Assessment of Retinal and Choroidal Thicknesses With Using Swept-Source OCT Technology After İntravenous Sodium Fluorescein Application in Patients With Non-prolipherative DRP And Non-neovascular AMD

Tugba Cetinkaya[1], Nurullah Kocak[2]

ABSTRACT

Purpose: To compare the central macular thickness (CMT), retinal nerve fiber layer thickness (RNFLT), ganglion cell layer thickness (GCLT), and choroidal thickness (CT) measurements in patients with diabetic retinopathy (DRP) and age-related macular degeneration (AMD) before and after intravenous sodium fluorescein application.

Methods: The study was conducted cross-sectionally on patients with non-prolipherative DRP and non-neovascular AMD who received intravenous sodium fluorescein for fluorescein angiography (FA). The CMT, RNFLT (in four quadrants), GCLT (in six sectors of two different boundaries), and CT (in five locations) measurements were obtained by swept-source optical coherence tomography (SS-OCT) at baseline, two days after, and one month after FA imaging.

Results: The mean age of the patients with DRP (20 women, 18 men) was 64.42 ± 8.98 years (49-87), and that of patients with AMD (20 women, 18 men) was 71.95 ± 10.38 years (48-97). Regarding SS-OCT measurements, all mean CMT, RNFLT (in four quadrants), CT (in five locations), and GCLT values (except temporal-superior quadrant of GCLT+ (p=0.007) and superior quadrant of GCLT++ (p=0.06) in patients with DRP) were similar in baseline, two days, and one month after imaging (p>0.05 for all).

Conclusion: The current study has shown that sodium fluorescein may be affect the measurements of ganglion cell layer thicknesses. This effect may be reversible, however due to the better understood of this issue, large-participated study groups are needed.

Keywords: Choroidal thickness, Retinal neurodegeneration, Sodium fluorescein, Swept Source OCT.

INTRODUCTION

The sodium fluorescein was first invented in 1871 by Adolf Von Baeyer[1]. Then, Novetny and Alvis started to use this drug to photograph the fundus in 1960[2]. From this date, fundus fluorescein angiography (FFA) has been an important diagnostic tool to determine ocular disease[3,4]. The retinal microaneurysms, macular edema, presence of ischemia, optic disc edema, neovascularizations, collateral vessels, etc., may have been shown by using FFA.

Though many systemic adverse effects of fluorescein angiography (FA) have been demonstrated in the literature, this method has been considered a relatively safe approach. The adverse effects can be classified as mild, moderate, and severe. The mild adverse effects have been reported as nausea, vomiting, itching, sneezing, and vaso-vagal disorder. The moderate adverse effects have been reported as urticaria, skin eruptions, syncope, thrombophlebitis, pyrexia, local tissue necrosis, muscular paralysis. And severe adverse effects have been reported as bronchospasm, laryngeal edema, circulatory shock, myocardial infarction, tonic-clonic seizures[5,6,7]. Previous studies demonstrated that the moderate and severe adverse effects were rare and nausea and vomiting were frequent[5,6,8].

The pathophysiology of the adverse effects is not clear. However, some proposed mechanisms include anaphylactoid reactions, vaso-vagal phenomenon, arterial

1- Specialist doctor, Gazi State Hospital, Department of Ophthalmology, Samsun, Türkiye

2- Associate professor doctor, Ondokuzmayıs University Medicine Faculty, Department of Ophthalmology, Samsun, Türkiye

Received: 10.10.2022
Accepted: 27.03.2023

J Ret-Vit 2023; 32:244-251

DOİ:10.37845/ret.vit.2023.32.41

Correspondence Adress:
Tugba Cetinkaya
Gazi State Hospital, Department of Ophthalmology, Samsun, Türkiye

Phone:

E-mail: mdtubacetinkaya@gmail.com

hypotension, reduced cardiovascular perfusion, anxiety-related medullary sympathetic discharge, eliciting tachycardia and myocardial stress; direct vasospastic toxic effect of intravenous injection and direct systemic effect of topical mydriatics[7]. Previous studies have not demonstrated a significant difference in these adverse effects between male and female patients. However, the mild adverse effects have mostly been seen in diabetic and hypertensive patients, but the mechanism has not been explained clearly[8,9].

In the current study, we aimed to investigate whether there is any effect of intravenous sodium fluorescein which leakage from the wall of vessel, on the measurements of the central macular thickness (CMT), the retinal nerve fiber layer thickness (RNFLT), the ganglion cell layer thickness (GCLT), and the choroidal thickness (CT) due to leakage from the wall of vessel.

MATERIALS AND METHODS

This cross-sectional study was conducted according to the tenets of the Helsinki Declaration. After obtaining the ethical approval from the Ethics Committee of Ondokuzmayıs University, each participant signed the informed consent.

