Wills Eye Hospital

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Acute Changes in Optic Nerve Head (ONH) and Macular Blood Flow after Caffeine Consumption in Glaucoma Patients and Healthy Subjects: A Quantitative Optical Coherence Tomography Angiography (OCTA) Study

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NCT03675412
IRB# 18-729

Study Protocol
April 25, 2019

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Objectives

The primary objective of this study is to assess the acute changes in peripapillary and macular blood flow after an intake of oral caffeine in glaucoma patients and healthy subjects, by using optical coherence tomography angiography (OCTA).

Hypothesis

Ingestion of caffeine in glaucoma patients and healthy subjects may decrease peripapillary and macular blood flow.

Background and Significance

Caffeine is the most widely consumed drinking nutrient in the world; it is naturally included in coffee, tea and cocoa beans.[1,2] Although caffeine is naturally or synthetically found in many dietary sources (energy drinks, soda-type beverages, juice, chewing gums, candy, etc.), it is mostly linked to coffee consumption since it is the most commonly ingested beverage worldwide.[1,3-5] Daily consumption of coffee varies among nations, for example, an average daily intake of caffeine of about 180 mg/day is reported in the United States[4,6], and 260 mg/day in Japan.[1,7] It is known that a regular cup of coffee (236 mL) contains approximately 135 – 150 mg of caffeine and a daily intake of about 200 mg/day is considered moderate.[5,8]

Caffeine works by binding to adenosine receptors of the central and peripheral nervous systems, heart and blood vessels.[1] It affects various organs and its effect on the vascular system can be explained by two possible mechanisms: binding to the vascular smooth muscle receptors and leading to vasoconstriction or increasing the intracellular calcium concentration which leads to increased nitric oxide synthesis and vasodilatation.[9,10] It decreases ocular blood flow due to vasoconstruction.[11-14] In a recent study, a significantly decrease in choroidal thickness after 200 mg oral caffeine intake was observed.[11] In other studies, decrease in retinal blood flow in healthy volunteers was demonstrated by using blue field simulation technique[12], laser speckle tissue circulation analyzer[14] and OCTA[13].

Optical coherence tomography angiography (OCTA) is a novel imaging tool that separates moving scatters from static background tissue to create three-dimensional angiograms[15] by assessing the change in the OCT signal caused by flowing blood cells.[16] This new technology enables a fast and non-invasive angiogram scan.[16,17] Numerous studies have validated the use of the OCTA in the evaluation of various diseases of the retina, choroid, and optic nerve by evaluation of the total blood flow and microvasculature structure.[18-25]

The correlation of IOP changes after caffeine intake was evaluated and a transient increase in IOP of approximately 1 - 2 mmHg within two hours were reported in previous studies[26-28]. Although an associated transient IOP elevation has been reported with caffeine, it is not considered as a risk factor for glaucoma.[26] In the present study, we aim to evaluate the optic nerve head and macular blood flow changes by using OCTA in glaucoma patients at different stages and healthy subjects before and after ingestion of 200 mg caffeine tablet.

Methods:

Study Design

Interventional Prospective Clinical Trial

Inclusion and Exclusion Criteria

Inclusion criteria:

Age 18-90

- Glaucoma patients
- Healthy subjects

Exclusion Criteria:

- Diseases, ophthalmic or systemic, that are likely to affect the OCTA test results.
- More than moderate grade cataract
- Nystagmus
- Inability to fixate for OCTA scan
- Macular degeneration other than mild drusen or pigmentary changes
- Diabetic retinopathy
- Neovascular glaucoma

- Current macular edema
- Prior laser treatment to the retina
- Inflammatory retinopathy or choroidopathy
- Keratoconus or other corneal ectasia
- Corneal scarring in central 4 mm
- Non-glaucoma optic neuropathies: ischemic and traumatic optic neuropathy, optic atrophy
- Rheumatologic diseases with vascular involvement: rheumatoid arthritis, systemic lupus erythematosus,
- Raynaud's phenomena
- Pregnant and lactating women
- Patients with mental illness (schizophrenia, bipolar disorder, anxiety symptoms)
- Alcohol addiction
- Pre-existing bladder symptoms
- Pre-existing cardiac disease
- Pre-existing sleep disorder
- Refractive spherical diopter >5 or cylinder > 3.
- Subjects who would develop a possible tolerance to caffeine (subjects drinking more than one cup of coffee per day)

Number of Patients to Enroll

- 20 patients with early stage primary open angle glaucoma
- 20 patients with moderate stage primary angle glaucoma

- 20 patients with advanced stage primary angle glaucoma
- 20 healthy subjects without glaucoma

Study Timeline

Patient enrollment will begin after IRB approval. We plan to complete enrollment and data acquisition within 1 year of IRB approval.

Study Data and Outcome Measures

All included patients will undergo a baseline examination involving case history. Measurement of best corrected visual acuity, visual field examination, corneal pachymetry, Axial length, and examination of the anterior and posterior segments of the eye.

The IOP, systolic and diastolic blood pressure, and heart rate will be checked before, and one hour and two hours after caffeine ingestion. The severity of glaucomatous damage was classified into early, moderate and severe stage according to Hodapp-Parrish-Anderson criteria.[29]

Macular and peripapillary blood flow index, vessel density, areas of capillary dropout or non-perfusion detected by OCT angiography will be assessed before, one hour and two hours after the ingestion of caffeine tablet.

Procedures Involved

Qualifying patients presenting to the Wills Eye Hospital Glaucoma Service will be asked for enrollment. Informed consent will be obtained from all participants. Subjects will undergo a comprehensive eye examination including Humphrey visual field and ocular biometry in both eyes. Scans will be obtained with the Avanti AngioVue HD OCTA (Optovue, Inc, Fremont, CA, USA), before and, one hour and two hours after a 200 mg caffeine tablet ingestion. All eyes will undergo imaging using the standard 4.5 mm HD Disc

scan protocol and the 6mm HD Retina scan protocol. In addition, a regular ONH structural scan (along with a 3D-Disc baseline scan) and a regular GCC structural scan will be acquired which provide comparison to normative database of the device to characterize the RNFL and GCC thickness status of the study eyes. Arterial blood pressure, heart rate and IOP will also be measured before and, one and two hours after the 200 mg caffeine tablet ingestion.

Data analysis

OCT Analysis

Acceptable images should have clear and sharp focus artifacts free (e.g., motion lines), without motion artifact (identified by horizontal misalignment of vessel segments on en face images), and Scan Quality of 6 or higher. The scans will be evaluated for vessel density, vessel length per unit area, flow index, foveal avascular zone area. Capillary dropout will also be recorded, if present.

Statistical Analysis

Continuous variables will be gathered for all groups using the following statistics: the mean, standard deviation, minimum, maximum, median, first quartile, and third quartile values. The frequency and percentages will be reported for the categorical measures. Subgroup analysis will be performed to determine differences in blood flow related to the diagnosis, IOP change and ocular perfusion pressure.

Confidentiality

Every effort will be made to protect the confidentiality of the data of the participants. All data will be de-identified and the assigned ID number will be used to track individual participants.

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6/27/18; 12/13/18; rev. 4/25/19