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Original Article

Does Choroidal Thickness Change with Fluorescein or Indocyanine Retinal Angiography Procedures?

Ihsan Yilmaz

University of Health Sciences Beyoglu Eye Training and Research Hospital, Istanbul, Turkey

Abstract

Objectives: This study was designed to examine effects of fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) procedures on retinal and choroidal anatomy using optical coherence topography (OCT).

Methods: Sixty eyes of 60 patients were included in this study. Patients who underwent FFA (14 females and 16 males) formed Group 1, and patients who underwent ICGA (17 females, 13 males) formed Group 2. After full ophthalmological examination, macular and choroidal thickness (CT) were measured via OCT. Approximately 15 to 20 minutes after dye was injected for angiography procedure, OCT scan was performed again. Statistical analyses were performed to compare measurements taken before and after procedure.

Results: Mean age was 58.9±10.7 years (range: 42-82 years) in FFA group and 54.9±16.1 (range: 27-77 years) in ICGA group. Mean macular thickness was 339±78 μm before FFA and 339±72 after FFA (p=0.792). Mean macular thickness was 340±80 μm before ICGA and 341±73 μm after ICGA (p=0.571). Mean subfoveal CT was 275±36 μm before FFA and 271±31 μm after FFA (p=0.389). Mean subfoveal CT was 338±36 μm before ICGA and 366±38 μm after ICGA (p=0.022). There was significant increase in CT after ICGA procedure.

Conclusion: CT may not change with FFA procedure, but may increase with ICGA procedure.

Keywords: Choroidal thickness, fluorescein angiography, indocyanine green angiography, macular thickness, optical coherence topography.

Introduction

Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) are important tools in diagnostic and pathogenetic evaluation of chorioretinal circulation (1). Both techniques have greatly expanded knowledge of retinal and choroidal circulatory physiology and fundus pathologies. Specifically, both can be used to confirm diagnosis, monitor progress of disease, and assess efficacy of certain treatments, including laser photocoagulation and intravitreal injection.

Fluorescein and indocyanine are fluorescent dyes often used in retinal angiography. Sodium fluorescein dye absorbs light energy in range of 465 to 490 nm and emits light of 520 to 530 nm. Roughly 80% of fluorescein binds to protein and is thus unavailable for fluorescence. First intravenous FFA was performed in the 1960s. (2, 3). In contrast, indocyanine green (ICG) dye absorbs light energy ranging from 790 to 805 nm and emits light of 770 to 880 nm, with peak emission of 835 nm, which falls in near-infrared spectrum (4). Since almost all of ICG (98%) binds with proteins (5), less dye escapes fenestrated choroidal vasculature than with fluorescein, thereby allowing enhanced imaging of choroidal vessels and choroidal lesions (6). First intravenous ICGA was performed by Flower et al. in 1972 (7). The following year, first simultaneous FFA and ICGA was performed by same team of investigators (8).

In retinal angiography, some parts of sodium fluorescein

Address for correspondence: Ihsan Yilmaz, MD. Beyoglu Goz Egitim ve Arastirma Hastanesi, Bereketzade Cami Sokak, 34421 Beyoglu, Istanbul, Turkey
Phone: +90 212 251 59 00 **E-mail:** ihsanyilmaz.dr@gmail.com

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and ICG pass freely through choroidal vessels into the extravascular space, which may influence choroidal blood flow through either osmotic or hemorheological effect. Though it has been impossible to examine tissue pathology, choroidal thickness (CT) can easily be evaluated and measured quantitatively using optical coherence topography (OCT) (9). Any change to CT after retinal angiography procedure can be detected via OCT.