Patients

Seventy-six eyes of 38 patients diagnosed with Diabetic Retinopathy (DRP) and 76 eyes of 38 patients diagnosed with Age-related macular degeneration (AMD) were included in this cross-sectional study. All participants underwent a detailed ophthalmic examination, including best-corrected visual acuity (BCVA, defined as logMAR), intraocular pressure measured with Goldmann applanation tonometry, anterior segment, and fundus examination by slit-lamp biomicroscopy. All participants had FA imaging for a detailed understanding of the disease etiology. Since to show the effect of intravenous sodium fluorescein which leakage from the wall of vessel on the retinal and choroidal parameters (such as CMT, RNFLT, GCLT, subfoveal, and mean choroidal thicknesses (sfCT/ mCT)), three measurements (including baseline, two days, and one month after the imaging) obtained by Swept-Source Optical Coherence Tomography (SS-OCT) were compared.

The patients whose spherical refraction less than +/- 6 diopters were included and who have high intraocular pressure (>21 mmHg), any history of the eye diseases such as glaucoma, ocular inflammation, choroidal or retinal disorders were not included to the study. Patients with non-prolipherative DRP and non-neovascular AMD were included, and who need any intravitreal injection or laser photocoagulation were not included in the study.

Fluorescein Angiography

A single 5ml sodium fluorescein 10% (Fluosine / pharmARGUS) was used in a single 5 ml dose, injected into the cubital vein, with a manual infusion speed of approximately 1 ml per second for the imaging. Approximately 10 seconds later, sodium fluorescein has been started to seen in retinal vascular system. The images were captured through a Topcon Retinal Camera 50 EX (Topcon, Tokyo, Japan) with the aid of a digital program.

The visibility of the sodium fluorescein in the retinal vascular system has been continuing for 10 minutes. FA image shows the retinal and choroidal lesions as hyper-fluorescence, hypo-fluorescence, or auto-fluorescence.

OCT

The retinal nerve fiber layer thickness, ganglion cell layer thickness, central macular thickness, subfoveal and mean choroidal thickness were evaluated by using DRI Triton SS-OCT (Topcon, Tokyo, Japan) with 1050 nm wavelength, 100.000 A-scans per second, and 8mm axial and 20 mm trasverse resolution.

The measurement of CMT was obtained from inner limiting membrane (ILM) to retinal pigment epithelium (RPE) on the fovea. RNFLT was measured between ILM and the GCL boundaries at four peripapillary quadrants (temporal, superior, nasal, inferior). The GCL thicknesses were obtained from two different layers and in six different sectors (superior, temporal-inferior, temporal-superior, inferior, nasal-inferior, and nasal-superior) of the macular region. One layer of them is GCL+ thickness that measured between RNFL and the inner nuclear layer (INL) limit. And the other one is GCL++ thickness that measured between ILM and the INL boundaries.

The measurements of SFCT obtained from the Bruch membrane to the sclera-choroidal interface under the fovea. The choroidal thickness values obtained from five different locations as subfoveal, and at 500m and 1,500m both temporal and nasal from the centre of the fovea. CT values were measured by an automated module of the Triton.

RESULTS

The mean age of the patients with DRP (20 women, 18 men) was 64.42 ± 8.98 years (49-87), and the mean age of the patients with AMD (20 women, 18 men) was 71.95

± 10.38 years (48-97). The mean visual acuity was 0.38 ± 0.29 logMAR in the DRP group, and that of patients with AMD was 0.35 ± 0.29 logMAR. The mean CMT and RNFLT measurements at three-time points in patients with DRP were displayed in table 1. There were no significant differences in any time-point measurements.

The mean GCLT+ and GCLT++ measurements in the six quadrants (temporal-superior, superior, nasal-superior, nasal-inferior, inferior, temporal-inferior) of the DRP group are displayed in table 2. There was not any significant difference between any time points except temporal-superior quadrant of GCLT+.

The mean CT obtained from five different locations in patients with DRP (subfoveal, 500mm, and 1500mm, both temporal and nasal from the center of the fovea) are represented in table 3. There were no significant differences in any time of the measurements. The mean subfoveal and 500mm nasal choroidal thickness have shown first a decrease at two days after imaging and then an increase at one month after imaging insignificantly (p>0.05).

