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Oral İsotretinoin Tedavisinin Santral Maküler Kalınlık, Koroid Kalınlığı ve Retina Sinir Lifi Tabakası Üzerindeki Etkisi

The Effect of Oral Isotretinoin Treatment on Central Macular Thickness, Choroidal Thickness and Retinal Nerve Fiber Layer

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ÖZ

Giriş: Literatürde oral isotretinoin tedavisinin birçok oküler yan etkiye neden olduğu bildirilmiştir. Bu çalışmadaki amacımız oral isotretinoin tedavisinin santral maküler kalınlık (SMK), koroid kalınlığı ve retina sinir lifi tabakası (RNFL) kalınlığı üzerindeki etkisinin spektral domain optik koherens tomografi (SD-OKT) cihazı ile değerlendirmektir.

Yöntem: Bu prospektif tek merkezli çalışmaya 45 oral isotretinoin tedavisi alan hasta dahil edildi. Oral isotretinoin tedavisinin başlangıcında ve üçüncü ayın sonunda SD-OKT cihazı ile SMK, koroid kalınlığı ve RNFL kalınlığı ölçüldü. Koroid kalınlığı ölçümleri subfoveal alan, foveaya nazal ve temporal 500, 1000, 1500 µm mesafeden yapıldı.

Bulgular: SMK ve subfoveal, nazal ve temporal 500, 1000 ve 1500 µm koroid kalınlığı ölçümlerinin başlangıç ve üçüncü ay takipleri arasında istatistiksel açıdan anlamlı farklılık izlenmedi (p=0,489, p=0,703, p=0,068, p=0,057, p=0,657, p=0,069, p=0,734, p=0,376, sırasıyla). Ortalama, superior, inferior, nazal ve temporal RNFL kalınlığı açısından başlangıç ve üçüncü ay takipleri arasında istatistiksel açıdan anlamlı farklılık yoktu (p=0,453, p=0,446, p=0,670, p=0,379, p=0,086, sırasıyla). Ayrıca ortalama günlük oral isotretinoin dozu (24±4,96 mg/ gün) ile, SMK, koroid kalınlığı ve RNFL kalınlığındaki değişim arasında istatistiksel açıdan anlamlı korelasyon izlenmedi (p> 0.05).

Sonuç: 3 aylık oral isotretinoin tedavisinin SMK, koroid kalınlığı ve RNFL kalınlığı üzerinde toksik etkisi izlenmedi.

Anahtar Kelimeler: santral maküler kalınlık, koroid kalınlığı, oral isotretinoin tedavisi, retina sinir lifi tabakası

ABSTRACT

Objective: In the literature, oral isotretinoin treatment has been reported to cause many ocular side effects. The aim of this study was to evaluate the effect of oral isotretinoin treatment on the central macular thickness (CMT), choroidal thickness, and retinal nerve fiber layer (RNFL) thickness by using the spectral domain optical coherence tomography (SD-OCT) device.

Method: A total of 45 patients receiving oral isotretinoin therapy were included in this prospective single-center study. The CMT, choroidal thickness, and RNFL thickness were measured with the SD-OCT device at baseline and at the end of the third month of oral isotretinoin treatment. Choroidal thickness measurements were performed at the subfoveal location and nasal and temporal to the fovea at a distance of 500, 1000, and 1500 µm.

Results: No statistically significant difference was observed between the baseline and the third month of follow-up for the CMT and the subfoveal, and nasal and temporal 500, 1000, and 1500 µm choroidal thickness measurements (p=0.489, p=0.703, p=0.068, p=0.057, p=0.657, p=0.069, p=0.734, p=0.376, respectively). No statistically significant difference was present between the baseline and the third month follow-up in terms of the mean, superior, inferior, nasal, and temporal RNFL thickness values (p=0.453, p=0.446, p=0.670, p=0.379, p=0.086, respectively). No statistically significant relationship was found between the mean daily oral isotretinoin dose (24±4.96 mg/day) and the change in CMT, choroidal thickness, and RNFL thickness (p> 0.05).