Recently, determination of CT has become important in diagnosis of certain diseases, such as polypoidal choroidal vasculopathy, central serous chorioretinopathy, retinal angiomatous proliferation, and age-related maculopathy (10–13). Choroid is thicker in eyes with polypoidal choroidal vasculopathy (10) and central serous chorioretinopathy (14) than in normal eyes. It has almost become diagnostic criterion of those diseases. Alternatively, choroid is thinner than normal in eyes with retinal angiomatous proliferation (12) and age-related maculopathy (13). If a physician thinks that a patient may have such a disease, evaluating the patient's CT is very important.

Since changes in macular and choroidal thickness following FFA and ICGA have not yet been studied, objective of the present research was to use OCT to reveal effects of both procedures on retinal and choroidal anatomy.

Methods

Study Design

This retrospective study was performed in Istanbul and conducted according to the principles of the Declaration of Helsinki. All participants provided written, informed consent and underwent routine angiographic procedure for diagnosis of their disorder. Approval of Local ethics committee was obtained.

Ophthalmic Examination

Participants received standard ophthalmological examination that included refraction, visual acuity, and axial length measurements (IOLMaster; Carl Zeiss Meditec, Jena, Germany), as well as slit-lamp biomicroscopy, Goldmann applanation tonometry, ultrasonic pachymetry, and dilated fundoscopy. OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) images were taken and assessed by experienced retinal specialist (I.Y.) who was blinded to angiographic procedure performed. OCT was performed both before procedure and 15 to 20 minutes post injection.

Eligibility Criteria

Inclusion criteria required that participants were non-smokers and did not abuse drugs, had not consumed any alcohol in the previous year or taken any medications in the previous 3 months, had refractive errors ranging from +2 to -2 D spherical equivalent, and had planned retinal angiography.

Exclusion criteria were intraocular pressure (IOP) of >21 mmHg, anterior segment disorder, diagnosis of glaucoma, history of intraocular surgery instead of cataract surgery, history of laser therapy, contact lens use, strabismus, amblyopia, cataract, and ocular inflammatory disease.

Sample was formed of patients who were to undergo retinal angiography between June 2015 and September 2015. Once each participant group was full (i.e., 30 eyes of 30 patients), no additional patients were added. For participants with unilateral disease, the affected eye was designated as the eye for study. For participants with bilateral disease, the right eye was designated as the eye for study in those with even-numbered birth month, while the left eye was selected for those with odd-numbered birth month.

Study Groups

Participants were sorted into 2 groups by type of planned angiographic procedure. Participants who were to undergo FFA formed Group 1, while patients scheduled for ICGA formed Group 2. Sample size was calculated using IBM SPSS SamplePower version 3.0 software (IBM Corp., Armonk, NY, USA). Based on the research design and strategy, minimum of 26 patients was required for each group to provide 90% power.

Angiography Procedure and Device

Spectralis was used for both procedures. For FFA, 5 mL of 10% solution (500 mg fluorescein) was injected intravenously. FFA was performed using standard currently accepted method and 1 or 2 photos were taken each second. For ICGA, 25 mg of ICG was dissolved in 1.5 mL of 0.9% sodium chloride, followed by flush of 3.5 mL of 0.9% sodium chloride, and 1 or 2 photos were taken each second.

Optical Coherence Tomography

Spectralis was used for OCT scans. The choroid was visualized with enhanced deep imaging technique using standardized scanning protocol. Good interobserver agreement and repeatability in manual segmentation of CT measurements has been demonstrated in previous studies (15, 16). OCT scans were obtained before angiographic procedures and 15 to 20 minutes after dye was injected intravenously. CT was measured at subfoveal area and at 500-μm intervals in the nasal and temporal divisions of the fovea up to 2000 μm. CT measurement points were named according to location and distance relative to the fovea. For example, nasal point 500 μm from the fovea was labeled N500, while temporal point 2000 μm from the fovea was labeled T2000. All measurements were performed between 9:00 and 10:00 am.