The mean CMT and the mean and four peripapillary quadrants of RNFLT measurements in patients with AMD, which were obtained at baseline, two days, and one month after FA, are represented in table 4. All results

Table 1*: Comparisons of the mean CMT and RNFL thickness measurements of the patients with DRP at different time points.*

Thickness Measurements (mm)	*Baseline mean± SD*	*Two days after imaging mean± SD*	*One month after imaging mean± SD*	*P* value*
Macula fovea	233.16 ± 23.06	239.33 ± 30.27	256.00 ± 50.81	0.22*
RNFL	87.50 ± 12.81	86.00 ± 17.79	73.50 ± 26.18	0.21*
RNFL_temporal	68.25 ± 17.15	65.25 ± 20.98	56.75 ± 32.22	0.27*
RNFL_superior	106.00 ± 9.59	97.00 ± 36.34	80.50 ± 31.28	0.20*
RNFL_nasal	80.25 ± 8.95	76.25 ± 14.84	68.25 ± 21.89	0.21*
RNFL_inferior	95.25 ± 18.62	104.25 ± 4.11	88.00 ± 29.04	0.54*

SD: Standart deviation; CMT: Central macular thickness;RNFL: Retinal nerve fiber layer,DRP: Diabetic Retinopathy; p*: Repeated measures analysis of variance test.

Table 2: *Comparisons of the six quadrants of the mean GCLT+ and the six quadrants of the mean GCLT++ measurements that obtained at baseline, two days and one month after FA of the eyes in patients with DRP.*

Thickness Measurements (mm)	*Baseline mean± SD*	*Two days after imaging mean± SD*	*One month after imaging mean± SD*	*P* value*
GCL+_Ts	65.33 ± 8.38	64.33 ± 7.57	39.33 ± 7.37	**0.007***
GCL+_S	63.33 ± 4.16	60.00 ± 11.53	33.33 ± 22.36	0.08*
GCL+_Ns	66.00 ± 8.18	65.00 ± 15.09	46.33 ± 30.02	0.27*
GCL+_Ni	66.33 ± 7.09	67.33 ± 5.13	50.33 ± 23.69	0.32*
GCL+_İ	60.66 ± 13.57	63.33 ± 4.04	60.00 ± 3.00	0.80*
GCL+_Ti	69.66 ± 13.31	65.66 ± 6.42	69.66 ± 7.50	0.49*
GCL++_Ts	88.66 ± 9.86	86.33 ± 8.73	73.33 ± 30.43	0.56*
GCL++_S	98.00 ± 9.16	92.33 ± 18.55	54.00 ± 29.13	0.06*
GCL++_Ns	110.00 ± 18.52	104.66 ± 27.09	82.33 ± 38.55	0.13*
GCL++_Ni	111.00 ± 12.52	112.00 ± 10.53	93.33 ± 28.29	0.36*
GCL++_İ	96.00 ± 18.08	100.00 ± 8.7	116.66 ± 29.48	0.45*
GCL++_Ti	97.50 ± 16.26	92.00 ± 7.07	91.00 ± 8.48	0.50*

SD: Standart deviation, FA: Fluorescein angiography, GCL+/++_Ts: Ganglion cell layer in temporal-superior, GCL+/++_S: Ganglion cell layer in superior, GCL+/++_Ns: Ganglion cell layer in nasal-superior, GCL+/++_Ni: Ganglion cell layer in nasal-inferior, GCL+/++_I: Ganglion cell layer in inferior, GCL+/++_Ti: Ganglion cell layer in temporal-inferior, DRP: Diabetic Retinopathy; p*: Repeated measures analysis of variance test.

Table 3: *Comparison of the mean ChT measurements that obtained at baseline, two days and one month after FA of the eyes in patients with DRP.*

Choroidal thickness Measurements (µm)	*Baseline mean± SD*	*Two days after imaging mean± SD*	*One month after imaging mean± SD*	*P* value*
Mean choroid	269.83 ± 121.30	258.86 ± 93.33	279.76 ± 115.15	0.26*
Subfoveal	287.50 ± 119.72	268.66 ± 92.22	311.50 ± 120.74	**0.052***
Temporal_500	286.50 ± 118.20	276.50 ± 78.42	294.66 ± 113.12	0.64*
Temporal_1500	275.00 ± 119.40	274.50 ± 89.84	277.66 ± 111.99	0.97*
Nasal_500	270.66 ± 124.46	256.83 ± 100.02	290.00 ± 127.97	**0.07***
Nasal_1500	229.50 ± 140.07	217.83 ± 121.12	225.00 ±134.90	0.41*

SD: Standart deviation, ChT: Choroidal thickness; FA: Fluorescein angiography, DRP: Diabetic Retinopathy; p*: Repeated measures analysis of variance test.