Conclusion: No toxic effects of 3-month oral isotretinoin treatment were observed on the CMT, choroidal thickness, and RNFL thickness.

Keywords: central macular thickness, choroidal thickness, oral isotretinoin treatment, retinal nerve fiber layer

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INTRODUCTION

Oral isotretinoin is a retinoid derived from vitamin A and has become the most effective treatment for nodular cystic acne in the 1980s. The side effects of oral isotretinoin, other than teratogenicity, are dose-dependent, preventable, and manageable (1). Retinoids have a broad side effect profile including those related to the cutaneous, neurological, musculoskeletal, hepatic, and ocular systems (2). The reported ocular side effects of oral isotretinoin are meibomian gland atrophy, dry eye, decreased contact lens tolerance, blepharoconjunctivitis, keratitis, photophobia, corneal opacity, refractive changes, day/night vision impairment, color vision impairment, lens opacities, retinal vascular occlusion, premacular hemorrhage, and vitreous disorders (3,4).

The choroid is a vascular layer that nourishes the outer retina and has a very high blood flow rate (5). Systemic and topical drugs affect the microvascular structure in the choroid and cause changes in choroidal thickness (6). Such changes in choroidal thickness play a role in many diseases affecting the retina (7,8). Retinoic acid and binding proteins have been demonstrated in normal choroidal tissue (9). Therefore, evaluation of the choroid in patients who are using oral isotretinoin is important in terms of retinal toxicity.

Previous studies have reported that oral isotretinoin use causes neurological side effects (10,11). Some of these side effects include optic neuritis, visual field defect, cortical blindness, and idiopathic intracranial hypertension (3). In addition, synthetic retinoids are known to affect the growth and differentiation of nerve tissue (11). The retinal nerve fiber layer (RNFL) consists of the axons of retinal ganglion cells that form the optic nerve. Measuring RNFL thickness in patients using oral isotretinoin can enlighten us about side effects that may occur in the optic nerve in the early period due to drug use.

The optic nerve and choroidal tissues can be evaluated non-invasively with the spectral domain optical coherence tomography (SD-OCT) device. Thanks to the SD-OCT device's enhanced depth imaging (EDI-OCT) mode, multiple scans are performed from the same area and the deep choroidal structures are imaged in detail (12). Our aim in this study was to evaluate the central macular thickness (CMT), choroidal thickness, and RNFL thickness with the SD-OCT device at baseline and at the end of the third month of treatment in patients using oral isotretinoin and to contribute to the literature regarding the ocular side effects.

MATERIALS AND METHODS

This retrospective study was conducted at Sabuncuoğlu Şerefeddin Training and Research Hospital's Dermatology and Ophthalmology Departments between June and December 2023. The ethics committee approval of the study was obtained from Amasya University. Our study was conducted in accordance with the ethical standards of the Helsinki Declaration and the measurements to be performed were explained to all patients before written informed consent was obtained.

The study included the 45 eyes of 45 patients who were examined at the Dermatology clinic due to nodular cystic acne and referred to the Ophthalmology clinic. After the ophthalmological examination, the patients were started on oral isotretinoin treatment at a dose of 0.5 -1 mg/kg/day. Complete blood count values, liver and kidney function tests, and serum lipid levels of all the participants were evaluated before the treatment and at monthly follow-ups. Additionally, all female participants had negative pre-treatment pregnancy tests. The patients' demographic characteristics, history of systemic disease, and drug use history were queried. Individuals under 18 and over 40 years old, those with BCVA below 20/20, those with a refractive error above ±3 diopters after cycloplegic examination; those with a history of glaucoma, uveitis, retinal disease, or ocular trauma; those with a neurological disease that could affect the visual field, those with a corneal or lens opacity that would prevent OCT imaging, those who had undergone intraocular surgery, those with a systemic disease such as diabetes or hypertension that could affect the choroidal blood flow, and those with a history of systemic corticosteroid or oculotoxic drug use were excluded from the study. Additionally, patients who experienced serious neurological and ocular side effects during oral isotretinoin treatment and patients who did not come for follow-up were also excluded from the study.

