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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

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CONTENTS

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EDITORIAL

2022 Issue 1 at a Glance:

This issue of our journal features eight original research articles, one review, and three case reports that we hope will be interesting and beneficial for our readers.

Microbial keratitis is a serious condition that can result in corneal scarring, perforation, and blindness. It usually occurs in the presence of predisposing factors such as contact lens (CL) use. Determining the incidence, the diversity of microbial agents, and predisposing factors of microbial keratitis are necessary for effective treatment and prevention. Yarımada et al. evaluated the medical records of 314 patients with corneal ulcers suggestive of microbial keratitis who presented to a tertiary center in Izmir and had cultures performed. They recorded the patients' demographic, clinical, and laboratory data; lesion characteristics including the location and number of keratitis foci; presence of predisposing factors such as CL use, trauma, recurrent corneal erosion, corneal graft, and ocular or systemic disease; and the type of microorganism detected in culture. The results showed that in western Turkey, CL use was the biggest risk factor for microbial keratitis and *Pseudomonas aeruginosa* was the most frequently isolated microbial agent. The authors emphasized that microbiological analysis and culture are important steps in the appropriate therapeutic management of microbial keratitis (see pages 1-5).

Ay and Alay determined the frequency of ocular symptoms and levels of inflammation markers in 53 patients treated in the intensive care unit due to severe acute respiratory tract infection coronavirus 2 (SARS-CoV-2) infection and prospectively investigated the association between these parameters and mortality. Congestion was observed in 13 patients (24.5%), serous secretion in 6 patients (11.3%), and chemosis in 3 patients (5.7%). Every 1 mg/dL increase in C-reactive protein level was associated with 1.9% lower odds of detecting inflammatory eye signs (95% confidence interval: 3.3%-0.4%). Their results draw attention to the importance of ocular surface examination in patients receiving intensive care treatment due to COVID-19 (see pages 6-13).

Bozkurt Oflaz et al. conducted a study to evaluate the effects of auditory biofeedback training using microperimetry in patients with foveal scar and a retinal locus eligible for better fixation. They observed that the retinal locus trained with biofeedback training increased average retinal sensitivity, fixation stability, and reading speed and improved contrast sensitivity and quality of life (see pages 14-22).

Altınbay and İdil examined 63 eyes of 63 patients with age-related macular degeneration (AMD) in their prospective study to determine fixation stability and characteristic features of the preferred retinal area (PRL) in advanced AMD. They determined that the distance of the PRL from the fovea was significantly associated with fixation stability, with greater PRL-fovea distance in patients with unstable fixation compared to patients with stable fixation (p=0.023). Considering the strong relationship between fixation stability and reading speed, this finding emphasizes the importance of knowing the factors associated with fixation stability in late AMD in terms of restoring reading ability in low vision rehabilitation (see pages 23-29).

Sönmez et al. analyzed the optical coherence tomography angiography (OCT-A) and peripheral visual field data of 11 patients with acute non-arteritic anterior ischemic optic neuropathy (NAION) and 14 controls. They determined that peripapillary and optic nerve head hypoperfusion areas correlated with visual field defects in 6 of the patients, and that the patients had lower optic disc head capillary density (p=0.008) and reduced radial peripapillary capillary density in all sectors except the inferonasal sector. The authors concluded that OCT-A is a current, rapid, and non-invasive method for the evaluation of peripapillary microcirculation in NAION patients (see pages 30-36).

Özdek et al. aimed to evaluate the effects of two- and four-quadrant partial-thickness sclerectomy and sclerotomy surgery on visual and anatomical outcomes in the treatment of nanophthalmus (NO)-related uveal effusion (UE). Of 14 eyes of 10 patients operated, 11 eyes underwent four-quadrant surgery and 3 eyes with glaucoma underwent two-quadrant surgery. External drainage of subretinal fluid was added in 1 eye with total retinal detachment. Because retinal reattachment occurred in only 1 of the 3 eyes that underwent primary two-quadrant surgery, in the other 2 eyes the remaining two quadrants were also operated to complete four-quadrant sclerectomy. At last follow-up, retinal reattachment was observed in 11 eyes (78.6%), partial reattachment in 1 eye (7.1%), and recurrence of macular detachment in 2 eyes (14.3%). The authors noted that partial-thickness sclerectomy and sclerotomy surgery are effective in the treatment of UE in eyes with NO, and external drainage of subretinal fluid may be an option to achieve a faster response in severe cases (see pages 37-44).

