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Retinal Nerve Fiber Layer Thickness in Opioid Abusers

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Abstract

Background: Opioids are addictive substances that have been shown to have neurotoxic effects on the brain. These neurotoxic effects may be associated with retinal nerve fiber layer (RNFL) thickness. This study aims to examine retinal neural fiber layer thickness by optical coherence tomography (OCT) among opioid addicts.

Methods: Therefore, both eyes of the 45 participants who met the diagnosis of opioid addiction according to DSM-5 (age:26.13±6.20 years) and 45 healthy control groups (age:28.87±9.04 years) were examined in seven quadrants (superior temporal, superior nasal, temporal, nasal, inferior temporal, inferior nasal quadrants and global RNFL thickness) with OCT.

Results: Mean RNFL thicknesses in any quadrant did not differ statistically significantly between the groups ($p>0.05$). Furthermore, there was no statistically significant correlation between the duration of substance use and RNFL thicknesses. There is a statistically significant inverse correlation that has been found between the daily amount of substance use (gr) and RNFL thicknesses in the right eye temporal inferior (r: - 0,499) and temporal superior (r: - 0,351) and left eye nasal inferior (r: - 0,387) quadrants, whereas there was not any statistically significant correlation in other quadrants.

Conclusions: This study suggests that RNFL thickness may be the same as healthy controls for several reasons in opioid addicts. It would be appropriate for this to be confirmed by broader studies and for its mechanism to be investigated.

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INTRODUCTION

Substance abuse is a problematic clinical condition for both individuals and societies worldwide. World Drug Report 2018 results reported that approximately 5.6 percent of the global population between the ages of 15 and 64 have used drugs at least once (United Nations Office on Drugs and Crime [1]. Opioids are highly addictive substances and heroin can be said to be the most commonly used opioid [2]. Opioids remain the most damaging substances and are at the origin of 76 percent of deaths caused by drug use disorders. According to the World Health Organization, approximately 450,000 people died as a result of drug use in 2015. While one-third of this figure is directly related to the effect of the drug (such as overdose use), the remainder depends on the other drug-related comorbidities (such as HIV, Hepatitis-C, infectious diseases) [1].

There are publications and meta-analyzes on the association of heroin abuse with structural changes in the brain [2-6]. Various regions such as cingulum, superior longitudinal fasciculus, corpus callosum, insular, orbital and inferior frontal gyrus frontal lobe, orbitofrontal cortex, insula, frontotemporal region have been seen among regions that show changes in neuroimaging studies. Also, structural changes such as decreased nucleus accumbens and hypothalamus volume and shrinking globus pallidus have been detected in the brain in post-mortem studies [7].

Early detection of neurotoxicity will also be important in preventing organ damage, especially in the brain. Although we may have information about the neurotoxic effects of drug abuse, especially heroin, with neuroimaging studies, the fact that it is an expensive method and not highly acceptable by patients may create usage limitations [8]. Therefore, cheaper, more acceptable by patients and easily applicable methods have been investigated. Retina examination is thought to be helpful in this regard. The

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retina originates from the same embryological layer with the brain and is considered an external extension of the brain [9]. For these reasons, retinal changes are thought to be parallel to brain tissue changes by most authors [10-12]. Retinal nerve fiber is the layer of axons of ganglion cells in the retina. Therefore, changes in the retinal nerve fiber layer (RNFL) have begun to be accepted as an easily accessible indicator of functional and/or structural brain integrity.

Several publications examine the effects of alcohol, cigarettes, and cocaine, among other substances on RNFL. These studies have shown the thinning of various quadrants of RNFL [13-15]. Studies are showing that even exposure to cigarettes, alcohol, and other substances maternally results in RNFL thinning [16].

However, when the literature so far has been examined, no study examining RNFL in heroin addicts by using OCT has been found. Detection of possible RNFL damage in heroin addicts can be helpful both in detecting eye and indirectly brain lesions easily and in taking precautions. Therefore, it was aimed in this study to investigate RNFL changes in heroin addicts by using OCT.

METHODS

The study is a cross-sectional study. The primary outcome measure is retinal nerve fiber layer thickness (RNFL) measured by optic coherence tomography in heroin users. 08/28/2019 dated and 2019-31 numbered local ethics committee approval was obtained for the study. The study was conducted following the principles of the Declaration of Helsinki, and written and verbal informed consent was obtained from the participants before the study.

Two groups were included in the study: heroin-dependent group and the control group composed of healthy volunteers matched in terms of age and gender. Heroin-dependent group consisted of the patients diagnosed with heroin addiction according to DSM-5 and accepted to participate in the study voluntarily among the patients who applied to the Alcohol and Substance Abuse Treatment Center at our university. The diagnosis was made by a specialist psychiatrist in the field working in the center. The inclusion criteria are determined to meet the criteria of heroin addiction according to DSM-5: to be between the ages of 18-65, to be in the first three days of sobriety, and to volunteer to participate in the study. The control group included participants who were admitted to the same hospital's eye outpatient clinic, who did not meet any axis-1 disorder diagnosis according to DSM-5, and who volunteered to participate in the study.