All participants underwent a complete ophthalmological examination including best-corrected visual acuity (BCVA) with the Snellen chart, refraction examination, slit-lamp biomicroscopic anterior segment and dilated fundus examination with a 90 diopter (D) lens, and intraocular pressure (IOP) measurement with the Goldmann Applanation tonometer at the beginning of oral isotretinoin treatment and at the end of the third month. Following these examinations, the CMT, choroidal thickness, and RNFL thickness measurements were performed by using the SD-OCT (3D OCT-2000, Topcon, Japan) device. The circle in the central part of the Early Treatment Diabetic Retinopathy Study (ETDRS) map, which covers a macular area of 6*6 mm2 and contains 9 areas, as calculated by the automatic software on the device, was recorded as the CMT. Choroidal thickness measurements were performed by the same technician by using the EDI mode of the SD-OCT device after pupil dilation in the morning to avoid being affected by diurnal variation. Images with an image quality index >45 were included in the study. The choroidal thickness measurements were made from 7 regions, including the subfoveal location and areas 500 µm, 1000 µm, and 1500 µm nasal and temporal to the subfoveal area. The distance between the outer border of the retinal pigment epithelium (RPE) and the inner border of the sclera was considered as the choroidal thickness and this distance was measured manually with vertical lines drawn with the help of digital calipers. These measurements were performed at different times and independently by two physicians (MT, NA). The measurements were repeated three times by each physician and the average of these three measurements taken.

RNFL thickness measurements were made by placing a 3.4 mm diameter circular ring around the optic nerve at equal distance to all quadrants. The mean of three consecutive circular scans was calculated. The mean, superior, inferior, nasal, and temporal RNFL thicknesses of all patients were obtained using an automatic computer algorithm and recorded. The CMT, choroidal thickness, and RNFL thickness measurements were performed at baseline and at the end of the third month of oral isotretinoin treatment.

Statistical Analysis

The data were analyzed with the Statistical Package For Social Sciences (SPSS) version 23.0 software package (IBM Inc., Chicago, IL, USA). Only

the right eye values were used for statistical purposes. The compliance with a normal distribution was evaluated with the Shapiro-Wilk test. The Wilcoxon test was used to compare non-normally distributed data and the paired sample t test was used to compare normally distributed data before and after treatment. The results of the analysis were presented as mean±standard deviation. A p value <0.05 was accepted as statistically significant.

RESULTS

The 45 eyes of 45 patients were included in this study. Of these patients, 31 (68.9%) were female and 14 (31.1%) were male. The mean age was 21.8±3.61 years (range 18-36 years). The mean isotretinoin dosage was 24±4.96 mg/day (range 20-30 mg/day) (Table 1). No statistically significant difference was present between the refraction and intraocular pressure values at baseline and at the end of the third month (p=0.715, p=0.185, respectively).

No statistically significant difference was observed when the baseline and third month CMT and the subfoveal and the nasal and temporal choroidal thickness measurements at 500, 1000 and 1500 µm were compared (p=0.489, p=0.703, p=0.068, p=0.057, p=0.657, p=0.069, p=0.734, p=0.376, respectively).

No statistically significant difference was found either when the baseline and third month measurements were compared in terms of mean, superior, inferior, nasal and temporal RNFL thickness (p=0.453, p=0.446, p=0.670, p=0.379, p=0.086, respectively). The CMT, choroidal thickness and RNFL thickness parameters are shown in tables 2 and 3. There was no statistically significant relationship between the daily oral isotretinoin dose and the difference between the central macular difference, choroidal difference and retinal nerve fiber layer before and after treatment (p> 0.05) (Table 4).