Idiopathic juxtafoveal telangiectasia (IMT) is associated with foveal thinning, crystalline deposits in the macula, telangiectatic vascular changes with leakage, and macular neovascularization (MNV). Macular telangiectasia type 2 (MacTel 2), a subgroup of IMT, is an acquired bilateral disease that causes decreased visual acuity and metamorphopsia, most commonly occurring in middle-aged adults. Çoban Karataş et al. compared the best-corrected visual acuity, central macular thickness (CMT), and central choroidal thickness (CCT) values

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

EDITORIAL

of MacTel 2 patients and a control group and evaluated the efficacy of intravitreal anti-VEGF therapy in MacTel 2 patients with MNV. The MacTel 2 group had significantly lower CMT and CCT than the control group, 8 eyes of 7 patients with MacTel 2 developed MNV during follow-up, and all patients were treated with intravitreal anti-VEGF. The authors concluded that MacTel 2 patients should be closely monitored for the development of MNV, and intravitreal anti-VEGF therapy may be beneficial in patients with proliferative MacTel 2 and reduced visual acuity (see pages 45-49).

Ceylan and Yeniad prospectively evaluated tear film changes with tear film break-up time and Schirmer tests, corneal staining patterns, Ocular Surface Disease Index scores, and corneal topography and autorefractometry results preoperatively and at postoperative 1 day, 1 week, 1 month, 3 months, and 6 months in 32 eyes of 20 patients who underwent ptosis surgery and/or upper lid blepharoplasty: blepharoplasty in 12 eyes (group 1), blepharoplasty with levator surgery in 8 eyes (group 2), and levator surgery only in 12 eyes (group 3). They determined that ptosis surgery and upper lid blepharoplasty can cause dry eye symptoms that vary according to the surgical procedure performed and can persist at postoperative 6 months, that levator surgery can cause temporary refractive changes, and upper lid blepharoplasty does not cause postoperative keratometric changes (see pages 50-56).

The space race began with the Soviet Union launching the artificial satellite Sputnik 1 on October 4, 1957, followed by animal and manned flights. Thanks to the International Space Station, the numbers of space flights and people exposed to space conditions are increasing. Space studies have revealed several problems that affect human biology, including low gravity, lack of atmosphere, galactic cosmic rays, and solar energetic particles. Microgravity (MG) and space radiation constitute a major part of these problems. In this issue's review, Özelbaykal et al. examines the literature on the effects of MG and space radiation on the eye and shares treatment methods and hypotheses about what can be done to mitigate the effects of MG and space radiation on biological structures (see pages 57-63).

Conditions involving disruptions in Descemet's membrane (DM) integrity such as rupture and detachment manifest with corneal edema and vision loss due to DM folds. Acute corneal hydrops is characterized by DM rupture as a result of stretching of the DM due to corneal ectasia. The DM rupture allows aqueous fluid to enter the corneal stroma and corneal epithelium. Although loss of DM integrity resolves spontaneously, severe visual symptoms or vision loss and long disease duration negatively influence quality of life and cause significant visual morbidity. Özcan and Özlenen Uçakhan evaluated treatment responses in a total of four patients, two who were treated with isoexpansile 14% C_3F_8 injection into the anterior chamber for acute hydrops due to keratoglobus or keratoconus, and two who were treated with intracameral 14% C_3F_8 injection with corneal compression sutures for chronic, large DM detachments due to keratoglobus and chronic hydrops complicated by multiple stromal clefts on anterior segment optical coherence tomography in one patient and after cataract surgery in the other patient. Complete and effective DM reattachment with surgery was reported in all patients. The authors stated that surgical treatment of corneal hydrops with intracameral gas injection and corneal compression sutures provides rapid symptomatic relief, better visual rehabilitation, less corneal scarring, and may reduce the need for corneal transplantation in this patient group (see pages 64-68).