The exclusion criteria are determined, for both group to be : high eye pressure disease, intraocular pressure above 21 mmHg, eye disorders above 1D, axial length of the eye different than 21-24 mm, a history of ocular surgery and ocular trauma, ocular or systemic disease and use systemic drugs because of this disease, and not to agree to participate in the research.

Complete ophthalmological examinations of the participants, including the best-corrected visual acuities, refraction defects, intraocular pressures, anterior segment, and fundus oculi examination findings were performed. Axial length measurements of the eye were taken with Nidek AL-scan (Nidek CO, Aichi, Japan) optical biometry. RNFL measurements, on the other hand, were made with Spectral-domain OCT (Heidelberg Engineering Spectral OCT, USA). Peripapillary RNFL thickness measurement was performed using a circular scan of 3.4 mm in diameter around the optic nerve. The thickness values of the temporal quadrant (T), temporal superior quadrant (TS), temporal inferior quadrant (TI), nasal quadrant (N), nasal superior quadrant (NS), nasal inferior quadrant (NI) and global (G) retinal nerve fiber layer was recorded. These values were compared between the groups.

Statistical analyzes were performed using SPSS version 22. The suitability of the groups for normal distribution was evaluated with the analysis of Shapiro Wilks and Kolmogorov Smirnov, Continuous variables in normally distributed groups were shown with mean ± standard deviation, while continuous variables that did not match normal distribution were shown with a median. The comparison of patient and control groups, student's t-test analysis was used for those who matched the normal distribution, while Mann Whitney U test analysis was used for those who did not match the normal distribution. Correlation analysis was performed with Spearman Correlation Analysis or Pearson Correlation Analysis. $p < 0.05$ was considered statistically significant.

RESULTS

The study was carried out with 180 eyes of 90 people in total. 45 of the participants were opioid addicts (26.13 ± 6.20 years) and the other 45 were healthy controls (28.87 ± 9.04 years). Two eyes were excluded from the study, one of them was from the study and the other one from the control group, because they did not meet the inclusion criteria, and 178 eyes were reported in the conclusion. There was no statistically significant difference since the groups were taken by matching age and gender ($p < 0.05$). The demographic and clinical characteristics of the participants are shown in Table-1.

Table 1: Demographic and clinical characteristics of the study participants

Parameters	Opioid group (n: 44 /%)	Control group (n: 44 /%)	p*
Age (years)	26,13 ± 6,20	28,87± 9,04	0,098**
Gender Female Male	 6 (%13,3) 39 (%86,7)	 4 (%8,9) 41 (%91,1)	0,739***
Average duration of use (years)	7,93±4,65		
Average amount of daily use (gr) 4,79 ± 2,80	4,79±2,80		

*p<0,05; ** chi-square test; ***t-test

The mean substance use duration of opioid addicts was 7.93 ± 4.65 years. All of them were using the substance daily and meeting severe addiction criteria according to DSM-5. They reported the average amount of daily substance use as 4.79 ± 2.80 g (min: 1gr, max: 10gr). There was no statistically significant difference between the average duration of substance use and RNFL thickness correlations (Pearson correlation coefficient r: - between 177 and 188, p was between 154 and 949). In the correlation between the daily use of the substance and RNFL thicknesses, there has been a statistically significant and inverse correlation in the right eye TS (r = -, 351, p = 039) and TI (r = -, 499 p =, 002) quadrant and left eye NI (r = -, 387, p =, 022) quadrant. There was no statistically significant correlation in other quadrants. Correlations between the duration of substance use, the amount of substance use, and RNFL thicknesses are shown in Table-2.

Table 2: Duration of substance use, amount of substance use and OCT findings correlations

Variable (n:44)		Right Eye							Left Eye						
		TS	NS	T	N	TI	NI	G	TS	NS	T	N	TI	NI	G
Average duration of substance use (year)	r	-,029	,188	-,177	-,130	,221	-,121	-,028	,045	-,075	,051	-,044	,072	-,024	,010
	p	,855	,227	,256	,406	,154	,440	,861	,776	,631	,747	,781	,647	,877	,949
Average amount of daily substance (mgr	r	**-,351***	-,218	,063	-,060	**-,499****	,196	-,200	-,300	-,254	-,146	,128	,101	**-,387***	-,257
	p	,039	,207	,720	,733	,002	,258	,249	,080	,141	,403	,465	,562	,022	,135

*p<0,05; **p<0,01; r: Pearson correlation coefficient

Table 3: Comparison of the optic nerve fiber thicknesses of the study participants