Table 4: *Comparisons of the mean CMT, the mean and four quadrants of RNFLT measurements that obtained at baseline, two days and one month after FA of the eyes in patients with AMD.*

Thickness Measurements (mm)	*Baseline mean± SD Median (min-max)*	*Two days after imaging mean± SD Median (min-max)*	*One month after imaging mean± SD Median (min-max)*	*P* value*
Macula fovea	221.47 ± 43.16	220.52 ± 75.56	202.23 ± 63.82	0.38*
RNFL	95.30 ± 18.15	92.25 ± 20.27	93.35 ± 16.24	0.72*
RNFL_temporal	65.35 ± 19.70	68.45 ± 15.00	67.15 ± 15,79	0.46*
RNFL_superior	113.02 ± 26.84 118.00 (44.00-162.00)	112.33 ± 28.70 118.50 (34.00-157.00)	110.21 ± 20.38 114.00 (56.00-140.00)	0.22**
RNFL_nasal	72.83 ± 21.90 75.00 (27.00-125.00)	70.86 ± 22.17 71.50 (4.00-118.00)	70.26 ± 14.17 74.00 (26.00-86.00)	0.44**
RNFL_inferior	116.83 ± 26.32 118.00 (41.00-169.00)	113.00 ± 36.83 121.50(5.00-161.00)	122.34 ± 24.59 128.00 (53.00-172.00)	0.59**

SD: Standart deviation, CMT: Central macular thickness; FA: Fluorescein angiography, RNFLT: Retinal nerve fiber layer thickness, AMD: Adult Macular Degeneration; p*: Repeated measures analysis of variance test; p**: Friedman test.

were compared between baseline and after FA imaging ($p > 0.05$, for all).

The mean GCLT+ and GCLT++ measurements in the six quadrants (temporal-superior, superior, nasal-superior, nasal-inferior, inferior, temporal-inferior) of the macular region in patients with AMD are displayed in table 5. Any statistically significant difference was not found between before and after imaging.

The mean ChT obtained from five different locations in patients with AMD are represented in table 6. There was no significant difference in any time.

DISCUSSION

FA, which is the diagnostic method used in the diagnosis, treatment planning, and follow-up of retinal disorders, including vasoproliferative diseases such as DRP and exudative AMD in adults, provides us very useful information. And also, it has an important place among children in the evaluation of retinal diseases such as retrolental fibroplasia, Coats disease, sickle cell retinopathy, choroidal neovascular membranes, ocular tumors, and other diseases[10]. However, studies have been limited due to the difficulty of fundus imaging in children.

Healthy retinal vessels prevent the leakage of the fluorescein molecules into the extravascular space. The hypo-fluorescence lesions originate from fluorescence blockage caused by opacity or hemorrhage or vascular filling defects caused by vascular occlusion. The hyper-fluorescence lesions are seen secondary to fluorescein leakage, fluorescein staining, fluorescein pooling, and window defect. The retinal microaneurysms, diverticulas, macular edema, neovascularisations, and collateral vessels may be demonstrated in patients with DRP as hyper-

Table 5: *Comparisons of the six quadrants of the mean GCLT+ and the six quadrants of the mean GCLT++ measurements that obtained at baseline, two days and one month after FA of the eyes in patients with AMD.*

Thickness Measurements (mm)	*Baseline mean± SD Median (min-max)*	*Two days after imaging mean± SD Median (min-max)*	*One month after imaging mean± SD Median (min-max)*	*P* value*
GCL+_Ts	67.53 ± 6.73	58.26 ± 19.58	64.86 ± 8.76	**0.09***
GCL+_S	61.64 ± 15.57 63.00 (9.00-86.00)	64.72 ± 14.45 67.00 (14.00-86.00)	63.64 ± 13.52 67.00 (21.00-81.00)	0.49**
GCL+_Ns	65.54 ± 17.36 69.00 (12.00-92.00)	68.48 ± 17.32 71.00 (21.00-95.00)	70.05 ± 13.15 69.00 (34.00-94.00)	0.65**
GCL+_Ni	66.24 ± 12.73 69.00 (23.00-86.00)	64.34 ± 18.60 70.00 (13.00-84.00)	64.52 ± 18.52 68.00 (15.00-84.00)	0.79**
GCL+_İ	61.67 ± 12.35 63.00 (27.00-80.00)	60.82 ± 15.59 65.00 (20.00-78.00)	58.52 ± 18.01 64.00 (5.00-72.00)	0.36**
GCL+_Ti	65.75 ± 13.16 69.00 (36.00-85.00)	62.72 ± 16.77 67.00 (27.00-83.00)	64.52 ± 16.95 71.00 (16.00-75.00)	0.50**
GCL++_Ts	86.59 ± 19.37 91.00 (23.00-110.00)	83.75 ± 22.06 89.00(17.00-118.00)	90.23 ± 22.08 93.00(39.00-155.00)	0.56**
GCL++_S	96.18 ± 24.30 99.00 (11.00-132.00)	99.62 ± 21.38 101.00 (27.00-136.00)	98.05 ± 21.26 102.00 (34.00-129.00)	0.92**
GCL++_Ns	112.06 ± 16.03	108.53 ± 21.17	109.20 ± 18.53	0.42*
GCL++_Ni	110.08 ± 17.39 114.00 (78.00-140.00)	106.27 ± 29.31 116.00 (30.00-150.00)	107.52 ± 28.73 117.00 (28.00-152.00)	0.98**
GCL++_İ	97.70 ± 19.83 100.00 (43.00-123.00)	100.24 ± 24.51 107.00 (28.00-138.00)	93.70 ± 28.43 104.00 (8.00-120.00)	0.76**
GCL++_Ti	88.70 ± 16.35 92.00 (50.00-115.00)	90.37 ± 23.13 99.00 (37.00-126.00)	87.17 ± 26.06 96.00 (20.00-111.00)	1.00**

