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Retinal nerve fiber layer analysis in cocaine users

Henrique Gemelli[a,*], Thiago M. Fidalgo[b], Carolina P. B. Gracitelli[c], Eric Pinheiro de Andrade[a]

[a] Department of Ophthalmology, Hospital do Servidor Público Estadual Francisco Morato de Oliveira, São Paulo, Brazil
[b] Department of Psychiatry, Universidade Federal de São Paulo, São Paulo, Brazil
[c] Department of Ophthalmology and Visual Science, Universidade Federal de São Paulo, São Paulo, Brazil

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ABSTRACT

Cocaine is a well-known factor of tissue ischemia and may be related to thinning of the inner retinal layers. The present study aimed to evaluate and determine whether cocaine users show retinal nerve fiber layer (RNFL) thinning by means of spectral-domain optical coherence tomography. A group of 17 cocaine users and 18 non-users were recruited for complete ophthalmologic examination. Spectral domain optical coherence tomography (Cirrus OCT) was used to evaluate peripapillary RNFL and macular thickness. The average RNFL measurement in the cocaine users group was significantly thinner compared to the control group. Subjects in the cocaine users group showed significant thinning in the nasal, superior and inferior quadrant. There were no significant differences in macular thickness or in the temporal quadrant between the two groups. This study supports further research with larger sample sizes to precisely determine the effect of cocaine on the RNFL.

1. Introduction

Cocaine is a benzoylmethylecgonine; the ecgonine base is a compound similar to atropine and scopolamine (Shanti et al., 2003; Inaba et al., 1989). These substances stimulate the sympathetic nervous system by inhibiting catecholamine reuptake in the presynaptic gap, increasing the sensitivity of the nerve terminals (Shanti et al., 2003; Inaba et al., 1989; Schwartz et al., 2010; Bloomstone, 2002). According to the Second Brazilian National Alcohol and Drugs Survey (II BNADS), 3.9% of the sample reported lifetime cocaine use (Abdalla et al., 2014).

Cocaine use releases endothelin-1, a potent vasoconstrictor (Schwartz et al., 2010; Wilbert-Lampen et al., 1998), and inhibits the production of nitric oxide (Schwartz et al., 2010; Wilbert-Lampen et al., 1998; Heesch et al., 2000), the main vasodilator produced by endothelial cells. Another detrimental effect of cocaine use is how it directly affects the calcium channels, leading to vasoconstriction, hypersensitivity and increase in platelet aggregation (Schwartz et al., 2010; Wilbert-Lampen et al., 1998; Heesch et al., 2000). In addition, it triggers an increase in fibrinogen and in the von Willebrand factor (Heesch et al., 2000).

Early studies using new technologies are providing more knowledge on the vascular effects associated with cocaine use. Ultra-high resolution optical coherence angiography and Doppler optical coherence tomography have shown that cocaine-induced neurovascular micro-ischemia interrupts cerebral blood flow for over 45 minutes (Ren et al., 2012). Furthermore, evidence from myocardial contrast echocardiography (MCE) showed decrease in the myocardial capillary blood flow rather than microvascular flow velocity after cocaine injection, suggesting a specific action of cocaine in terminal feed arteries (Gurudevan et al., 2013).

By using a technique that combines laser speckle contrast imaging and spectral-domain doppler OCT, which offers enhanced spatio-temporal resolution compared to functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon-emission computed tomography (SPECT), it was possible to obtain a quantitative measurement of local cerebral blood flow (CBF) changes in the rat cortex in response to cocaine administration, after it being anesthetized with α-chloralose or isoflurane. In the study, the CBF in the α-chloralose group was 40% lower than that in the isoflurane group. Since α-chloralose minimally interferes with autonomic functions of the brain and neurovascular coupling, cocaine-induced CBF changes in α-chloralose anesthetized rats were more likely to truly reflect the neurometabolic changes induced by cocaine (Luo et al., 2009).

