objectives: In this study, we aimed to investigate whether the symptoms of vertigo related to hypertension resulted from endolymphatic hydrops and the efficacy of the thiazides in the treatment.

Patients and Methods: A total of 24 vertigo patients without peripheric or central vestibular pathologies or hyperlipidemia were included. The study group comprised 15 patients with hypertension, including nine with regulated non-insulin-dependent diabetes mellitus (DM). The control group comprised nine patients without hypertension or DM. The patients in the study group received hydrochlorothiazide treatment. The European Evaluation of Vertigo Scale (EEVS) and Vertigo Handicap Questionaire (VHQ), puretone audiometry, tympanometry, electronystagmography (ENG) for nystagmus tests, oculomotor tests, and caloric test were carried out initially and at three weeks for both groups. The results of the study group were compared to those of the control group.

Results: There was a statistically significant decrease in the scores of EEVS and VHQ at three weeks in the study group, compared to the baseline scores (for both groups $p \leq 0.01$).

Conclusion: Our study results showed that thiazides alleviated vertigo symptoms in hypertensive patients, as measured by qualitative methods (i.e. EEVS, VHQ), but not with quantitative measurements (i.e. ENG).

Key Words: Endolymphatic hydrops; hypertension; thiazides; vertigo.

Amaç: Bu çalışmada hipertansiyonun neden olduğu vertigo semptomlarının endolenfatik hidrops sonucunda oluşup oluşmadığı ve tiazidlerin tedavideki etkinlikleri araştırıldı.

Hastalar ve Yöntemler: Çalışmaya vertigosu olan, periferik veya santral vestibüler patolojisi ve hiperlipidemisi olmayan toplam 24 hasta dahil edildi. Çalışma grubuna, dokuzu regüle edilmiş, insuline bağımlı olmayan diabetes mellitus (DM) hastası olmak üzere, 15 hipertansif hasta alındı. Kontrol grubuna hipertansiyon ve DM olmayan dokuz hasta dahil edildi. Çalışma grubundaki hastalar hidroklotrtiazid ile tedavi edildi. Her iki gruba, başlangıçta ve üç hafta sonra Avrupa Vertigo Değerlendirme Ölçeği (AVDÖ) ve Vertigo Yetersizlik Anketi (VYA), saf ses odyometri, timpanometri, nistagmus testleri için elektronistagmografi (ENG), okülomotor testler ve kalorik testler yapıldı. Çalışma grubunun sonuçları, kontrol grubu ile karşılaştırıldı.

Bulgular: Çalışma grubunda başlangıca kıyasla, üçüncü haftada tekrarlanan AVDÖ and VYA sonuçlarında istatistiksel olarak anlamlı bir düşüş görüldü (her ikisi için $p \leq 0.01$).

Sonuç: Çalışma bulgularımız, tiazidlerin kalitatif yöntemler ile (örn; AVDÖ, VYA) hipertransif hastaların vertigo semptomlarını azalttığını gösterdi, ancak kantitatif ölçümler ile (ENG) aynı sonuçların alınamadığını gösterdi.

Anahtar Sözcükler: Endolenfatik hidrops; hipertansiyon; tiazidler; vertigo.

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Dizziness and vertigo are present in most patients of all ages with high blood pressure, diabetes mellitus (DM), and more so in elderly people, with about 20% of the population older than 60 years experiencing dizziness.[1] A study among 256 dizziness patients with average age of 66 years identified the common underlying causes as hypertension in 32.4%, diabetes mellitus in 13.8%, arthritis in 8.1%, and heart disease in 4.4%.[2] Non-insulin-dependent diabetes mellitus (NIDDM) is frequently associated with hypertension which may be present even before the diagnosis of NIDDM. The mechanism is thought to be through hyperinsulinemia, sodium and water absorption, sympathetic nervous activity and the increase in vascular tonus and finally hypertension. It differs in that way from insulin dependent DM, which causes diabetic nephropathy.[3,4]

Symptoms of high blood pressure may include vertigo. Hydrochlorothiazide is a diuretic which reduces the reabsorption of electrolytes from the renal tubules. The use of hydrochlorothiazide has been indicated for the edema of menstrual tension, where there is evidence of fluid retention. Endolymphatic hydrops (EH) is defined as increased hydraulic pressure in the endolymphatic system of the iner ear. Endolymphatic hydrops may cause fluctuating hearing loss, episodic vertigo, tinnitus and aural fullness. In this aspect thizaides have been effective for treatment of Meniere's disease. Vestibular complaints have decreased significantly with hydrochlorothiazide and triamterene treatment.[5] Vertigo may present as a symptom in hypertensive patients. Idiopathic EH may be present in hypertension independent of the presence of DM.