Arıcı et al. detected diffuse corneal edema, DM folds, and an intact upside-down graft on slit-lamp examination of a 29-year-old woman who was referred for corneal edema after uneventful pterygium excision with conjunctival autograft. Within two weeks of treatment with topical dexamethasone, a complete response was observed, but severe endothelial cell loss was observed in the operated eye on specular microscopic examination. In long-term follow-up, mild corneal haze causing a decrease in visual acuity to 20/50 was observed. With this case report, the authors emphasize that povidone iodine should be carefully cleared during pterygium surgery and its penetration into the anterior chamber should be prevented to avoid potentially serious complications (see pages 69-71).

Erlotinib is a tyrosine kinase inhibitor that specifically targets the epidermal growth factor receptor and is frequently used in the treatment of lung cancer. It can cause ocular complications ranging from mild dry eye syndrome to corneal perforation requiring corneal transplantation. Mangan presents a patient who was using erlotinib for 3 years for non-small cell lung cancer and was referred from the oncology clinic with complaints of burning, stinging, pain, and dryness in both eyes and outward turning of both lower eyelids. One week after temporarily discontinuing erlotinib with approval from the oncology department, the patient's cicatricial ectropion had improved dramatically and all complaints completely resolved. The author noted that good communication between oncologists and ophthalmologists along with risk assessment and joint decision-making can reduce systemic and ocular complications (see pages 72-74).

We hope that the articles in our first issue of the year will make for interesting reading and provide guidance in your professional practice.

Respectfully on behalf of the Editorial Board,

Özlem Yıldırım, MD

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Original Article

Comparison of Culture-Positive and -Negative Microbial Keratitis

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Abstract

Objectives: To evaluate and compare the risk factors, presenting features, and outcomes of patients with culture-positive and culture-negative microbial keratitis (MK) who presented to a tertiary referral center.

Materials and Methods: We conducted a retrospective review of the medical records of 314 patients who were diagnosed with MK in our clinic between 2012 and 2019.

Results: Among 314 patients, 142 had positive cultures (45.2%). The mean ages of the culture-positive and -negative patients at the time of diagnosis were 51.39±21.31 (range, 14-90) years and 56.68±21.34 (7-94) years, respectively (p=0.028). The mean best corrected visual acuity (BCVA) of the culture-positive and -negative patients were1.74±1.25 (0-3.1) LogMAR and 1.91±1.23 (0-3.1) LogMAR prior to treatment and increased to 1.21±1.30 (0-3.1) LogMAR and 1.27± 1.29 (0-3.1) LogMAR at last visit, respectively. There was no statistically significant difference between culture-positive and -negative patients' BCVA levels at presentation or last visit. Ninety-two patients (64.7%) were infected with bacteria and 50 patients (35.2%) with fungi. The most common pathogen was *Pseudomonas aeruginosa* (18.3%), followed by *Streptococcus pneumoniae* (11.2%) and *Fusarium* spp. (11.2%). Keratitis foci were either centrally or paracentrally located in 105 eyes (73.9%) of culture-positive patients and 149 eyes (86.6%) of culture-negative patients. Multiple foci were present mostly in culture-positive patients (p=0.001). There was no significant difference between the culture-positive and -negative groups in terms of hypopyon presence (p=0.364). The proportion of contact lens (CL) wearers was 33% (n=47) among culture-positive MK patients and 13.3% (n=23) among culture-negative MK patients, respectively (p<0.001). Culture positivity was found to be significantly higher in keratitis associated with CL use (p=0.0001).

Conclusion: Microbiological analysis and culture evaluation are important steps in order to manage proper treatment in microbial keratitis. Prognosis mostly depends on the infectivity of the microbiological agent.

Keywords: Contact lens, culture, microbial keratitis

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Introduction

Microbial keratitis is a severe disease that can result in corneal scarring, perforation, and finally blindness. Predisposing factors such as contact lens (CL) usage are usually present in the incident of the disease. Determining the incidence, microbial agent diversity, and predisposing factors of microbial keratitis are necessary for effective diagnosis, management, and prevention.[1]

The demographics and microbiological profile of the disease differ, and various reports have been published through the world.[2,3] Shifting trends in the microbiological profile of keratitis have also been reported in some studies.[4,5,6] Therefore, regular studies of the microbial profile are essential in order to determine local microorganisms and their antimicrobial sensitivities.[7]

The present study aimed to identify the features of culture-positive and culture-negative microbial keratitis in a tertiary referral center in İzmir, Turkey.

