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Does the use of cannabinoids affect the ocular surface?

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Abstract

Aim: To examine tear functions and ocular surface variables in patients with cannabis addiction.

Materials and Methods: This clinical trial was planned as a prospective case-control study. In this study, 51 male patients with cannabis addiction (group 1) and 51 healthy volunteers (group 2) with similar demographic characteristics were included. Visual acuity, spherical equivalent, biomicroscopic examination, Schirmer test, tear break-up time (TBUT), and impression cytology (Nelson scores) results were recorded, and the 2 groups were compared with each other.

Results: The mean Schirmer values were 9.68 ± 6.8 mm and 8.39 ± 4.08 mm in group 1 and group 2 ($p = 0.97$), respectively, whereas the mean TBUT values were 9.96±3.9 and 9.29±4.01s. ($p = 0.35$) and the mean Nelson scores were 1.49±1 and 1.25±0.97 in group 1 and group 2, respectively ($p = 0.26$).

Conclusion: In this study, the effects of cannabis addiction on the ocular surface were evaluated using Schirmer, TBUT, and impression cytology methods. In the statistical analysis, no significant difference was found compared to the control group. This study showed that tear production, tear film stability, and impression cytology of patients with cannabis addiction were not different from the control group.

Introduction

Cannabis has been reported to be the most commonly used psychoactive substance in the world according to the reports published by the United Nations Office on Drugs and Crime, and this finding has been supported by the World Health Organization [1]. According to the drug report issued by the General Directorate of Security, Turkey, in 2019, 21% of the patients treated for substance abuse involved addiction to cannabis and synthetic marijuana derivatives [2].

The active ingredient in cannabis is tetrahydrocannabinol (THC). It has been reported that THC exposure in humans causes long-term depression of cannabinoid 1 (CB1) receptors in the cerebellar cortex, causing disruption of the associative learning process and delay in the blink reflex [3, 4]. The effects of substance and psychosocial addictions on the eye have been well studied. In a research conducted in our clinic by Cumurcu et al. [5], it was found that Schirmer, tear break-up time (TBUT) and impression cytology values of patients with alcohol addiction were different from the values of the control group. In another study, Gündüz et al [6], reported that the conjunctival flora changes and *Staphylococcus aureus* colonization increases in cases with heavy alcohol use. However, our survey of the relevant literature revealed that the effects of cannabis addiction on the ocular surface are yet to be investigated. In the light of this information, we hypothesized that the delay in the blink reflex may increase tear evaporation and cause changes in ocular surface variables such as Schirmer, TBUT, and impression cytology, and we aimed to examine the effects of cannabis addiction on the ocular surface in this study.

Materials and Methods

This clinical study was planned as a prospective case-control study and was conducted in accordance with the Helsinki declaration principles with the approval of the University Ethics Committee (Approval No: 2015/133; Date: 09/09/2015). Fifty-seven patients who applied to the Department of Psychiatry between September 2015

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and March 2016 with a history of active cannabis use for at least 3 months and 53 healthy volunteers with similar demographic characteristics were included in the study. Informed consents were obtained after providing detailed information about the purpose of the study and the procedures to be performed.

Patients were excluded if they were female (due to the insufficient number of female patients with cannabis addiction that applied to our clinic), had a corneal and conjunctival pathologies (such as herpetic keratitis, trachoma sequela, pannus, pterygium, etc.), had use topical medications (glaucoma, dry eye, etc.), had an eyelid and eyelash deformities that may affect the ocular surface, wore contact lenses, had a history of ocular trauma or ocular surgery, had systemic (such as rheumatoid arthritis) or dermatological (such as acne rosacea, Stevens–Johnson syndrome) diseases that may cause changes in the ocular surface. We know that addicted patients often use other substances as well. All patients who participated in the study were smokers and half of the patients reported occasional alcohol use. Patients with substance use other than alcohol, cigarettes and cannabinoids were excluded from the study. Also heavy drinkers excluded from the study. The control group was demographically similar in terms of alcohol, cigarette and substance use.