Table 1. Baseline Characteristics of the Study Population (n=45)

Parameters	
Age, years mean±SD	21.8±3.61 (range 18-36)
Sex (%) Female Male	31 (%68.9) 14 (%31.1)
Isotretinoin dose (mg/ day) mean±SD	24±4.96 (range 20-30)

Tablo 2. Central Macular Thickness and Choroidal Thickness Before and After Systemic Isotretinoin Therapy

Parameters		Baseline	Third month	P value
CMT (µm)	Mean ± SD Range	222.58±9.83 (202 to 247)	221.91±10.70 (202 to 248)	0.489*
SCT (µm)	Mean ± SD Range	354.36±29.80 (286 to 411)	353.20±24.75 (308 to 410)	0.703*
N 500 µm	Mean ± SD Range	345.16±29.72 (278 to 401)	339.22±20.11 (300 to 380)	0.068*
N 1000 µm	Mean ± SD Range	334.38±33.24 (244 to 393)	333.31±23.66 (291 to 381)	0.057**
N 1500 µm	Mean ± SD Range	325.22±32.35 (243 to 381)	323.69±28.24 (270 to 385)	0.657*
T 500 µm	Mean ± SD Range	347.13±33.55 (268 to 400	341.42±21.97 (298 to 388)	0.069*
T 1000 µm	Mean ± SD Range	339.07±32.83 (263 to 399)	338.09±24.32 (285 to 388)	0.734*
T 1500 µm	Mean ± SD Range	331.82±31.35 (265 to 387)	329.67±26.60 (274 to 385)	0.376*

CMT: Central Macular Thickness, SCT: Subfoveal Choroidal Thickness,
N: Nasal T: Temporal,
*: Paired Sample t Test , **: Wilcoxon test,
A p value <0.05 Was Considered Significant.

Table 3. Retinal Nerve Fiber Layer Thickness Before And After Oral İsotretinoin Therapy

Parameters		Baseline	Third month	P value
Mean RNFL (µm)	Mean ± SD Range	111.96±9.92 (99 to 148)	112.60±10.39 (85 to 145)	0.453*
Superior RNFL (µm)	Mean ± SD Range	137.47±16.18 (103 to 174)	136.84±16.73 (102 to 175)	0.446**
Inferior RNFL (µm)	Mean ± SD Range	143.20±15.82 (111 to 191)	144.07±18.01 (92 to 183)	0.670*
Nazal RNFL (µm)	Mean ± SD Range	85.49±11.97 (59 to 111)	86.42±12.14 (64 to 116)	0.379**
Temporal RNFL (µm)	Mean ± SD Range	82.60±11.93 (60 to 112)	81.76±11.99 (64 to 112)	0.086*

RNFL: Retinal Nerve Fiber Layer,
*: Wilcoxon Test, **: Paired Sample t Test
A p value <0.05 Was Considered Significant.

Table 4. The Relationship of The Daily Oral Isotretinoin Dose with The Macular Thickness, Choroidal Thickness, and Retinal Nerve Fiber Layer Thickness Difference Before and After Treatment

Parameters		20 (mg/day)	30 (mg/day)	P value
CMT (µm)	Mean ± SD	1.07±7,76	0.06±3.69	0.607*
SCT (µm)	Mean ± SD	-1.41±22.25	5.00±15.80	0.524**
N 500 µm	Mean ± SD	4.00±25.02	8.83±13.97	0.586**
N 1000 µm	Mean ± SD	-2.04±29.82	5.72±10.78	0.531**
N 1500 µm	Mean ± SD	1.33±28.99	1.83±9.21	0.586**
T 500 µm	Mean ± SD	4.33±22.33	7.78±17.89	0.908**
T 1000 µm	Mean ± SD	-0,93±21.67	3.83±14.80	0.728**
T 1500 µm	Mean ± SD	1.07±16.77	3.78±15.57	0.538**
Mean RNFL (µm)	Mean ± SD	-1.26±30.68	0.28±1.93	0.165**
Superior RNFL (µm)	Mean ± SD	0.85±6.67	0.28±2.85	0.944**
Inferior RNFL (µm)	Mean ± SD	-1.30±9.79	-0.22±3.41	0.861**
Nasal RNFL (µm)	Mean ± SD	-1.04±8.91	-0.78±2.69	0.779**
Temporal RNFL (µm)	Mean ± SD	3.11±6.04	-2.56±12.56	0.151**