SD: Standart deviation, FA: Fluorescein angiography, GCL+/++_Ts: Ganglion cell layer in temporal-superior, GCL+/++_S: Ganglion cell layer in superior, GCL+/++_Ns: Ganglion cell layer in nasal-superior, GCL+/++_Ni: Ganglion cell layer in nasal-inferior, GCL+/++_I: Ganglion cell layer in inferior, GCL+/++_Ti: Ganglion cell layer in temporal-inferior, AMD: Adult Macular Degeneration; p*: Repeated measures analysis of variance test; p**: Friedman test.

fluorescence areas, and the reason of hyper-fluorescence areas or fluorescein leakages are the abnormal vascular permeability due to the deterioration of the internal blood-retina barrier. All types of drusens (such as hard drusen, soft drusen, cuticular drusen, pseudoreticular drusen) which are caused by local accumulation of materials under the basement membrane of the retinal pigmentary epithelium (RPE) or small RPE detachments, and pigmentary epithelium alterations which are associated with atrophic areas may be demonstrated on FA imaging as hyper-fluorescent spots in patients with AMD. FA can also differentiate the shunt vessels as neovascularizations which occur as an alternative to impaired venous drainage between retina and choroid.

The non-invasive alternatives to the FA, such as OCT angiography (OCT-A), have been investigated because of the FA-related complications and risks[11,12]. However, OCT-A systems are not common due to their high cost, inability to show the vascular leakages, the necessity to stay in the same anatomical location for the patient, and limited field of view. Therefore, FA still maintains its importance in the diagnosis and follow-up the vascular diseases[13].

There are numerous studies about the systemic adverse effects associated with intravenous sodium fluorescein which has been using during FA. As far as we know, there was no previous study about any structural effects of intravenous sodium fluorescein which leakage from the wall of vessel on the retinal and choroidal layers.

In the literature, it has been shown that the thickness of macula, RNFL, GCL and choroid can be affected by many diseases and drug use[14-19].

Table 6: *Comparison of the mean ChT measurements that obtained at baseline, two days and one month after FA of the eyes in patients with AMD.*

Choroidal thickness Measurements (µm)	*Baseline mean± SD Median (min-max)*	*Two days after imaging mean± SD Median (min-max)*	*One month after imaging mean± SD Median (min-max)*	*P value*
Mean choroid	244.24 ± 95.17 224.20 (112.80-464.60)	245.28 ± 90.46 226.60 (118.80-439.40)	245.77 ± 91.19 235.20 (133.20-468.20)	0.69**
Subfoveal	258.81 ± 101.04 233.00 (112.00-507.00)	258.31 ± 90.62 240.00 (137.00-455.00)	260.13 ± 92.00 241.00 (148.00-489.00)	0.84**
Temporal_500	259.18 ± 99.37 240.00 (115.00-489.00)	260.06 ± 92.06 243.00 (125.00-481.00)	253.21 ± 87.88 239.00 (133.00-463.00)	0.69**
*Tempor*al_1500	258.36 ± 92.18	267.84 ± 104.40	266.26 ± 95.45	0.48*
Nasal_500	245.86 ± 101.43 215.00 (92.00-509.00)	246.68 ± 92.16 226.00 (101.00-446.00)	249.04 ± 90.18 239.00 (129.00-468.00)	0.10**
Nasal_1500	213.21 ± 99.39 188.00 (62.00-426.00)	207.03 ± 94.03 187.00 (72.00-402.00)	250.13 ± 94.49 233.00 (123.00-485.00)	0.19**

SD: Standart deviation, ChT: Choroidal thickness; FA: Fluorescein angiography, AMD: Adult Macular Degeneration; p*: Repeated measures analysis of variance test; p**: Friedman test.