The retinal nerve fiber layer (RFNL) is composed primarily of retinal ganglion cell axons, neuroglia and astrocytes, and is the main component of the optic nerve. Retinal ischemia can result in RNFL defects, and the severity of those defects is related to the severity of the ischemia itself (Chow et al., 2013). Reduction in RNFL thickness may be observed in ischemic diseases, such as sickle cell disease (Chow et al., 2013), diabetic retinopathy (Van Dijk et al., 2010) and Behçet's disease

* Correspondening author at: Rua Pedro de Toledo, 1222 Apt 173,Vila Clementino CEP: 040390-900, São Paulo, SP, Brazil.
E-mail address: henriqueoft@gmail.com (H. Gemelli).

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(Oray et al., 2015). In addition to these diseases, cocaine is also a major ischemic factor that may cause lesions on the RNFL.

However, there are no studies in literature so far that evaluate the association between cocaine use and possible structural damage in RNFL thickness using OCT. Therefore, this study aims to analyze and determine the topography and thinning of RNFL thickness in cocaine users.

2. Methods

The primary outcome measure of this cross-sectional study is the retinal nerve fiber layer thickness measured by optical coherence tomography in cocaine users. The study protocol was approved by the Committee of Ethics in Research of the *Hospital do Servidor Público Estadual de São Paulo* and conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from patients and subjects before testing.

2.1. Study sample

Two subject groups were included in the study: cocaine users (cocaine-dependent group) and non-users (control group). The cocaine-dependent group was composed of patients being treated in the Addiction Unit at the Federal University of São Paulo, all of which had been diagnosed with cocaine dependence at least 24 months prior to the study. A psychiatrist following the criteria of the Diagnostic and Statistical Manual of Mental Disorder – 5th Edition (DSM-5), established the diagnosis. All patients from this facility were invited to participate voluntarily, as long as they fulfilled the inclusion criteria. The control group was formed by subjects with no prior history of cocaine use recruited at the ophthalmology clinic at the *Hospital do Servidor Público Estadual de São Paulo* - IAMSPE. Complete psychiatric evaluation was performed by a medical psychiatrist. No patient had any other psychiatric comorbidity.

The exclusion criteria for both groups included: retinal or optic nerve pathologies; media opacity or a maximum of C1 (cortical opacity), NC1 (nuclear color) or NO1 (nuclear opacity), following the LOCS III (Chylack et al., 1993); subjects under the age of 18 and over the age of 80; refractive error with cylindrical and spherical equivalent within ± 3D and a best optical-corrected visual acuity worse than

0.4 logMAR. Use or dependence of other substances did not affect eligibility. Any subject with a history of crack-cocaine use was also disqualified. In addition, the study did not include patients who presented diagnosis or symptoms of neurological pathologies that could alter the nerve fiber layer.

2.2. Procedures

All patients underwent a comprehensive ophthalmologic examination, including review of medical history, best optical-corrected visual acuity, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, dilated fundoscopic examination using a 78-diopter (D) lens and stereoscopic optic disc photography.

This study was conducted using a Cirrus HDOCT (software v. 5.2, Carl Zeiss Meditec Inc., Dublin, CA, model 4000) to measure RNFL thickness. This device uses a superluminescent diode scan, with a center wavelength of 840 nm and an acquisition rate of 27,000 A-scans per second at an axial resolution of 5 µm. The protocol used for measuring RNFL thickness was the optic disc cube with circumpapillary RNFL thickness measurements calculated from a 3.46-mm diameter circular scan (10.87-mm length) automatically placed around the optic disc. An experienced examiner, masked to the results of other tests, evaluated the quality of all OCT scans. High-quality scans had to display focused images from the ocular fundus, signal strength greater than 7 and presence of a centered circular ring around the optic disc. Scans were also evaluated as to the adequacy of the algorithm for detection of the RNFL. Only scans without overt algorithm failure in detecting the retinal borders were included in the study.

The mean average peripapillary thickness in the temporal, nasal, inferior and superior quadrants was measured using the optic disc cube 200 × 200 protocol. The macular thickness was acquired using the macular cube 512 × 128 protocol, where a 6 × 6 mm macular area is covered, collecting 512 × 128 scans (horizontal and vertical).