CMT: Central Macular Thickness, SCT: Subfoveal Choroidal Thickness,
N: Nasal T: Temporal, RNFL: Retinal Nerve Fiber Layer
***:** Independent Two-Sample t-Test, **: Mann-Whitney U test

DISCUSSION

Isotretinoin is a retinoic acid derivative and is used in the treatment of severe nodular cystic acne and various skin disorders. Many ocular side effects have been reported during and after oral isotretinoin treatment, and certain side effects have been found to be dose dependent (1). Our aim in this study was to evaluate the CMT, choroidal thickness, and RNFL thickness in patients using oral isotretinoin and to investigate the toxic effects of the drug on ocular structures.

The choroid is a highly vascular structure, and the choroidal blood flow constitutes more than 85% of the blood flow in the eye. The choroid is responsible for providing nutritional support to the RPE and outer retinal layers, the absorption of excessive light penetrating the retina and RPE, the stabilization of heat, and providing the vascular supply of the foveal avascular zone and the prelaminar part of the optic nerve (13). Therefore, the choroid plays a role in diseases of the retina, optic nerve, and RPE (14).

Systemic drug use affecting the microvascular structures in the body also affects the choroidal circulation (6). While oral retinoids increase the synthesis of vasorelaxant substances, they also inhibit the effect of vasoconstrictor agents (15). Prostaglandins (PGs) and nitric oxide (NO) have very important roles in the regulation of the vascular tone and also play a major role in the regulation of retinal and choroidal hemodynamics (16). Isotretinonin has been observed in previous studies to increase the synthesis of Prostaglandin I2 (PGI2) and NO, which are vasorelaxant molecules (15,17).

Evaluating the choroidal thickness provides information on the choroidal circulation. No statistically significant difference was observed when the baseline and third month choroidal thickness measurements at the subfoveal location and the nasal and temporal 500, 1000 and 1500 μm locations were compared in our study. Similar to our study, no significant difference was found in the choroidal thickness between the baseline and the third month of isotretinoin treatment measurements in the study of Karadağ et al. (18). No significant change was observed in the subfoveal choroidal thickness after the treatment compared to the pretreatment value in the study on the ocular effects of systemic isotretinoin treatment conducted by Elubous et al. (19). Besides, while Dehghani et al. found a CMT lower than the baseline in their measurements at the third and sixth months of oral isotretinoin treatment, they did not observe a statistically significant change in choroidal thickness (20). However, Yavuz et al. have found an increase in the peripapillary choroidal thickness in the superotemporal and temporal quadrants compared to the baseline in the third month of isotretinoin treatment in their study where they evaluated the peripapillary choroidal thickness (21). The peripapillary region is responsible for the vascular supply of the prelaminar region of the optic nerve head and plays a role in many ocular pathologies (22). This increase, thought to be due to isotretinoin increasing the synthesis of vasorelexant molecules, also shows that the peripapillary region is affected more strongly than the macular region by oral isotretinoin treatment. A study conducted by Gediz et al. has reported that the choroidal thickness and the choroidal vascular index (CVI) were significantly higher in the group receiving oral isotretinoin compared to the control group after an average of 7 months of treatment and an average 38 mg daily dose of oral isotretinoin, and that no significant difference was observed between the groups in terms of the choriocapillaris (CC) flow area (23). We think that the reason for the different results obtained in our study is the cumulative effect of isotretinoin used for a longer period of time and in higher doses.