Materials and Methods

We performed a retrospective data analysis of patients who presented to our clinic between 2012 and 2019 with corneal ulcer findings suggestive of microbial keratitis (central and/or large (≥3 mm) corneal infiltrates or corneal infiltrates extending to the mid to deep stroma, Figure 1) and underwent culture. The medical records of 314 patients were reviewed for demographic, clinical, and laboratory findings. Lesion characteristics including the location and number of keratitis foci were noted. Lesion location was defined as central if it invaded within 2 mm of fixation, peripheral if it involved a zone within 2 mm of the limbus, and paracentral if it was between the central and peripheral zone. Predisposing factors such as CL use, trauma, recurrent corneal erosion, corneal graft, and ocular or systemic disease, as well as the type of microorganism detected in culture were noted. The study adhered to the tenets of Declaration of Helsinki and was approved by the institutional ethics committee of our university.

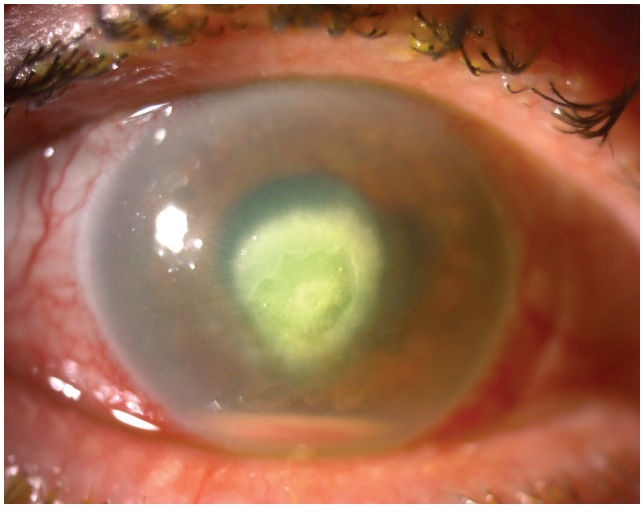

Figure 1. Central deep corneal infiltrates extending to the middle to deep stroma

Microbiological samples for Gram staining and cultures were obtained from the patients by a cornea specialist using a scalpel blade and cotton-tipped swab. If present, CLs and their solutions were also sent to the laboratory for microbiological investigation. Collected samples routinely underwent Gram staining and were inoculated on 5% sheep blood agar, EMB agar, chocolate agar, and Sabouraud agar for culturing. A culture result was noted as positive if microorganism growth was observed along the inoculation line in plates at 48 hours for bacteria or detected on Sabouraud agar after 6 weeks of incubation for fungi. Cultured microorganisms were identified using standard microbiological procedures. Antibiotic sensitivities were demonstrated based on antibiotic susceptibility testing standards of the Clinical Laboratory Standards Institute, using the VITEK 2 (Biomerioux, France) automated system. Patients were hospitalized and empirically initiated on topical fortified vancomycin (Vancotek 50 mg/mL vial, Kocak Farma, Turkey), ceftazidime (Iesetum 50 mg/mL vial, I.E. Ulagay, Turkey), and fluconazole (Fungan 0.2% vial, I.E. Ulagay, Turkey) drops hourly for the first 48 hours along with 1% cyclopentolate (Siklоplejin, Abdi Ibrahim, Turkey) 3 times a day and non-preserved artificial tear drops every 2 hours. Disruption of the tear film by the infection can lead to increased risk of ocular surface dryness and promote bacterial adhesion. Thus, to mimic tear film function and protect the ocular surface from dryness, preservative-free artificial tear solutions were used as a part of medical treatment. Moreover, artificial tears dilute the load of microbial and inflammatory agents in the tear film.

Statistical Analysis

According to microbiological results, treatment was modified to target the specific microorganism. Clinical improvement with this treatment was followed up until complete resolution of keratitis foci, seen as unstained stromal opacity with no signs of inflammation.