2.3. Statistical analysis

Descriptive statistics included mean and standard deviation for normally distributed variables. The groups (user and control) were compared and analyzed using unpaired Student's *t*-tests. Skewness and Kurtosis tests and histograms were used to check normality. Whenever both eyes were eligible, the right eye was chosen for analysis.

All statistical analyses were performed with commercially available software (Stata, version 11; StataCorp LP, College Station, Texas, USA). The alpha level (type I error) was set at 0.05.

3. Results

A total of 35 eyes of 35 subjects, consisting of 17 cocaine users (62.5 ± 13.8 years) and 18 healthy subjects (52.6 ± 11.9 years), were enrolled in the study. There was no statistically significant age difference between the two groups ($p = 0.174$, t test). Seventy eyes from 35 subjects were recruited for the study. Two eyes (5.8%) were disqualified from the control group due to the presence of subretinal fluid and chorioretinal scarring, and one eye (3%) was disqualified from the user group due to persistent peripapillary myelinated nerve fibers.

There were no significant differences between groups regarding gender, race and comorbidities ($p > 0.05$ for all comparisons, t test). Table 1 shows the demographic and clinical characteristics of each group.

On average, the cocaine users fulfilled the 17.7 ± 8.5 years (addiction criteria with drug abuse history ranged from 4 to 30 years). The average daily dose was of 2.7 ± 1.5 grams (ranging between 1.0 and 5.0 gs). All participants were daily users during the time of use.

Regarding the comorbidities, the cocaine group included two patients with systemic hypertension, two patients with dyslipidemia, two diabetics and one patient with chronic kidney disease. The control group contained four patients with systemic hypertension, one patient with chronic kidney disease, one patient with benign prostatic hyperplasia, two diabetic patients and one patient with previous deep venous thrombosis.

There were no significant differences between the user and control group regarding intraocular pressure, cup-to-disk ratio, macular thickness, corneal pachymetry and symmetry of optic nerve ($p > 0.05$ for all comparisons, t test).

Table 2 shows the results of the OCT analysis for the two groups.

Table 1
Demographic and clinical characteristics of study subjects.

Parameter	User group (*N* = 17 eyes, 17 patients)	Control group (*N* = 18 eyes, 18 patients)	*P* Value 0.493, t test
Age	62.5 (13.8)	52.6 (11.9)	0.174
Gender			0.237
Female	2 (11.7%)	5 (27.7%)	
Male	15 (88.3%)	13 (72.2%)	
IOP	13.2 (3.3)	13.9 (1.7)	0.391
Visual acuity	0.0	0.0	1.000
C/D Ratio	0.41 (0.1)	0.39 (0.2)	0.675
Corneal Pachymetry	542.1 (35.5)	535.6 (41.1)	0.630

Abbreviations: SD, standard deviation; IOP, intraocular pressure; C/D ratio, cup-to-disk ratio; RNFL, retinal nerve fiber layer

Table 2
Clinical characteristics of the eyes included in the study.

Variable	User group (N = 17 eyes, 17 patients)	Control group (N = 18 eyes, 18 patients)	Difference	P value, t test
Macular thickness, µm	259.6 (26.6)	260.6 (23.4)	1.0	0.901
Quadrants				
Inferior, µm	114.6 (18.9)	121.5 (15.4)	6.9	0.025
Superior, µm	104.7 (16.1)	112.4 (10.5)	7.7	0.040
Nasal, µm	67.5 (10.4)	75.8 (12.7)	8.3	0.048
Temporal, µm	60.7 (13.5)	63.6 (9.5)	2.9	0.465
Average RNFL, µm	86.2 (11.4)	92.8 (9.3)	6.6	0.007

Abbreviations: SD, standard deviation; RNFL, Retinal nerve fiver layer

The user group presented smaller values when compared to the control group with statistically significant results in the inferior ($p < 0.025$, t test), superior ($p = 0.040$, t test) and nasal ($p < 0.048$, t test) quadrants. The temporal quadrant did not indicate any substantial difference ($p = 0.465$, t test). Overall mean RNFL thickness was thinner in the user group, recording a statistically significant result ($p < 0.007$, t test).