The RNFL consists of the axons of retinal ganglion cells, and the evaluation of RNFL thickness is of great importance in the diagnosis of optic nerve anomalies and disorders. Besides, since the retinal ganglion cells and axons are in direct contact with the brain, the RNFL thickness can also give us information about the brain (24). SD-OCT can detect the effect of drugs that have retinal toxicity, such as hydroxychloroquine, in the visual field and the anomalies in areas that appear unaffected on funduscopic examination (25). Therefore, the evaluation of RNFL thickness with the SD-OCT device is important for the early detection of neurological and optic nerve-related side effects of isotretinoin.

Optic nerve-related ocular side effects due the use of oral isotretinoin such as decreased color vision and dark adaptation, optic neuritis, and peripheral visual field loss have been reported (3). A significant increase in P-100 wave latency has been detected in 18% of patients with the visual evoked potential (VEP) test after oral isotretinoin treatment (26). Additionally, subclinical changes in electroretinography (ERG) may continue months or years after the discontinuation of drug treatment in patients receiving oral isotretinoin (27). It is known that retinoids affect the development, differentiation and function of nervous tissue, and previous studies have reported that they may have side effects related to both the central and peripheral nervous systems (11,26). A nerve biopsy has revealed that isotretinoin caused axonal degeneration and an abnormal Schwann cell complex as well as a decrease in myelinated nerve fibers (28). Additionally, changes in the lipid content of the nerve cell membranes due to isotretinoin negatively affect nerve conduction (26).

No statistically significant difference compared to the baseline was found in the RNFL thickness at the end of the third month of isotretinoin treatment used at a dose of 0.5-1 mg/kg/day in our study. No change in RNFL thickness compared to baseline was found after 3 months of isotretinoin treatment in the study of Karadağ et al. (18). No difference was again observed in terms of RNFL thickness measurements and visual field defects between the baseline and the second and third month follow-ups of oral isotretinoin treatment in the study of Bakbak et al. (29). No change in RNFL thickness and ganglion cell layer (GCL) thickness was found during the 4-8 month follow-up period of oral isotretinoin treatment compared to the pre-treatment period in the study of Şekeryapan et al. (30). Yılmaz et al. have found the mean RNFL thickness in the temporal quadrant and the mean macular thickness in the superior outer, nasal outer, temporal outer and superior inner quadrants to be lower than the baseline values after 3 months of isotretinoin treatment (31). Uçak et al. have found a decrease in inferior temporal RNFL thickness following 0.5-2 mg/kg/day of oral isotretinoin treatment for a mean duration of 5.4 months (32). These results indicate that oral isotretinoin may have toxic effects on the optic nerve, depending on the drug dose and duration of use.

Limitations of the Study

Our study had certain limitations. The first of these was that our study was conducted at a single center and with a small sample group. A second limitation was that the patients only had a 3-month follow-up period. Another limitation of our study was that our patients had received a low

dose (mean 24±4.96 mg/day) of oral isotretinoin treatment.

CONCLUSION

In conclusion, no change was observed in terms of CMT, choroidal thickness, or RNFL thickness compared to the baseline in patients who were receiving oral isotretinoin treatment at a mean daily dose of 24±4.96 mg for 3 months in our study. Therefore, data from oral isotretinoin treatment at higher doses and for longer periods and a larger sample group should be evaluated to investigate the retinal toxic effects of oral isotretinoin

Ethics Committee Approval: This study was approved by the Ethics Committee of Amasya University (Approval number:125210). All procedures were conducted in accordance with the Declaration of Helsinki.

Author contributions: Concept: NA, MT, CK; Study Design: NA, MT, CK; Data collection: NA, MT, CK; Analysis: NA, MT; Literature search: MT, CK; Writing manuscript: NA, MT; Critical rewiev: MT, NA, CK. All authors read and approved the final manuscript.

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