Detailed ophthalmologic examination of the right eyes of all subjects included in the study was performed, and the results of visual acuity, spherical equivalent, Schirmer, TBUT, and impression cytology were recorded. Anesthetized Schirmer (modified Schirmer) test was performed to evaluate basal secretion. Lower fornices were dried after a drop of the topical anesthetic proparacaine hydrochloride ophthalmic solution [Alcaine ® (AlconCouvreur, Puurs, Belgium)] was instilled. Standard Schirmer filter paper (Clement Clarke Int.) was placed at the junction of the $1/3^{rd}$ outer and $1/3^{rd}$ middle parts of the lower eyelid, in the lower fornix, and left for 5 minutes. The distance of the wetted part from the edge of the lid was measured in mm. For TBUT, paper strips containing standard 1 mg sodium fluorescein (Fluorets, Smith-Nephew) were used. The time period from the last blink until the tear film first broke up was determined. This measurement was repeated thrice to record the mean value. Corneal and conjunctival staining was performed with fluorescein after TBUT was measured. For impression cytology, a cellulose acetate filter paper (GEHC Whatmann TM) was cut into a rectangular shape and held with a pair of forceps, and samples were taken from the temporal part of the bulbar conjunctiva of the patients. After the samples were spread, they were fixed with 95% ethyl alcohol. The diffusions were stained with periodic acid–Schiff and Papanicolaou stains. The stained slides were evaluated under the light microscope by a pathologist who was unaware of which patient group each sample belonged to, and the samples were staged according to the Nelson staging system [7, 8].

Statistical evaluation

SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.was used for statistical analyses. Quantitative data were expressed as mean±standard deviation. Mann–Whitney U Wilcoxon W and Z tests were used for the statistical evaluation of the data. According to Kolmogorov–Simirnov test statistic, when the data were not normally distributed, Mann-Whitney U test was used to compare two independent groups. A p value < 0.05 was considered statistically significant.

Table 1. Ocular surface paramaters

	Grup	N	Mean ± Standart Deviation	Median (Min/Max)	p Value
Age	Addict	51	25.63±7.05	23(16/52)	0.078
	Control	51	24.1±7.23	23(15/45)	
Refraction	Addict	51	-0.16±0.69	0(-3.25/1.25)	0.352
	Control	51	-0.48±1.11	0(-4/1)	
TBUT *	Addict	51	9.96 sec±3.92	10(2/20)	0.347
	Control	51	9.29 sec±4.01	9(3/20)	
Schirmer	Addict	51	9.69 mm±6.84	7.5(2/25)	0. 979
	Control	51	8.39 mm±4.09	8(2/20)	
Nelson	Addict	51	1.49±1	1(0/3)	0.259
	Control	51	1.25±0.98	1(0/3)	

The table shows age, refraction, tear breakup time *(TBUT), Schirmer, p values and Nelson scores in the cannabis addicts and control group

Results

Due to insufficient number of applications from female cannabis addicts, 3 female patients were excluded from the study, whereas 2 patients from the control group and 3 patients from the study group were excluded due to insufficient sampling. Fifty-one patients with cannabis addiction (group 1) with at least 3 months of cannabis use history and 51 healthy volunteers (group 2) with similar demographic characteristics who applied to our clinic and who met the study criteria at the age of 18–45 years were evaluated.

The respective mean ages of the participants in groups 1 and 2 were 25.62 and 24.10 years. Spherical equivalent mean values were −0.15 and −0.48 dioptric for group 1 and group 2, respectively. Mean Schirmer values were 9.68 and 8.39 mm in group 1 and group 2, respectively. The respective mean TBUT values were 9.96 and 9.29 s in groups 1 and 2, whereas the respective mean impression cytology Nelson scores of subjects in groups 1 and 2 were 1.49 and 1.25. The p values of the differences in the aforementioned results of the two groups were found to be $p = 0.08$, $p = 0.35$, $p = 0.98$, $p = 0.35$, $p = 0.26$, respectively. Impression cytology Nelson scores in the study group were as follows: stage 3 in 11 patients, stage 2 in 8 patients, stage 1 in 24 patients, and stage 0 in 8 patients. In the control group, impression cytology Nelson scores were as follows: stage 3 in 6 subjects, stage 2 in 11 subjects, stage 1 in 21 subjects, and stage 0 in 13 subjects. (Table 1)

