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A comparison of the effects of perindopril arginine and amlodipine on choroidal thickness in patients with primary hypertension

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Background/aim: This study aimed to investigate the effects of two different medical treatment options on choroidal thickness (CT) in patients with primary hypertension.

Materials and methods: Forty newly diagnosed primary hypertension patients and 21 healthy volunteers were included. The patients were randomly divided into two subgroups. Group I started on perindopril arginine and Group II started on amlodipine. Submacular CT using optical coherence tomography (OCT) was measured before treatment and at the third and sixth months after treatment.

Results: Initial mean arterial pressure (MAP) values in Groups I and II and the control group were 113.4, 109.8, and 89.4 mmHg, respectively, and mean CT values were 257.9, 286.5, and 300.9 μm. Mean MAP values in Groups I and II and the control group at the sixth month after treatment were 99.7, 99.6, and 90.2 mmHg, respectively, and mean CT values were 293.1, 286, and 297.4 μm. Analysis of the changes occurring during the study revealed significant variation in MAP in Groups I and II, and in CT in Group I only.

Conclusion: A gradual increase in CT developed with perindopril arginine therapy in patients with primary hypertension, while no significant change occurred in CT in the amlodipine group.

Key words: Amlodipine, hypertension, perindopril, choroid, optical coherence tomography

1. Introduction

Hypertension, defined as systemic blood pressure elevation, is a relatively common public health problem capable of causing morbidity and mortality (1,2). It can affect all organs and systems in the body. Patients with preexisting hypertension are at greater risk of stroke, myocardial infarction, heart failure, peripheral vascular disease, kidney disease, and various potential ocular complications, particularly in the retina and optic nerve (3–5). Hypertension is therefore an important modifiable risk factor in terms of treatment and of preventing such complications (3).

In addition to the modification of predisposing lifestyle habits, the treatment of hypertension may involve such medical options as angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), or thiazide-type diuretic therapies (5).

ACEIs prevent the formation of angiotensin II, a powerful vasoconstrictor, by inhibiting the enzyme ACE that catalyzes the conversion of angiotensin I into angiotensin II. This enzyme also breaks down bradykinin, a vasodilator peptide. ACEIs thus cause an increase in bradykinin levels. The end result is an antihypertensive effect, as peripheral vascular resistance decreases due to vasodilatation (6). Perindopril arginine is an antihypertensive drug from this group (7).

CCBs reduce muscle tone by inhibiting voltage-dependent calcium channels in the vascular smooth muscle and myocardial cell membrane. This again leads to an antihypertensive effect as peripheral vascular resistance decreases due to vasodilatation. Amlodipine is an antihypertensive drug from this group (8).

Approximately 95% of the blood flow entering the eye passes into the uveal tissue, the vascular layer of the eye. Approximately 70% of it reaches the choroidal segment of the uvea (9). Choroidal circulation is largely controlled by autonomic innervation (10). The main function of the choroid, the tissue with the greatest blood flow per unit weight, is to provide oxygen and metabolite support to the outer part of the retina (11).

Choroidal tissue is implicated in ocular involvement in various systemic diseases and in the development of several

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diseases of the eye. Advances in imaging technologies have greatly facilitated the examination of the choroidal structure, in turn illuminating the etiopathogenesis of several diseases of choroidal origin. Optical coherence tomography (OCT) is a noninvasive, repeatable, and reproducible cross-sectional tissue-imaging modality employed by ophthalmologists (12,13). Data elicited by means of OCT, such as peripapillary retinal nerve fiber layer thickness, ganglion cell complex, retinal thickness, and choroidal thickness (CT), are of considerable importance in the diagnosis and monitoring of numerous ocular and systemic diseases (9,12–17).

Hypertension causes various changes in the microvascular structure of the eye (4,18). Akay et al. reported relatively lower CT values in hypertensive subjects compared to a healthy control group (18). However, due to the cross-sectional design of that study, changes in CT occurring with the treatment of hypertension could not be evaluated. The purpose of this study was to investigate CT values in hypertensive patients and to evaluate the probable effects on CT of two different therapeutic options used in the treatment of hypertension.