4. Discussion

The results of this study show that cocaine users present a thinner RNFL thickness compared to the control group in the superior, inferior and nasal quadrants. All of the patients selected were chronic users with a history of heavy drug abuse.

There are currently few studies conducted with rats that evaluate the changes in the retinal nerve fiber layer after administration of cocaine. The effect of prenatal exposure to cocaine on the development of the retinal ganglion cell layer was studied in rats through subcutaneous administration of cocaine. A thinning of the nerve fiber layer and loss of ganglion cells was recorded in rats exposed to the substance (Silva-Araujo et al., 1995). To the best of our knowledge, this is the first study, to describe and evaluate the RNFL thickness in cocaine users.

Peripheral retinal ischemia due to retinal vasoconstriction in terminal feed arteries (similar to what occurs in coronary and cerebral arteries) may be connected to greater thinning in the superior, inferior and nasal areas. From earlier studies, we know that there are up to two retinal vascular networks: the superficial capillary plexus (which lays in the nerve fiber layer) and a deeper one (Provis, 2001). Toward the periphery, the retina becomes thinner, the capillary plexus becomes less dense and the vessels become narrower (Toussaint et al., 1961), which could facilitate the ischemic process of the RNFL in the superior, inferior and nasal area.

The temporal area of the optic disk, which did not show a significant thinning, is composed by the RNFL of the macular area. The increased number of anastomosis and the large-caliber of the vessels in this area may act as a protective factor to the macular nerve fiber layer. A new technology called OCT angiography is emerging as a non-invasive device and will clearly have its value, as a research tool, in evaluating the macular capillary plexus in cocaine users.

In contrast, the macula may be affected during drug use. Two cases of acute macular neuroretinopathy, a rare condition characterized by paracentral scotomas and wedge-shaped intraretinal lesion, were reported after intranasal cocaine use, possibly secondary to the retinal vasospasm of the deep capillary plexus (Introini et al., 2015).

Furthermore, evaluating these patients' OCT scans when diagnosing glaucoma and assessing its progression must be done with attention. Thinning of RNFL is helpful in differentiating glaucomatous from normal eyes (Chen et al., 2005; Huang et al., 2005). It is recommended to evaluate RNFL in glaucomatous eyes by primarily looking at the overall, superior and inferior RNFL thicknesses (Lu et al., 2008). We have demonstrated that cocaine users may have thinning in these topographies and may require different peripapillary RNFL thickness thresholds for glaucoma evaluations.

Our study has some limitations. First, this is a relatively small sample size and, because of this, we cannot create correlations for these findings, such as, for example, the relationship between RNFL thickness and time of drug abuse. However, although the present study has only 35 patients, this is the first study investigating a connection between chronic use of cocaine and RNFL thickness. Second, this is a cross-sectional study that does not allow us to find any cause-effect for our findings. Future longitudinal studies will help us clarify the relationship between dosage and usage history with RNFL damage. Another limitation of the present study is that the measurement of the ganglion cell layer and inner plexiform layer, which are shown to be important determinants of neurodegeneration, was not performed. Also, there was a 10-year age difference between the groups and it has already been established that RNFL starts thinning with age. Furthermore, the mean age of the cocaine users is 62.5. By that age, most cocaine users have given up using the drug.

In conclusion, this study indicates that cocaine-dependent patients show significant RNFL thinning. The retina shares developmental, physiological and anatomical features with the brain (Cordeiro, 2016). Retinal imaging is increasingly being used to study neurodegenerative diseases and the direct relationship between RNFL thinning and cerebral atrophy has already been shown in recent studies regarding diseases such as multiple sclerosis (Saidha et al., 2015; Pietroboni et al., 2017) and the natural aging process (Casaletto et al., 2017). The use of cocaine causes cerebral atrophy, which increases the user's tolerance to the substance and decreases the effect of pleasure and euphoria (Pascual-Leone et al., 1991). As a result, the user consumes a greater amount of the drug to achieve the desired effect (Bartzokis et al., 2000). Further study is necessary to determine the role of OCT imaging in evaluating the association between thinning of the RNFL and neurodegeneration in cocaine users.

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Conflict of interest

The authors have no conflict of interest regarding the present study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.11.058.

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