For example, the RNFL thinning and abnormal optic nerve appearence have been detected in the normal course of disease in patients with DRP independent from glaucomatous optic nerve damage and also as a result of the panretinal photocoagulation therapy[20]. These results have been attributed to the glycosylation end products caused by direct damage and thermal damage[21]. Different laser methods have been developed to reduce this damage, and it has been reported that pattern scanning laser photocoagulation causes less RNFL thinning compared to the conventional laser method, since it is limited only to the retina pigment epithelium(RPE) and photoreceptor layers without reaching the inner and outer retinal layers[22-26]. In this study, our patients were in non-prolipherative stage of the disease and any of them need intravitreal injection or laser photocoagulation.

Additionally, the systemic hypertension causes to the thinning of the GCL and RNFL thickness, due to decreased ocular blood flow and chronic ischemia[27-29].

Furthermore, chronic alcohol using may reduce the thickness of RNFL, GCL, IPL and choroid[30].

An increase in the radial peripapillary capillary vascular density with using oral Ginkgo Biloba has been demonstrated in the literature[31].

At the same time, Moriguchi et al. have demonstrated dosage dependent reversible and irreversible photoreceptors and RPE cells damage by intravenous sodium iodate[32].

Besides these, the choroidal thickness has been affected by AMD[33],degenerative myopia[34], CSCR[35], Alzheimer's disease[36,37], Parkinson's disease[38], systemic hypertension[39], smoking, caffeine consumption and sunlight. Since the choroid has a dense vascular component, it can also be affected by drugs that can be effective on vascular tissues. An increase in the choroidal thickness has been shown with using a lytic therapy[40], antiglaucomatous drops (especially prostaglandins) [41],and dopamin agonists[42].

According to the studies, drugs with sympathomimetic effects, such as phenylephrine, can decrease the choroidal thickness through contraction of the choroidal vascular bed and non-vascular smooth muscle cells[43,44]. Additionally, drugs with anticolinergic effects, such as atropine and cycloplejin, can increase choroidal thickness through nitric oxide and dopamine extraction[45].

In ophthalmology practice, the FA (with using intravenous sodium fluorescein) is used many times to same patient for both diagnosis and follows-up of the retinal diseases. Therefore, in the current study, we hypothesized that frequent FA and fluorescein leakages due to the damaged retinal layers, may affect the measurements of macular thickness, RNFLT, GCL and choroidal thickness. In the current study, we found statistically significant decrease in the temporal superior quadrant of GCL thickness, and an insignificant decrease in the superior quadrant of GCL thickness in patients with DRP at one month after FA. Additionally, we determined an insignificant decrese in the choroidal thicknesses of subfoveal and 500mm nasal

from the centre of the fovea in patients with DRP at two days after FA, and then an insignificant increase in that measurements at one month after FA. However, although not significant in patients with AMD, the temporal superior quadrant of GCL thickness has first decreased at two days after FA, then has increased at one month after FA. According to these results, we thought that decreasing in the measurements of GCL thicknesses may be attributed to the fluorescein leakage from defective vessel wall in DRP patients and defective retinal layers in AMD patients. However, decreasing of the choroidal thicknesses at two days after FA and then increasing of the measurements at one month after FA may be showing the reversible effect of sodium fluorescein on choroidal layers.

The current study had some limitations which are the small number of participants that might have prevented statistical significance on retinal and choroidal parameters, the measurements that were taken manually and could have caused differences in the results, lastly the participants that were limited to DRP and AMD.

In conclusion, we can say that the measurements of GCL and choroidal thicknesses may be affected from sodium flourescein reversibly which used in FA. Even if we thought it might be a reversible effect, it may cause permanent damage to retinal and choroidal layers in the long term due to frequent imaging. However, larger study groups are needed to support this hypothesis.

To our best knowledge this might be the first study reporting the comparative results regarding retinal neurodegenerative alterations and choroidal thickness measurements associated with intravenous sodium fluorescein.

REFERENCES

1- Von Baeyer A. Uber ein neue Klasse von Farbstoffen. Ber Deut Chem Ges. 1871;4:55

2- Novotny HR, Alvis DL. A method of photographing fluorescein in circulating blood in the human retina. Circulation. 1961;24:82-6.

3- Berkow JW, Flower RW, Orth DH, Kelley JS. Fluorescein and Indocyanine Green Angiography: techniques and interpretation. 2nd ed. San Francisco: The Foundation of the American Academy of Ophthalmology; 1997, 224.

4- Alvis DL. Twenty-fifth anniversary of fluorescein angiography. Arch Ophthalmol.1985;103:1269.

5- Stein MR, Parker CW. Reactions following intravenous fluorescein. Am J Ophthalmol. 1971;72:861-8.