2. Materials and methods

This prospective study was performed between August 2014 and May 2015 at the Karadeniz Technical University Faculty of Medicine's Department of Ophthalmology in Trabzon, Turkey. Ethical committee approval was received for the research. Forty newly diagnosed primary hypertension patients presenting to the ophthalmology clinic for hypertensive retinopathy check-up and 21 healthy volunteers presenting for refractive error examination were included in the study. Informed consent was received from all participants.

Inclusion criteria for the hypertensive cases were age over 18, hypertension being newly diagnosed, no previous history of antihypertensive drug use, and no eye disease or additional systemic disease capable of affecting blood flow in the eye or CT, other than hypertension. Inclusion criteria for the control group were age over 18 and having no eye disease or additional systemic disease capable of affecting blood flow in the eye or CT. Patients diagnosed with forms of hypertension other than primary hypertension, with a history of ocular surgery or trauma, with a spherical equivalent of ±5 diopters, or with additional systemic disease such as diabetes mellitus, heart disease, kidney disease, thyroid disease, or any disease that may affect CT were excluded.

All participants underwent basal arterial blood pressure measurements and detailed eye examination. Systemic blood pressure was measured from the right arm in a quiet room after subjects had been allowed to rest in chairs, using a sphygmomanometer. All measurements were performed by the same experienced nurse who was blinded to the groups to which the subjects belonged, from the same arm, allowing subjects time to rest, with subjects in a seated position, and in the same time interval (1300–1500 hours).

Eye examinations included best corrected visual acuity measurement, anterior-posterior segment examinations with the help of a biomicroscope, and intraocular pressure (IOP) measurement. CT measurements were performed using an OCT device (Optovue RTVue, RT100, software version 6.3, Optovue Inc., Fremont, CA, USA). CT was measured as previously described elsewhere (12,19). Briefly, the scan protocol was established as a retina cross-line consisting of two orthogonal 6-mm lines made up of 1024 A-scans. Subsequently, in order to elicit improved visualization of the choroidal layer, the numbers of scans were adjusted to 80 by selecting the chorioretinal scanning mode on "Manual Tab" and the "Auto All" function on "Auto Tab." Choroidal imaging was carried out in cross-line scanning mode. CT was measured from three different levels: the fovea, 1000 μm nasal to the fovea, and 1000 μm temporal to the fovea, using the manual method, by determining the region between the outer margin of the retinal pigment epithelium and the inner margin of the sclera (Figure 1). Mean values for these measurements were subsequently calculated and adopted as the CT value for the eye concerned. Measurements were performed by the same author and in the same time interval (1300–1500 hours).

Hypertensive patients were randomly assigned to one of two systemic therapy groups. Group I (n = 19) was started on perindopril arginine (Coversyl 5 mg tablets, Les Laboratoires Servier Industrie, Gidy, France) once a day and Group II (n = 21) on amlodipine besylate (Norvasc 5 mg tablets, Pfizer Labs, New York, NY, USA) once a day. Arterial blood pressure measurements and detailed ocular examinations were performed three times as described in all cases at the third and sixth months of follow-up.

Arterial blood pressure values measured at three consecutive examinations in all three groups were recalculated using the formula mean arterial pressure (MAP) = diastolic blood pressure + (systolic blood

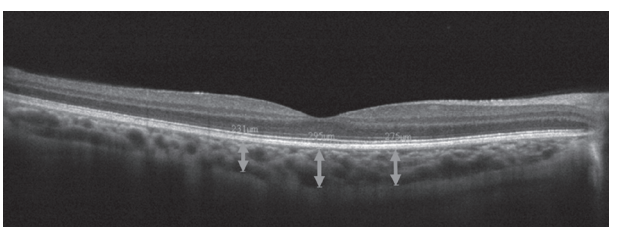

Figure 1. Choroidal thickness measured manually at OCT imaging in one case.

pressure – diastolic blood pressure) / 3. IOP and CT values were calculated based on mean measurements for both eyes.