The statistical analysis was performed using SPSS software for Windows version 15.0 (SPSS Inc, Chicago, Illinois, USA) and Microsoft Office Excel (Microsoft, Redmond, Washington, USA). Statistical analyses were performed using frequency tables, paired t-test for within-group comparisons of best corrected visual acuity (BCVA) at presentation and last follow-up visit, unpaired t test for comparisons of BCVA between the culture-positive and culture-negative groups, and chi-square test for qualitative data. A value of $p<0.05$ was accepted as statistically significant.

Results

Among 314 patients, 142 had positive cultures (45.22%). The mean ages of the culture-positive and -negative patients at the time of diagnosis were 51.39±21.31 (range, 14-90) years and 56.68±21.34 (range, 7-94) years, respectively ($p=0.028$). The male to female ratio in the culture-positive and culture-negative patients was 0.8 and 1.17, respectively ($p<0.001$, chi-square test).

The mean time from symptom onset to diagnosis in the culture-positive and -negative patients was 27±24 (range, 0-90) days and 13.2±16.8 (range, 1-90) days, respectively (p=0.014). The mean BCVAs of the culture-positive and -negative patients were 1.74±1.25 (range, 0-3.1) LogMAR and 1.91±1.23 (range, 0-3.1) LogMAR prior to treatment and increased to 1.21±1.30 (range, 0-3.1) LogMAR and 1.27±1.29 (range, 0-3.1) LogMAR at the end of the follow-up, respectively (p=0.0002; p<0.001, paired t test). There was no statistically significant difference between culture-positive and -negative patients' BCVAs at presentation (p=0.316, unpaired t test) or at last visit (p=0.716, unpaired t test) (Table 1).

In the culture-positive group, 92 patients (64.7%) were infected with bacteria and 50 patients (35.2%) with fungi. Among the cultured microorganisms, 30 different strains were identified (43.3% gram-negative bacteria, 16.6% gram-positive bacteria, and 40% fungi). The most common pathogen was *Pseudomonas aeruginosa* (18.3%), followed by *Streptococcus pneumoniae* (11.2%) and *Fusarium* spp. (11.2%). Culture results were positive for multiple species in 10 patients (7%) (Table 2). No statistically significant difference was observed in BCVA after treatment in polymicrobial infections (p=0.068, Wilcoxon nonparametric test). Evisceration surgery was performed to only one eye which had polymicrobial infection. According to culture results, fungal infections were associated with significantly worse BCVA. The mean BCVA of the fungal infection group was 2.15±1.14 (range, 0.1-3.1) LogMAR, versus 1.61±1.26 (range, 0-3.1) LogMAR in bacterial infection group (p=0.044, unpaired t test).

Keratitis foci were either centrally or paracentrally located in 105 eyes (73.9%) of the culture-positive patients and 149 eyes (86.6%) of the culture-negative patients (p=0.001, chi-square test). A single focus was present in 92 (64.7%) culture-positive and in 161 (93.6%) culture-negative patients (p=0.0001, chi-square test). Multiple foci were present in 50 eyes (35.2%) of culture-positive and 11 eyes (6.4%) of culture-negative patients (p=0.0001, chi-square test).

Table 1. The presenting features of the patients with microbial keratitis

	Patients with culture-positive MK (mean ± SD, range)	Patients with culture-negative MK (mean ± SD, range)	p value
Initial BCVA (LogMAR)	0.84±1.04 (0-3.1)	1.91±1.23 (0-3.1)	0.649
Last BCVA (LogMAR)	0.28±0.46 (0-3.1)	1.27± 1.29 (0-3.1)	0.170
Mean duration of symptoms (days)	27 ± 24 (0-90)	13.2 ± 16.8 (1-90)	0.014
Number of keratitis foci, n (%) Single focus Multiple foci	 92 (64.7) 50 (35.2)	 161 (93.6) 11 (6.4)	0.0001
Location of keratitis foci, n (%) Central/paracentral Peripheral	 105 (73.9) 37 (26.1)	 149 (86.6) 23 (13.3)	0.001
Hypopyon (n, %)	55 (38.7)	56 (32.5)	0.364
Risk factors Contact lens wear Trauma with organic material Corneal graft	 47 (33) 38 (26.7) 19 (13.3)	 23 (13.3) 24 (13.9) 15 (8)	 0.0001 0.007 0.225

MK: Microbial keratitis, SD: Standard deviation, BCVA: Best corrected visual acuity

Table 2. Culture results of patients with microbial keratitis

Group and species	n (%)
Gram-negative bacteria *Pseudomonas aeruginosa*	43.3%* 26 (18.3)
Gram-positive bacteria *Streptococcus pneumoniae* *Staphylococcus aureus*	16.6%* 16 (11.2) 6 (4.2)
Fungi *Fusarium* spp.	38.7%* 16 (11.2)

*Percentage of the microorganism among all species isolated from culture (n=30)

Repeated corneal scrapings were performed in 14 patients (8.1%) due to the lack of clinical regression, but cultures of these samples were negative.