RNFL QUADRANTS	Opioid group (n:44) Thicknesses (µm)	Control Group (44) Thicknesses (µm)	P value t-test
RIGHT EYE			
TS	144,9±22,2	146,7 ± 15,3	,660
NS	115,0 ± 19,4	112,5 ± 19,3	,545
T	79,2 ± 14,4	80,8± 11,2	,564
N	81,3 ± 13,7	75,4± 14,0	,052
TI	140,7 ± 29,8	144,3± 23,8	,534
NI	130,7± 31,1	124,1± 25,5	,281
G	106,6± 11,9	105,0± 8,3	,484
LEFT EYE			
TS	138,8±23,3	141,4±16,6	,535
NS	124,5±19,7	124,5±19,7	,723
T	76,6±13,6	77,2±9,2	,812
N	78,2±16,7	72,9±12,2	,090
TI	144,4±28,8	147,2±28,8	,613
NI	126,7±22,6	123,2±23,7	,480
G	105,5±10,9	104,3±8,7	,578

TS: superior temporal quadrant; NS: superior nasal quadrant; T: temporal quadrant; N: nasal quadrant; TI: inferior temporal quadrant; NI: inferior nasal quadrant; G: global RNFL; µm: micron

The comparison results of average RNFL thicknesses of the opioid and control groups are shown in Table-3. Accordingly, retinal nerve fiber layer thicknesses were not found statistically significant in any of the seven quadrants examined in opioid addicts and the healthy control group (p <0.05).

DISCUSSION

According to the results of our study, RNFL thicknesses of opioid users did not differ statistically significantly from healthy control groups in any quadrant. Opioid users were all meeting the severe addiction criteria, according to the DSM-5 [17]. They had also been using opioids for eight years on average and were using an average of about five grams of opioids daily.

As far as we know, our study is the first study to measure RNFL thicknesses in opioid addicts by using OCT. Therefore,

we cannot compare the study results directly with the literature. However, we could not meet our expectations that the RNFL thickness of opioid addicts at the beginning of the study will be lower than healthy controls. There may be several reasons for this.

It is widely accepted in the literature that opioids have neurotoxic effects in the brain, and this has been demonstrated by various meta-analyses [2,6]. Mechanisms such as chronic hypoxia, oxidative stress, micro DNA damages of opioids, neurotoxic effects of substances taken alongside opioids during substance use can be accepted among the mechanisms mediating these effects [18–21]. Among these mechanisms, oxidative stress can be said to be one of the important mechanisms.

The eye has been shown to have three types of opioid receptors, and there are publications on how opioids, with these receptors, contribute to the regulation of iris function, aqueous humor dynamics, and corneal wound healing [22–24]. Also, opioids contribute to the development of the retina [25] and there are publications about how stimulation of opioid receptors shows neuroprotective effects against retinal damage [26–28]. Someya and colleagues published in a 2017 animal study that stimulation of retinal μ-opioid receptors induces vasodilation of retinal blood vessels by neuronal NO synthase activation and that retinal neurons play an important role in this process. Starting from this, the authors suggested that retinal μ-opioid receptors may contribute to the regulation of retinal vascular tonus [29]. Based on this information, it can be said that even if opioids have neurotoxic effects on the brain, the expected damage cannot be detected due to the neuroprotective effects present in the optic nerve.

Additionally, the ganglion layer (GCL) and inner plexiform layer (IPL) were not included in our study. GCL consists of ganglion cell bodies of the retina, IPL ganglion cell dendrites, and RNFL ganglion cell axons. Although changes in the RNFL are expected to reflect the GCL and IPL, there may not be complete parallelism in the changes between layers for temporal or other reasons. Indeed, Lopez and his colleagues found reductions in all three of the GCL, IPL, and RNFL in their OCT study of MS patients, but said that the decrease in GCL and IPL was more specific than the decrease in RNFL [30]. Also, in studies related to MS [31], optic neuritis [32] and schizophrenia [33], GCL and IPL volume correlations with disease parameters exhibited a better correlation than RNFL parameters. In our study, it's possible that neurotoxic effects are present in the ganglion layer and may not yet be reflected in optic nerve thickness. In the same way, perhaps more significant correlations could be detected between the duration of substance use and the amount of substance use and GCL and IPL. Also, Ascaso and colleagues have said that the RNFL may not fully reflect the GCL and IPL by mechanisms such as blood build-up, neuroinflammation, and gliosis [34]. There are also publications on neuroinflammation occurrence in opioid users [35]. Due to the inflammatory effects of opioids, the living conditions of opioid users, and the additional substances they take with opioids, thinning in the RNFL may be suppressed. In our study, measurements were made in the first three days of sobriety. In the later days of sobriety, more different results may be determined.

This study has many limitations. The number of participants is relatively small, and a causal relationship cannot be established since it is a cross-sectional study. Furthermore, although the included patients were found to be patients that meet severe addiction criteria according to DSM-5, the fact that the addiction severity index was not applied limited considerably the correlation between dependency severity and RNFL thickness. Another limitation of the study is that the ganglion layer and inner plexiform layer, which are also more specific to neurodegeneration, have not been studied. Besides, comorbid diseases that are thought to significantly affect the parameters of OCT were questioned only by Anamnesis and not scanned. In subsequent studies, examining the ganglion layer with a larger number of participants, prospectively, and using the addiction severity scale will help further our understanding of effects of opioid use on the optic nerve. Also, comparing subsequent OCT and brain imaging studies will be able to provide more information on whether OCT can show neurotoxic effects in opioid addicts or not .

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