2.1. Statistical analysis

Measurement data were expressed as mean ± standard deviation and descriptive data as number and percentage. All data were analyzed with SPSS 13.0.1 (SPSS Inc., Chicago, IL, USA). Nonparametric tests were employed in statistical comparisons since the sample size was less than 30 in all three groups. Friedman's test was used to compare consecutive dependent data measured in all groups. Wilcoxon's test was used in two-way comparisons of measurement data identified as significant in the first test. Comparisons between groups were performed using the Kruskal–Wallis test. The Mann–Whitney U test with Bonferroni correction was applied to data for which significant variation was observed. The chi-square test was used to compare descriptive data. $P < 0.05$ was regarded as statistically significant.

3. Results

The mean ages of our subjects were 49.63 ± 7.98 years (33–60) in Group I (n = 19), 48.76 ± 10.29 (23–60) in Group II (n = 21), and 44.9 ± 7.29 (30–55) in the healthy control group (n = 21). The differences between the three groups were not statistically significant (P = 0.119). Eight (57.9%) subjects in Group I were female and 8 (42.1%) were male. In Group II, 13 (61.9%) subjects were female and 8 (38.1%) were male, while in the control group, 14 (66.7%) subjects were female and 7 (33.3%) were male. No statistically significant difference was determined between the three groups in terms of sex distribution (P = 0.848).

No significant difference was observed between the hypertensive groups (I and II) in terms of baseline MAP, IOP, and CT values (P = 0.054, P = 0.421, and P = 0.236, respectively). However, a significant difference was determined between the hypertensive groups and the control group in terms of baseline MAP values (for Group I vs. the control group, $P < 0.0001$, and for Group II vs. the control group, $P < 0.0001$). No significant difference was determined in terms of basal IOP values (for Group I vs. the control group, P = 0.915, and for Group II vs. the control group, P = 0.449) and CT (for Group I vs. the control group, P = 0.117, and for Group II vs. the control group, P = 0.651).

We subsequently assessed whether any significant difference was present among the groups in terms of third month data. No significant difference was determined in MAP, IOP, or CT values between the hypertensive groups (Groups I and II) (P = 0.63, P = 0.036, and P = 0.592, respectively). A significant difference was determined between the hypertensive groups and the healthy control group in terms of MAP values ($P < 0.0001$ for Group I vs. the control group and $P < 0.007$ for Group II vs. the control group). However, no significant difference was observed in IOP (P = 0.668 for Group I vs. the control group, P = 0.71 for Group II vs. the control group) or CT (P = 0.537 for Group I vs. the control group, P = 0.96 for Group II vs. the control group) values.

There was no significant difference between the hypertensive groups in terms of the sixth month data (Groups I and II) in terms of MAP, IOP, or CT values (P = 0.748, P = 0.017, and P = 0.81, respectively). However, we determined significant differences in MAP values between the hypertensive groups and the healthy control group ($P < 0.0001$ for Groups I and II vs. the control group). There was no significant difference in terms of IOP (P = 0.592 for Group I vs. the control group, and P = 0.042 for Group II vs. the control group) or CT (P = 0.957 for Group I vs. the control group, and P = 0.88 for Group II vs. the control group).

MAP values for the study groups obtained at the three different study intervals are shown in Table 1. While no significant difference was determined between consecutive MAP values in the control group, MAP values decreased significantly in Groups I and II (Figure 2). This decrease in Group I was significant in the third and sixth months compared to baseline ($P < 0.0001$ for both), while the decrease in MAP values between the third and sixth months was insignificant (P = 0.238). The decrease in Group II was also significant in the third and sixth months compared to baseline (P = 0.007 and $P < 0.0001$, respectively), while the difference between the third and sixth months was insignificant (P = 0.813).

IOP values in the groups from the three different time intervals are shown in Table 2. Analysis revealed no significant difference in consecutive IOP measurements in the three groups (Figure 3).