6- Kwiterovich KA, Maguire MG, Murphy RP, Schachat AP, Bressler NM, Bressler SB et al. Frequency of adverse systemic reactions after fluorescein angiography: results of a prospective study. Ophthalmology. 1991;98:1139-42.

7- Yannuzzi LA, Rohrer KT, Tindel LJ, Sobel RS, Costanza MA, Shields W et al. Fluorescein angiography complication survey. Ophthalmology. 1986;93:611-7.

8- Karhunen U, Raitta C, Kala R. Adverse reactions to fluorescein angiography. Acta Ophthalmol. 1986;64:282-6.

9- Lepri A, Salvini R, Rizzo L, Cetica P, Grechi S, Di Filippo A et al. Accidenti durante angiografia retinica con fluoresceina. Minerva Anesthesiol.1997;63:133-40.

10- Cantolino SJ, O'Grady GE, Herrera JA, et al. Ophthalmoscopic monitoring of oxygen therapy in premature infants. Fluorescein angiography in acute retrolental fibroplasia. Am J Ophthalmol. 1971;72:322–31.

11- Wang, R. K. et al. Three dimensional optical angiography. Opt. Express 15, 4083–97 (2007).

12- De Carlo, T. E., Romano, A., Waheed, N. K. & Duker, J. S. A review of optical coherence tomography angiography (OCTA). Int.J.Retina Vitreous 1, 5 (2015).

13- Zhang, Q. et al. Wide-field optical coherence tomography based microangiography for retinal imaging. Sci. Rep. 6, 1–10 (2016).

14- Yannuzzi LA, Slakter JS, Sorenson JA, Guyer DR, Orlock DA. Digital indocyanine green videoangiography and choroidal neovascularization. Retina. (1992) 12:191–223. doi: 10.1097/00006982-199212030-00003

15- Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D. Digital indocyanine green videoangiography of central serous chorioretinopathy. Arch Ophthalmol. (1994) 112:1057–62. doi: 10.1001/archopht.1994.01090200063023 Frontiers in Medicine. www.frontiersin.org 13 December 2021;8:797428 Kim and Oh Choroidal Thickness Profile

16- Prunte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol. (1996) 121:26–34. doi: 10.1016/S0002-9394;70531-8

17- Spaide RF, Yannuzzi LA, Slakter JS, Sorenson J, Orlach DA. Indocyanine green videoangiography of idiopathic polypoidal choroidal vasculopathy. Retina. (1995) 15:100–10. doi: 10.1097/00006982-199515020-00003

18- Yannuzzi LA, Wong DW, Sforzolini BS, Goldbaum M, Tang KC, Spaide RF, et al. Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. Arch Ophthalmol. (1999) 117:1503–10. doi: 10.1001/archopht.117.11.1503

19- Khan S, Engelbert M, Imamura Y, Freund KB. Polypoidal choroidal vasculopathy: simultaneous indocyanine green angiography and eye-tracked spectral domain optical coherence tomography findings. Retina. (2012) 32:1057–68. doi: 10.1097/IAE.0b013e31823beb14

20- Lim MC, Tanimoto SA, Furlani BA, et al. Effect of diabetic retinopathy and panretinal photocoagulation on retinal nerve fiber layer and optic nerve appearance. Arch Ophthalmol 2009;127:857-62.

21- Hsu SY, Chung CP. Evaluation of retinal nerve fiber layer thickness in diabetic retinopathy after panretinal photocoagulation. Kaohsiung J Med Sci 2002;18:397-400.

22- Nagpal M, Marlecha S, Nagpal K. Comparison of laser photocoagulation for diabetic retinopathy using 532-nm standard laser versus multispot pattern scan laser. Retina 2010;30:452-8.

23- Maeshima K, Utsugi-Sutoh N, Otani T, Kishi S. Progressive enlargement of scattered photocoagulation scars in diabetic retinopathy. Retina 2004;24:507-11.

24- Marshall J, Hamilton AM, Bird AC. Histopathology of ruby and argon laser lesions in monkey and human retina: a comparative study. Br J Ophthalmol 1975;59:610-30.

25- Palanker D, Lavinsky D, Blumenkranz MS, Marcellino G. The impact of pulse duration and burn grade on size of retinal photocoagulation lesion: implications for pattern density. Retina 2011;31:1664-9.

26- Muqit MM, Gray JC, Marcellino GR, et al. Fundus autofluorescence and Fourier-domain optical coherence tomography imaging of 10 and 20 millisecond Pascal retinal photocoagulation treatment. Br J Ophthalmol 2009;93:518-25.

27- Choi J, Kook MS. Systemic and Ocular Hemodynamic Risk Factors in Glaucoma. Biomed Res Int 2015;2015:141905

28- Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res 2002;21:359-93.