Data Analysis

Data were expressed as mean±standard error of the mean. Kolmogorov-Smirnov test was used to assess normali-

Table 1. Demographic characteristics of the patient groups

	Group 1 (FA)		Group 2 (ICGA)		p
	Mean±SD	Min./Max.	Mean±SD	Min./Max.	
Age (years)	58.9±10.7	42/82	54.9±16.1	27/77	0.269
Refractive error (SE, D)	0.59±0.83	-1.25/+2.50	-0.69±0.51	-1.50/+0.25	0.075
BCVA	0.57±0.36	0.01/1	0.62±0.26	0.02/1	0.565
Axial length (mm)	23.04±1.07	20.41/24.50	23.25±0.89	21.85/24.36	0.422
Pachymetry (µm)	553±33	492/641	561±22	526/607	0.275
IOP (mmHg)	14.9±1.7	12/18	15.4±1.5	13/18	0.231

FFA: fundus flourescein angiography; ICGA: indocyanine green angiography; SE: spherical equivalent; SD: standard deviation; Max.: maximum; Min.: minimum.

Table 2. Choroidal thickness measurements in Group 1 (µm) (Mean±SD, Min./Max.)

	T2000	T1500	T1000	T500	Subfoveal	N500	N1000	N1500	N2000
Before the procedure	228±38 (142/333)	244±34 (150/355)	260±33 (157/386)	267±31 (151/404)	275±36 (155/422)	259±34 (137/413)	240±38 (109/406)	218±34 (75/383)	193±34 (60/359)
After the procedure	231±31 (132/344)	246±35 (134/359)	260±39 (158/397)	267±38 (150/405)	271±31 (143/418)	254±30 (126/410)	240±36 (119/385)	217±36 (78/372)	192±35 (54/351)
p value (before-after)	0.463	0.527	0.969	0.829	0.389	0.145	0.951	0.794	0.749

SD: standard deviation; Max.: maximum; Min.: minimum.

Table 3. Choroidal thickness measurements in Group 2 (µm) (Mean±SD, Min./Max.)

	T2000	T1500	T1000	T500	Subfoveal	N500	N1000	N1500	N2000
Before the procedure	279±38 (145/462)	290±42 (166/474)	308±40 (166/502)	313±38 (168/520)	338±36 (171/540)	318±38 (145/520)	296±30 (116/506)	283±38 (101/480)	249±36 (88/440)
After the procedure	298±36 (158/498)	317±48 (174/518)	328±42 (170/526)	339±38 (180/538)	366±38 (174/558)	332±36 (165/536)	311±32 (130/531)	298±32 (110/512)	269±38 (92/490)
p value (before-after)	**0.018***	**0.032***	**0.030***	**0.018***	**0.022***	**0.038***	**0.036***	**0.038***	**0.032***

SD: standard deviation; Max.: maximum; Min.: minimum. *significant difference; p<0.05 (paired samples t-test).

ty of each variable. Demographic characteristics of groups were compared using independent samples t-test. For before-and-after CT comparison in each group, paired samples t-test was performed. IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) was used for data analysis, and value of $p<0.05$ was considered to be statistically significant.

Results

Demographic Characteristics

The study included 60 eyes of 60 individuals: 31 females and 29 males. All participants were Caucasian. Patients who underwent FFA (14 females and 16 males) formed Group 1 and patients who underwent ICGA (17 females, 13 males) made up Group 2. Clinical characteristics of age, refractive error, visual acuity, axial length, pachymetry, and IOP were not significantly different between groups ($p>0.05$ for all) (Table1).

In Group 1, 12 patients had systemic hypertension, 8 patients had diabetes mellitus, 6 patients had systemic hypertension and diabetes mellitus, 4 patients had age-related macular degeneration. In Group 2, 14 patients had central serous chorioretinopathy, 12 patients had age-related macular degeneration, and 4 patients had retinal angiomatous proliferation.

Choroidal Thickness

Mean CT measurements before and after procedures are provided in Table 2 and Table 3.