Hypopyon was present in 55 eyes (38.7%) of culture-positive and in 56 eyes (32.5%) of culture-negative patients (p=0.364, chi-square test).

The prevalence of ocular/systemic comorbidity in culture-positive and -negative patients was 28.1% (n=40)/30.2% (n=43) and 33.1% (n=57)/37.2% (n=64), respectively (p=0.251 and p=0.133, chi-square test). The most common accompanying systemic diseases in culture-positive and -negative patients were diabetes (12/142, 8.4%) and hypertension (25/172, 14.5%), respectively. The most common accompanying ocular disease in both culture-positive and -negative patients was glaucoma (8.1% for both). Other associated ocular diseases were dry eye syndrome, bullous keratopathy, keratoconus, and exposure keratopathy.

Twenty-five (14.5%) of the 172 culture-negative patients had a history of steroid use due to corneal transplantation (n=18), bullous keratopathy (n=6), and marginal keratitis (n=1).

The most common predisposing factor for culture-proven microbial keratitis was CL usage. The proportion of CL wearers was 33% (n=47) among the culture-positive patients and 13.3% (n=23) among culture-negative patients. Culture positivity was found to be significantly higher in keratitis associated with CL use (p=0.0001, chi-square test). All patients used frequent replacement soft CLs except one, who used a rigid gas-permeable CL. History of overnight wear and showering/swimming was reported by 50% and 58.9% of the CL wearers, respectively.

History of ocular trauma with organic material was present in 26.7% (n=38) of culture-positive patients and 13.9% (n=24) of culture-negative patients. Presence of corneal grafts was a predisposing factor in 13.3% (n=19) and 8% (n=15) of culture-positive and -negative patients, respectively.

The rate of antibiotic use before admission to our clinic was 36.7% in the culture-positive group and 45.9% in the culture-negative group (p=0.097, chi-square test). Positive clinical response to empiric antimicrobial treatment was observed in 59.1% and 86.6% of culture-positive and -negative patients, respectively (p<0.001).

Despite proper treatment according to antibiogram results, 47 patients (33%) in the culture-positive group needed evisceration and penetrating keratoplasty surgery. In the culture-negative group, 18 (10.4%) of the patients needed evisceration and penetrating keratoplasty surgery (p<0.001, chi-square test). In order to limit infection and protect the eye, therapeutic keratoplasty was performed in 19.0% (n=27) of the culture-positive and 8.7% (n=15) of culture-negative patients (p=0.011, chi-square test). Unfortunately, 8 patients in the culture-positive group and 3 patients in the culture-negative group underwent evisceration surgery.

Discussion

Microbial keratitis is one of the most common causes of corneal blindness worldwide. Although microbial agent characterization according to corneal scraping assessment is essential for effective treatment, clinicians need to start the antimicrobial regimen before culture and antibiogram results are available. The local microbial distribution pattern is one of the key factors in making this decision accurately.[1] As geographical and climatic influences result in regional differences in the pattern of microbial isolates, local epidemiologic studies are important for this decision.[2]

Although microbial determination is essential, culture positivity rates reported in the literature range from 25.6 to 78%.[1,2,4,5,6,7,8,9,10,11,12,13] Even though our clinic is a regional tertiary center and most patients were referrals who already received broad spectrum antimicrobial therapy before presentation, the positive culture rate for microbial keratitis was 45.2%, consistent with the literature.

Microbial keratitis generally occurs in the presence of predisposing factors such as ocular trauma and CL wear. CL wear was reported to be the major risk factor for microbial keratitis in developed countries, with a prevalence of 34-50%.[7,14,15] In developing countries, trauma remains the main risk factor, reported in 48-83% of cases.[16,17,18] In the present study, CL wear (33%) and trauma history (26.7%) were the major risk factors.