CT values from the three time intervals are shown in Table 3. While no significant difference was determined between consecutive CT values in Group II or the control group, a gradual increase in CT values was observed in Group I (Figure 4). This increase in Group I was significant at months 3 and 6 compared to baseline (P = 0.02 and P = 0.009, respectively), but the difference between months 3 and 6 was insignificant (P = 0.059).

The decreases in MAP obtained with medical treatment at the sixth month compared to baseline in the hypertensive groups were 11.49 ± 9.39 (1.67–26.67) mmHg in Group I and 9.44 ± 14.35 (13.33–46.67) mmHg in Group II. There was no significant difference between the two groups in terms of decreases in MAP values (P = 0.668).

4. Discussion

Choroid tissue, the most richly vascularized area in the entire body, provides nourishment and oxygenation for

Table 1. MAP values at different time intervals in the study groups.

Groups	Mean arterial pressure (mmHg)			P-value
	Baseline	3rd month	6th month	
Group I	113.4 ± 6.8 (103.3–133.3)	101.9 ± 9.1 (83.3–121.7)	99.7 ± 7.8 (80–110)	<0.0001
Group II	109.8 ± 4.1 (105–120)	100.4 ± 12.8 (70–123.3)	99.6 ± 6.2 (90–111.3)	0.007
Control	89.4 ± 9 (70–100)	90.7 ± 7.9 (73.3–106.7)	90.2 ± 7.7 (71.7–100)	0.474
P-value I vs. II I vs. control II vs. control	 0.054 <0.0001 <0.0001	 0.63 <0.0001 0.007	 0.748 <0.0001 <0.0001	

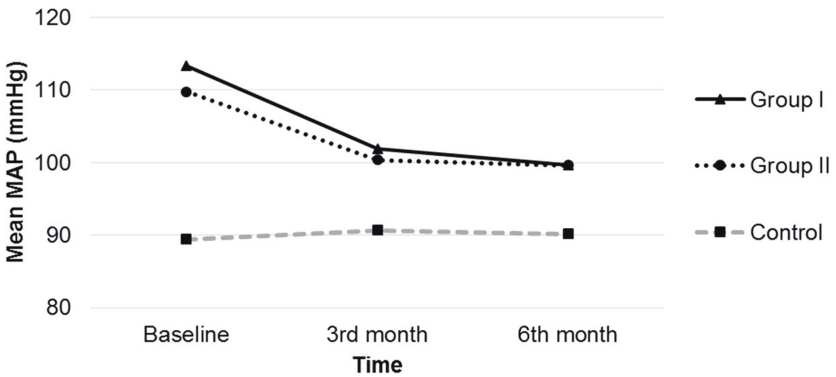

Figure 2. Changes in MAP values obtained at consecutive measurements in the study groups.

Table 2. Mean IOP values at different time intervals in the study groups.

Groups	Mean intraocular pressure (mmHg)			P-value
	Baseline	3rd month	6th month	
Group I	14.8 ± 2.4 (10.5–19)	15.6 ± 1.9 (12.5–18.5)	15.3 ± 2.2 (10.5–19)	0.521
Group II	14.2 ± 2.4 (10.5–20)	13.9 ± 3.4 (9.5–21.5)	13.6 ± 2.2 (11–19)	0.63
Control	15 ± 3 (9.5–21)	15.3 ± 2.8 (10.5–22.5)	15 ± 2.8 (8.5–21.5)	0.692
P-value I vs. II I vs. control II vs. control	 0.421 0.915 0.449	 0.036 0.668 0.071	 0.017 0.592 0.042	

the outer layers of the retina, and is also responsible for temperature regulation in the eye. Impacts on choroidal blood flow can therefore lead to photoreceptor cell dysfunction (20–22). Due to its role in the essential functions of the eye, impairment of choroidal blood flow plays a key role in the pathogenesis of various