There was no significant difference in CT at any measured point after FFA procedure (Table 2); however, there was significant increase in CT after ICGA procedure at all measured points (Table 3).

Table 4. Central macular thickness measurements in Group 1 and Group2 (μm) (Mean±SD, Min.-Max.)

	Before the procedure	After the procedure	p value (before-after)
Group 1 (FFA)	339±78 (140/768)	339±72 (145/770)	0.792
Group 2 (ICGA)	340±80 (42/553)	341±73 (45/537)	0.571

FFA: fundus fluorescein angiography; ICGA: indocyanine green angiography; SD: standard deviation; Max.: maximum; Min.: minimum.

Macular Thickness

No significant difference in central macular thickness was observed after procedures (Table 4).

Discussion

The choroid is vascularized, pigmented tissue that forms posterior part of the uveal tract. The word choroid is derived from the Greek for "membrane" and "form." Choroidal circulation exhibits one of the highest rates of blood flow in the human body (17) and nourishes not only the choroid but also the retinal pigment epithelium and outer retina (18). Usually, the ophthalmic artery splits into medial and lateral posterior ciliary arteries. Before piercing the sclera, each of these vessels divides into 1 long posterior ciliary artery (total of 2) and variable number of short posterior ciliary arteries (total of 15 to 20).

The choriocapillaris is the final capillary part of the system, and unique structure is crucial to enabling the choroid to perform its functions. The capillaries are large in diameter (about 40–60 μm) and have very thin walls. There are multiple fenestrations, which are 600 to 800 angstroms in diameter, and covering diaphragms present on the capillary wall. During angiography, these fenestrations leak dye molecules.

FFA and ICGA have long been used in ophthalmology and are proven to be valuable diagnostic tools for a host of retinal and choroidal disorders (19). Sodium fluorescein ($C_{20}H_{12}O_5Na$) has a low molecular weight (376 Da) and readily diffuses through most bodily fluids and the choriocapillaris, though not through blood-retinal barriers. Since ICG ($C_{43}H_{47}N_2NaO_6S_2$) has higher molecular weight (775 Da), less dye escapes the fenestrated choroidal vasculature, which allows for enhanced imaging of choroidal vessels and choroidal lesions (6).

Few studies have examined choroidal changes following angiographic procedures. Pekel et al. evaluated choroidal changes after FFA using dynamic contour tonometry that measured changes in IOP and ocular pulse amplitude (OPA), and reported that both mean IOP and OPA values decreased following FFA, though difference was not statistically significant (20) In the present study, we used OCT device, a non-invasive diagnostic and monitoring tool for chorioretinal diseases (21), to detect possible changes following angiographic procedures. We found no significant differences in CT before and after FFA; however, there were significant differences in CT following ICGA.

As results indicated, CT increased with ICGA since greater percentage of indocyanine molecules bind with serum proteins than fluorescein molecules (98% versus 80%) and since indocyanine molecules are larger and heavier than fluorescein molecules (775 Da versus 376 Da), less ICG dye leaks into the choriocapillaris than fluorescein dye. We may thus extrapolate that ICG dye, which is better retained in the vessels, influences choroidal blood flow through an oncotic effect.

The main limitation of the study was that there was no control group. Also, ideal timing of CT measurement after angiographic procedure is difficult to determine. Though taking photographs is crucial in the first 5 minutes of the procedure, it was inappropriate to disturb the examination. However, we quickly sought to measure CT 15 to 20 minutes after dye injection.

In conclusion, though FFA did not affect CT, ICGA did. Subfoveal CT is reported to increase in some diseases, such as polypoidal choroidal vasculopathy (11) and central serous chorioretinopathy (22), yet in contrast is reported to decrease in retinal angiomatous proliferation (23). If a physician thinks that a patient may have such a disease, extra care must be taken while evaluating the patient's CT. In such a case, it may be better to measure CT before ICGA; however, further studies evaluating the possible mechanisms of this phenomenon are needed.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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