29- Flammer J. The vascular concept of glaucoma. Surv Ophthalmol 1994;38 Suppl:S3-6.

30- Orum MH, Kalenderoglu A. Decreases in retinal nerve fiber layer thickness correlates with cumulative alcohol intake. J Addict Dis. Oct-Dec 2020;38:400-410. doi: 10.1080/10550887.2020.1776083. Epub 2020 Jun 25.

31- Mehmet Cem Sabaner, Mustafa Dogan, Salih Samed Altin, Cemil Balaman, Ceyda Yilmaz, Aysegul Omur, Irem Zeybek, Muserref Palaz. Ginkgo Biloba affects microvascular morphology: a prospective optical coherence tomography angiography pilot study. Int Ophthalmol (2021) 41:1053–61.

32- Mayu Moriguchi, Shinsuke Nakamura, Yuki Inoue, Anri Nishinaka, Maho Nakamura, Masamitsu Shimazawa, and Hideaki Hara. Irreversible Photoreceptors and RPE Cells Damage by Intravenous Sodium Iodate in Mice Is Related to Macrophage Accumulation. Invest Ophthalmol Vis Sci. 2018;59:3476-3487. doi: 10.1167/iovs.17-23532.

33- Spaide RF. Enhanced depth imaging optical coherence tomography of retinal pigment epithelial detachment in age-related macular degeneration. Am J Ophthalmol. 2009;147:644–52.

34- El-Shazly AA, Farweez YA, ElSebaay ME, El-Zawahry WMA. Correlation between choroidal thickness and degree of myopia assessed with enhanced depth imaging optical coherence tomography. Eur J Ophthalmol. 2017;27:577–84.

35- Maruko I, Iida T, Sugano Y, Ojima A, Sekiryu T. Subfoveal choroidal thickness in fellow eyes of patients with central serous chorioretinopathy. Retina. 2011;31:1603–8.

36- Gharbiya M, Trebbastoni A, Parisi F, Manganiello S, Cruciani F, D'Antonio F, et al. Choroidal thinning as a new finding in Alzheimer's disease: evidence from enhanced depth imaging spectral domain optical coherence tomography. J Alzheimers Dis. 2014;40:907–17.

37- Bayhan HA, Aslan Bayhan S, Celikbilek A, Tanık N, Gürdal C. Evaluation of the chorioretinal thickness changes in Alzheimer's disease using spectral-domain optical coherence tomography. Clin Exp Ophthalmol. 2015;43:145–51.

38- Moschos MM, Chatziralli IP. Evaluation of choroidal and retinal thickness changes in parkinson's disease using spectral domain optical coherence tomography. Semin Ophthalmol. 2018;33:494–7.

39- Akay F, Gundogan FC, Yolcu U, Toyran S, Uzun S. Choroidal thickness in systemic arterial hypertension. Eur J Ophthalmol. 2016;26:152–7.

40- Maddalena De Bernardo, Vincenzo Altieri, Alessia Coppola, Marco Gioia, Nicola Rosa. Choroidal evaluation in patients under alpha-lytic Therapy. Graefe's Archive for Clinical and Experimental Ophthalmology (2020) 258:2729–36.

41- Nurettin Akyol, Ahmet Kalkisim, Adem Turk, Mehmet Kola, Halil Ibrahim Imamoglu. Evaluation of the effects on choroidal thickness of bimatoprost 0.03% versus a brinzolamide 1.0%/ timolol maleate 0.5% fixed combination. Cutan Ocul Toxicol, 2017; 36: 397–403

42- Debora L. Nickla, Kristen Totonelly, Balprit Dhillon. Dopaminergic agonists that result in ocular growth inhibition also elicit transient increases in choroidal thickness in chicks. Exp Eye Res. 2010 November; 91: 715–720. doi:10.1016/j.exer.2010.08.021.

43- Kara N, Demircan A, Karatas G, Ozgurhan EB, Tatar G, Karakucuk Y, et al. Effects of two commonly used mydriatics on choroidal thickness: direct and crossover effects. J Ocul Pharm Ther. 2014;30:366–70.

44- Yuvacı İ, Pangal E, Yuvacı S, Bayram N, Ataş M, Başkan B, et al. An evaluation of effects of different mydriatics on choroidal thickness by examining anterior chamber parameters: the scheimpflug imaging and enhanced depth imaging-OCT study. J Ophthalmol. 2015;2015:981274.

45- Zhengwei Zhang, Yuanting Zhou, Zhifang Xie, Tiantian Chen, Yan Gu, Shui Lu, Zhifeng Wu. The effect of topical atropine on the choroidal thickness of healthy children. Scientific Reports | 6:34936 | DOI: 10.1038/srep34936.