In this study we focused on the effects of thiazides on hypertensive patients experiencing vertigo. Patients with NIDDM were also included.

PATIENTS AND METHODS

A total of 24 patients with vertigo were examined at Başkent University İstanbul Hospital. A systolic blood pressure greater than 14.0 millimeters of mercury (mmHg) and a diastolic blood pressure greater than 90.0 mmHg were considered as high arterial blood pressure.[6] A systolic blood pressure less than 120 mmHg and a diastolic pressure less than 80 mmHg were considered normal arterial blood pressure. Peripheral or central vestibular pathologies and hyperlipidemia were exclusion criteria. Normal brain magnetic resonance imagings (MRI) and neurological consultations, and no previous diuretic therapy were inclusion criteria. The study group comprised 15 patients with high arterial blood pressure (mean age 61±14 years; range 30 to 78 years) who were examined for vertigo. Patients who had regulated NIDDM (n=9) were included in this group. The control group comprised nine patients, (mean age 40±11 years; range 25 to 54 years), with vertigo but without hypertension and no evident DM.

The European Evaluation of Vertigo Scale (EEVS) and Vertigo Handicap Questionaire (VHQ) were administered to the patients.[7,8] Puretone audiometry was measured with a Clinical Audiometer AC-40 Interacoustics (DK-5610 Assens Denmark), and tympanometry with an Impedance Audiometer AZ 26 Interacoustics (DK-5610 Assens Denmark). Nystagmus and oculomotor tests were carried out with visual eye 4 Channel Micromedical Technologies Electronystagmograpy (ENG, Micromedical Technologies, Chatham, Illinois, USA). Nystagmus tests were spontaneous nystagmus, gaze-vertical, gaze-horizontal, Dix-Hallpike Left, Dix-Hallpike Right, and positional head tests. Oculomotor tests were saccade-random, pursuit, optokinetic-fixed. In addition caloric tests were also performed.

The study group was treated with oral hydrochlorothiazides once a day, for a minimum three weeks and no specific treatment was given to the control group. The treatment of patients was later continued under the control of specialists. All the tests were repeated for both groups three weeks later. The results of the study group were compared to those of the control group. The results were reanalyzed by a reviewer blinded to the treatment arm.

NCSS (Number Cruncher Statistical System) 2007 & PASS 2008 Statistical Software (Utah, USA) package was used for statistical analyses. Student t-test was used in comparing the data of the two groups where the parameters showed normal distribution and Mann-Whitney U-test was used where the parameters did not show normal distribution. Paired sample t-test was used for intra-group comparisons of parameters showing normal distribution and Wilcoxon sign test was used for parameters not showing normal distribution. Comparative analysis of qualitative data were made by chi-square test, Fisher's exact

Table 1. European Evaluation of Vertigo Scale and Vertigo Handicap Questionaire evaluation

	Study group	Control group	
	Mean±SD	Mean±SD	¶*p*
European Evaluation of Vertigo Scale			
Initial	9.46±2.23	7.67±2.23	0.080
Three weeks later	1.67±3.18	5.67±1.32	0.001**
¶¶*p*/inital-3 weeks later	0.001**	0.066	
			‡*p*
Vertigo Handicap Questionaire			
Initial	46.60±15.20	27.44±15.59	0.007**
Three weeks later	25.33±16.65	24.00±7.98	0.825
‡‡*p*/initial-3 weeks later	0.001**	0.479	

SD: Standard deviation; ¶ Mann-Whitney U-test; ¶¶ Wilcoxon sign test; ‡ Student t-test; ‡‡ Paired sample t-test; ** p<0.01.

test, and Mc Nemar test. Significance was accepted at p<0.05 level.

This study was approved by the Başkent University Institutional Review Board (Project no: KA 10/57) and supported by the Başkent University Research Fund.

This study was performed in consonance with Helsinki Declaration 2008 principles.