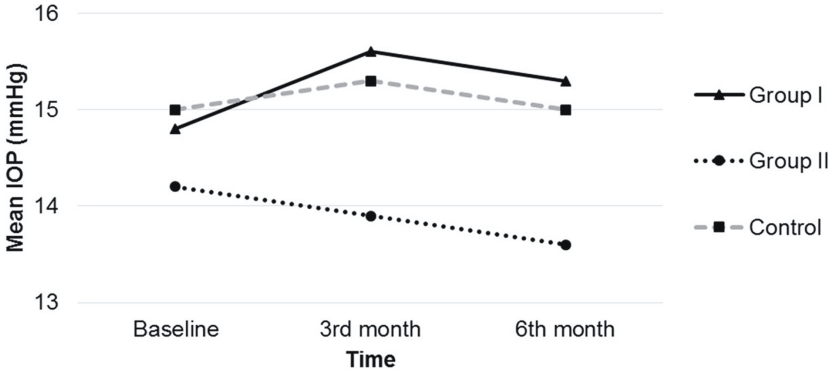

Figure 3. Changes in mean IOP values obtained at consecutive measurements in the study groups.

Table 3. Mean CT values at different time intervals in the study groups.

Groups	Mean choroidal thickness (μm)			P-value
	Baseline	3rd month	6th month	
Group I	257.9 ± 85.8 (119.3–479.7)	279.8 ± 68.1 (167.7–459.5)	293.1 ± 68.6 (178.5–437.8)	0.003
Group II	286.5 ± 81.1 (140.2–475.2)	291.8 ± 88.7 (140.3–531.2)	286 ± 74.7 (141.3–411.5)	0.055
Control	300.9 ± 87.2 (152.8–559)	295.1 ± 82 (175.3–511.5)	297.4 ± 82.5 (166.3–532.8)	0.64
P-value I vs. II I vs. control II vs. control	 0.236 0.117 0.651	 0.592 0.537 0.96	 0.81 0.957 0.88	

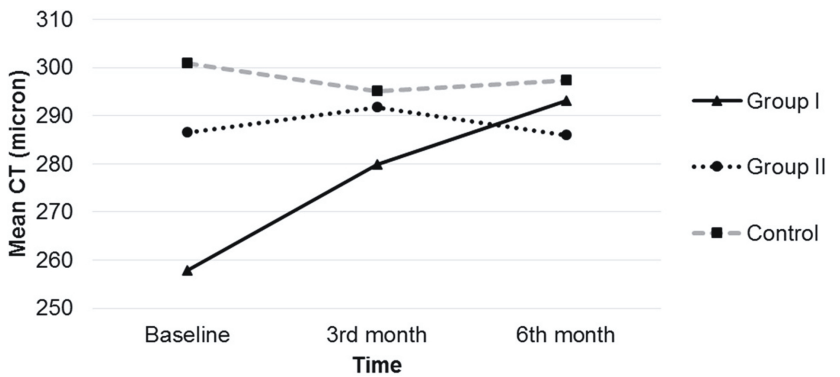

Figure 4. Changes in mean CT values obtained at consecutive measurements in the study groups.

diseases, such as diabetic retinopathy, age-related macular degeneration, and glaucoma (23). Various studies have reported that the thickness of choroid tissue is affected by various diseases, including high myopia and retinal dystrophy, age-related macular degeneration, angioid streak, polypoidal choroidal vasculopathy, central serous

chorioretinopathy, and Vogt–Koyanagi–Harada disease (24–29). Impacts on CT are thus implicated in various pathologies. Since choroidal tissue has a dense vascular structure, any pathological condition affecting the vessels may compromise choroid health.

This study investigated changes in MAP, IOP, and CT in patients with primary hypertension receiving perindopril arginine, from the ACEI group, and amlodipine, from the CCB group. Significant and similar decreases in MAP were achieved with both perindopril arginine and amlodipine therapies. Similarly, Zannad et al. (30) compared the antihypertensive effects of perindopril arginine and amlodipine and determined no statistically significant difference in the peak effects of the two drugs.