Discussion

There are multiple studies examining the effects of various addictions on the ocular surface. In a study conducted in our clinic by Cumurcu et al. [5], in which 35

patients with severe alcohol addiction and 35 healthy volunteers were compared, it was detected that TBUT and Schirmer results decreased significantly compared to the control group, whereas Nelson scoring of impression cytology (group 1: 2.08, group 2: 1.37, p = 0.001) increased significantly. In addition, it was emphasized in this study that the decrease in TBUT and Schirmer scores and the increase in cytology scores demonstrated a significant correlation with the increase in alcohol consumption. In a study group consisting of 60 smokers who had been smoking heavily for at least 5 years and 34 healthy individuals, Altınörs et al. [9], examined the ocular surface variables and found that TBUT was decreased significantly in smokers; however, there was no significant difference in terms of the mean Schirmer test results. Moreover, Nelson scores and goblet cell densities were not monitored. In a study consisting of 19 smokers who had been smoking heavily for at least 20 years (1 pack/day) and 20 healthy individuals, Matsumoto et al [10]. observed that squamous metaplasia was observed more frequently in impression cytology, goblet cell densities decreased significantly, and prolonged smoking was causing changes on the ocular surface at the histological level. They stated that a wide variety of chemicals contained in tobacco or the systemic ischemic effect of smoking may cause these conditions. In a study by Dasilva et al. [11], on 22 patients who were addicted to cocaine for at least 3 years, Schirmer test was performed after 24 hours of cocaine cessation, repeated after cocaine inhalation, and the results were compared. In this study, an approximately 27% decrease in mean Schirmer test values after cocaine exposure and a decrease in Schirmer values in 17 out of 22 patients were found; however, in this study, examinations evaluating tear functions, such as TBUT and impression cytology, and ocular surface health were not conducted. In a study conducted on 41 healthy individuals by Osei et al. [12], they found that the use of 5 mg/kg caffeine significantly increased tear production at the 45^{th} and 90^{th} minutes compared to the placebo group, through Schirmer test. In our study, Schirmer values, TBUT values, and Nelson scores did not demonstrate any statistically significant difference in both groups. According to our results of ocular surface functions, no significant difference was found in the variables including Schirmer, which indicates tear production; TBUT, which indicates lipid layer function; and Nelson score, which provides cytological information; compared to the control group. Altınörs and Matsumoto et al. evaluated lipid distribution in the tear film layer with a DR-1 tear interferometry measuring device (DR-1 Kowa Co., Nagoya, Japan)in patients with smoking addiction and reported that patients with addiction were scored with a significantly higher stage compared to the control group, according to the staging system described by Yokoi [9, 10, 13]. As a result, these 2 studies found that heavy smoking affects the lipid layer and disrupts the structure of the tear film layer.

Several studies have shown that cannabinoid receptors are present in the corneal epithelium and conjunctiva on the ocular surface [14, 15]. Iribane at al. [15], explains that activation of conjunctival receptors can regulate epithelial regeneration and inflammation processes by affecting intracellular stress-related signaling pathways. Assimakopoulou at al. [16], showed that there are cr1 and cr2 receptors in all layers and goblet cells in healthy conjunctival epithelial tissue, but cannabinoid receptors are decreased in pterygium tissue. Based on all these studies, Bielory at al. [17], suggested that cannabinoids can be used as anti-inflammatory and antiallergenic on the ocular surface. In a study by Thapa et al. [18], in mice with cauterized corneal epithelium, topical administration of THC and its synthetic derivatives has been reported to reduce ocular pain and inflammation. We believe that due to the reduction of pain and inflammation in patients with cannabis addiction, tear production and quality are not impaired, and therefore, the damage to the ocular surface is compensated.

There are some limitations in our study. Since test systems to assess a tear interferometry measuring device were not available in our clinic, that variable could not be assessed in the study. We believe that measuring the tear osmolarity will make the study more effective.

In conclusion, in this study, the effects of cannabis addiction on the ocular surface were evaluated using the results of Schirmer, TBUT, and impression cytology tests. In the statistical analysis, no significant difference was found in these variables compared to the control group. Our study showed that the structure and functions of the ocular surface and the systems it interacts with, such as tear production, tear content, and conjunctival cell cytology did not change due to cannabis exposure.

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Ethical approval

All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Institution review board/Ethics Committee has approved the study

Informed consent

Informed consent was obtained from all individual participants included in the study. The article has not been presented at any conference or meeting.

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