RESULTS

The blood pressure levels of the study group were evaluated as normal three weeks after thiazide treatment. There was no statistically significant difference between the initial EEVS results of the study and the control groups (p>0.05). The three weeks later EEVS results of the study group was found to be significantly lower than those of the control group (p<0.01). The decrease in the three weeks later EEVS results of the study group was statistically significant with respect to the initial results (p<0.01). There was no statistically significant difference observed between the initial and the three weeks later EEVS results of the control group (p>0.05). The initial VHQ results of the study group was found to be significantly greater than those of the control group (p<0.01). The difference between the three weeks later results of the study and the control groups were not found to be significantly different (p>0.05). The decrease in the three week later VHQ results of the study group was found to be statistically significant compared to its initial VHQ results (p<0.01). There was no statistically significant difference between the initial and the three weeks later VHQ results of the control group (p>0.05; Table 1).

In the study group, nine (60%) of the patients had mild sensorineural hearing loss. The control group had normal audiometric results. All the tympanometric values were normal for both groups.

There was no statistically significant difference between the initial and three weeks later nystagmus findings of the study group and of the control group (p>0.05). The differences between nystagmus findings of the three weeks later (post treatment) results of the study group compared to the initial results were not statistically significant (p>0.05) despite being noteworthy. It was observed that nystagmus results regressed from 53.3% positive at the beginning to 20% positive three weeks later, but this was not found to be statistically significant.

There was no statistically significant difference between the initial and three weeks later nystagmus findings of the control group (p>0.05; Table 2).

There was no statistically significant difference between the initial and the three weeks later

Table 2. Nystagmus evaluation

	Study group		Control group		
	n	%	n	%	¶*p*
Initial					
Positive	8	53.3	2	22.2	0.134
Negative	7	46.7	7	77.8	
Three weeks later					
Positive	3	20	0	0	0.266
Negative	12	80	9	100	
¶¶*p*/initial-3 weeks later	0.063		0.500		

¶ Chi-square test; ¶¶ Mc Nemar test.

saccade-random results of the study group and of the control group (p>0.05). The results were found to be normal in both groups. The three weeks later saccade-random results of the study group were not significantly different (p>0.05) compared to its initial results. The three weeks later saccade-random results of the control group were not significantly different (p>0.05) compared to its initial results. There was no statistically significant difference between the initial and the three weeks later pursuit results of the study and of the control groups (p>0.05). The results were found to be normal in both groups. There was no statistically significant change observed between the initial and the three weeks later pursuit results of the study group (p>0.05). There was no statistically significant change observed between the initial and the three weeks later pursuit results of the control group (p>0.05). There was no statistically significant difference between the initial and the three weeks later OPK-Fixed results of the study and of the control groups (p>0.05). The results were found to be normal in both groups. There was no statistically significant change observed between the initial and the three weeks later OPK-Fixed results of the study group (p>0.05). There was no statistically significant change observed between the initial and the three weeks later OPK-Fixed results of the control group. (p>0.05; Table 3).

There was no canal palsy in caloric tests of the study and the control group patients.

DISCUSSION

The pathophysiology of endolymphatic hydrops has always been an exciting topic. Animal models of endolymphatic hydrops have shown that there are complicated biochemical and morphological alterations effected by hormonal and systemic disturbances. Lately it has been accepted that the endolymphatic sac plays the most important role in endolymphatic pressure regulation. Systemic isoproterenol increases endolymphatic pressure and decreases the potential of the endolymphatic sac lumen.[9] Vasopressin receptors have been detected in both the cochlear lateral

Table 3. Oculomotor test results

	Study group		Control group		
	n	%	n	%	¶*p*
Saccade-Random					
Initial					
Normal	15	100	9	100	1.000
Three weeks later					
Normal	15	100	9	100	1.000
Initial -3 weeks later ¶¶*p*	1.000		1.000		
Pursuit					
Initial					
Low gain	1	6.7	0	0	1.000
Normal	14	93.3	9	100	
Three weeks later					
Low gain	–	–	–	–	1.000
Normal	15	100	9	100	
Initial -3 weeks later ¶¶*p*	1.000		1.000		
OPK-Fixed					
Initial					
Low gain	2	13.3	0	0	0.511
Normal	13	86.7	9	100	
Three weeks later					
Low gain	2	13.3	0	0	0.511
Normal	13	86.7	9	100	
Initial -3 weeks later ¶¶*p*	1.000		1.000		

¶ Chi-square test; ¶¶ Mc Nemar test.

wall and the endolymphatic sac.[10] Animals given vasopressin showed a dose dependent increase in endolymphatic volume.[11]

The endolymphatic sac reacts to changes in inner ear blood flow, fluid volume, and/or pressure. Takumida et al.[12] have worked on the effect of inner ear blood flow changes in mouse models of Meniere's. In this study, injections of epinephrine into the round window caused vestibular dysfunction, whereas injections of sodium nitroprusside did not elicit any such signs. The main difference was that epinephrine caused an immediate reduction of inner ear blood flow which recovered slowly and, in contrast, sodium nitroprusside induced a rapid and noticeable increase in inner ear blood flow. They thus showed that the endolymphatic sac reacts to changes in inner ear blood flow.