Analysis of the final CT measurements revealed a statistically significant increase in CT levels in the perindopril arginine group, but no significant change in the amlodipine group. Drugs from the CCB group, such as nifedipine and amlodipine, are dihydropyridine derivatives that bind to smooth muscle cells with high selectivity. Calcium levels in smooth muscle cells are partly regulated by endothelin-1, which has vasoconstrictor effects (31,32). Studies have shown that amlodipine and nifedipine prevent vasoconstriction by affecting endothelin-1 (33–35). ACE and renin-angiotensin system components, which enable the conversion of angiotensin I into angiotensin II, are also known to be present in ocular tissue (36). In light of the pharmacological effect mechanisms of the antihypertensive drugs used in the study, it seems possible that perindopril arginine use is also involved in an increase in CT with an additional mechanism leading to a rise in bradykinin in tissues.

Similar decreases in MAP observed in the groups using perindopril arginine and amlodipine in our study suggest that changes in CT may be independent of decreases in MAP. Zengin et al. (37) examined CT changes emerging after 1 month of treatment in hypertensive patients using a lisinopril dihydrate + hydrochlorothiazide combination. They reported that the decrease in blood pressure with antihypertensive therapy did not affect CT. They also attributed this to the intense sympathetic innervation and autoregulation mechanisms in the choroid (37). In contrast to that study, we used perindopril arginine, another drug from the ACEI group, and observed a progressive increase in CT values in cases using it. These differing results for CT changes in the two studies may be due to Zengin et al.'s (37) follow-up period being considerably shorter than our own, or due to the drugs having different chemical contents and thus to having exhibiting differing pharmacological effects.

Various drugs used systemically may affect IOP levels. Ganekal et al. (38) showed that the application of CCB group drugs lowered IOP in rabbits. Although the mechanism underlying this effect of CCB group drugs is uncertain, it has been suggested that this may occur by altering aqueous humor secretion by affecting connections between pigmented and nonpigmented ciliary epithelial cells or cation transfer in nonpigmented ciliary cells (39,40). In contrast to Ganekal et al. (38), Beatty et al. (41) stated that topical use of CCBs caused an increase in IOP levels. Payne et al. (42) reported that topical use of CCBs in rabbits had no effect on IOP, but that systemic application caused a decrease in IOP levels. Kelly et al. (43) reported that systemic use of the CCB nifedipine had no significant effect on IOP. Another study reported that topical application of enalaprilat, from the ACEI group, led to a fall in IOP in monkeys (44). One study involving healthy volunteers reported that oral use of ACEI medications had no significant effect on IOP, despite causing a significant decrease in blood pressure (45). Two different drugs were used in our study, one from the CCB group and one from the ACEI group, and no significant change in IOP values was determined in either group, despite a decrease in MAP values.

One study reported that a fall in IOP developing as a result of the systemic application of 20% mannitol infusion in glaucoma patients with asymmetric glaucoma resulted in an increase in CT values (46). That study also observed a greater increase in CT in eyes with a greater decrease in IOP. The change in CT resulting from treatment in the hypertensive groups in our study may therefore be associated with changes in IOP. However, no significant difference was observed between the perindopril arginine and amlodipine groups in changes in IOP after treatment. The statistically significantly greater increase in CT in patients using perindopril arginine, even though similar decreases in IOP were achieved with different therapies in the two groups, may derive from the different effect mechanisms of the two antihypertensive drugs.

The significant increase in CT in the perindopril arginine group in this study, the first of its kind in the literature, may be attributed to vasodilation emerging in choroidal tissue, additional pharmacological effects such as bradykinin accumulation, or drug idiosyncrasy. However, long-term studies with larger numbers of participants are now needed to clarify these cause-and-effect relations. Another limitation of this study is that factors such as smoking and sildenafil citrate and caffeine use that might affect CT measurements were not investigated. Long-term follow-up studies with greater participation and investigation of all factors that might impact CT may thus shed more light on these subjects.

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