Arterial hypertension is subject of many studies of hearing loss, vertigo, and tinnitus. Mosnier et al.[13] studied the permeability of the blood-perilymph, and of the labyrinthine barrier between endolymph and perilymph, to small molecules during chronic and acute hypertension in normotensive and spontaneously hypertensive rats. In this study, these barriers were not found to be altered. The endocochlear potentials in hypertensive rats were found to be lower than normal rats. This potential decreased after acute hypertension in 40% of the normotensive rats. After an acute hypertensive peak, the presence of vascular protective mechanisms in the cochlea have been explained as the cause of the stable endocochlear potential recorded in all hypertensive and in 60% of normotensive rats. Chronic hypertension in rats did not affect the permeability of the blood-perilymph and blood-cerebrospinal fluid barriers by small water soluble molecules.

In a study by Warninghoff[14] on co-morbidities of vertiginous diseases, it has been shown that hypertension was present in 29.0% of the patients, with considerably higher prevalence (63.3%, p=0.014) in those with Meniere's Disease, and lower prevalence (15.8%, p=0.27) in those with benign paroxysmal positional vertigo. The higher prevalence of hypertension in those with Meniere's Disease may be explained by hypertension causing hydrops in the inner ear.

However, the above studies conflict with other clinical studies. Abate et al.[15] found no difference in balance tests between normotensive and hypertensive subjects. A study by Esparza et al.[16] found an association between inner ear dysfunction and retinal vascular changes related to systemic arterial hypertension. Subjects with arterial hypertension with no DM history and no hyperlipidemia were compared with a control group. Although subjects with hypertension reported vertigo more frequently than control subjects, conventional oculomotor and bithermal caloric tests showed no difference between the two groups. The results of this study suggest that patients with systemic arterial hypertension may have cochlear dysfunction associated with vascular disruption, but without any clear evidence of parallel vestibular dysfunction. Parfenov[17] also claimed that, although vertigo occurred in 20% of hypertensive people, no cause and effect relationship was found between hypertension and vertigo.

The EEVS and VHQ results are important because they evaluate the state of discomfort of subjects, rather than measuring symptomatic parameters. In our study, the decrease in levels of discomfort, as evaluated by EEVS and VHQ, were very significant. In ENG tests, we observed nystagmuses which were not strong and not of long durations. In fact, the reduction of nystagmuses after thiazide treatments were very close to being statistically significant (p=0.063). Accordingly, we think that it would be beneficial to administer thiazides to hypertensive patients with vestibular symptoms, both for controlling blood pressure, and for relieving discomfort caused by dizziness and vertigo, by its diuretic nature. The symptoms may regress in time without thiazide, but thiazide will help alleviate discomfort much faster through its highly probable effects of relieving endolymphatic hydrops which occurs in the vestibule during arterial hypertension.

The EEVS and VHQ are both subjective qualitative evaluations of the discomfort felt by patients experiencing vertigo. The EEVS evaluates illusion of movement, duration of illusion, motion intolerance, neurovegetative signs, and instability. VHQ is developed to evaluate the functional, emotional, and physical aspects of dizziness and its handicapping effects on the vestibular system. This preliminary work has shown that both the EEVS and the VHQ results decrease with three weeks of thiazide treatment, thus indicating that thiazides relieve discomfort of patients. However this discomfort relief was not corroborated by the results of the quantitative evaluations (ENG tests),

although some quantitative results were close to being statistically significant. We think that studies with larger numbers of patients would corroborate qualitative results quantitatively and we are continuing our work accordingly.

Study limitations

The number of patients are limited because it was not easy and usual to find patients with all the inclusion and exclusion criteria explained above. That is why we are presenting this paper as a preliminary study and continuing analysing the patients. We purposely designed the flaw of the materials and methods as the study group with hypertension treated with hydrochlorothiazides and the control group without hypertension and any teatment. Through this, the endolmphatic hydrops and vertigo and hypertension connection and similarities would be more accurate.

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Declaration of conflicting interests

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