As mentioned above, geographic and climatic influences result in regional variation in the pattern of microbial isolates, thus the microbiological profile of microbial keratitis differs between countries. Although gram-positive bacteria are more frequent in microbial keratitis according to the literature,[1] *Pseudomonas aeruginosa* has been reported as the most common pathogen in several studies.[14] In the present study, the most common microbial agent of culture-proven microbial keratitis was *P. aeruginosa.* In 2007, Yilmaz et al.[19] reported the most common agents as gram-positive microorganisms among culture-proven microbial keratitis in the western part of Turkey, with a relatively high rate of 68.8%. In their study, the most common predisposing factors were reported as trauma (26.6%) and recent intraocular surgery (17%). Only 3.2% of the patients were reported as CL wearers. The inconsistency between these two studies from the same region may be due to the substantial difference in predisposing factors and the increasing popularity of CLs in the last 13 years.

The proportion of fungal keratitis among microbial keratitis cases also varies by country due to topographic features and climatic effects. Fungal keratitis is much more prevalent in agricultural areas.[14] The percentage of fungal keratitis was reported to be 5.3-40% in the literature.[4,9,13,16] In our series, fungal keratitis accounted for 35.2% of the cases, and 75% of these patients had a history of ocular trauma with organic material. The high rate of fungal keratitis might be related to agriculture being common in Turkey.

Medical management was successful in 68.1% of the culture-positive patients and 89.6% of the culture-negative patients, which is consistent with the literature.[20] We also observed that empirical treatment was more effective in the culture-negative group. Despite a higher rate of globe loss due to the infection in the culture-positive group, visual prognosis was similar in

both groups. Similarly, Bhadange et al.[20] reviewed culture-positive and -negative patients and reported that visual outcomes were comparable. In the culture-positive group, gram-negative microorganisms (e.g., *P. aeruginosa)*, which have prominent destructive nature, were found to be the most common causative agents. The potential causative microorganisms in the culture-negative group were assumed to be gram-positive agents due to the ocular microbiota distribution. Thus, devastating complications were observed less frequently in the culture-negative group.

Study Limitations

The most important limitation of the present study was its retrospective nature. The most vital contribution was demonstrating the distribution of microbial agents in bacterial keratitis in a specific geographic region with a noteworthy amount of patient data.

Conclusion

The present study showed that CL wear was the major risk factor for microbial keratitis in the western part of Turkey, and *P. aeruginosa* was the most commonly isolated microbial agent. These results differ substantially from those of a previous study conducted in Turkey 13 years earlier and may demonstrate the current local microbial distribution pattern.

Ethics

Ethics Committee Approval: Ege University Medical Research Ethics Committee (approval number: 19-5.2T/68).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.P., Ö.B.S., A.Y., S.E., S.H.P., S.Ş.A., Concept: M.P., Design: Ö.B.S., A.Y., Data Collection or Processing: S.Y., Analysis or Interpretation: S.E., M.P., Literature Search: S.Y., M.P., Writing: Ö.B.S.

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Original Article

Prospective Study: Frequency of Ophthalmic Findings, Relationship with Inflammation Markers, and Effect on Prognosis in Patients Treated in the COVID-19 Intensive Care Unit

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Abstract

Objectives: To prospectively evaluate the frequency of ocular findings and inflammation markers levels in patients treated in the intensive care unit due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to determine the relationship between these parameters and mortality.

Materials and Methods: We prospectively evaluated 53 patients who were treated in the intensive care unit of a pandemic hospital between January 1 and June 30, 2021 and whose SARS-CoV-2 diagnosis was confirmed by reverse transcriptase polymerase chain reaction test from nasopharyngeal swab samples. Ocular findings were evaluated together with white blood cell, neutrophil, lymphocyte count, C-reactive protein, lactate dehydrogenase and ferritin levels, and mortality rate.

Results: There was no statistically significant correlation between lactate dehydrogenase, white blood cell, neutrophil, and lymphocyte count elevation and the frequency of inflammatory eye signs (p=0.308, p=0.694, p=0.535, p=0.374). In multivariate analyses, no statistically significant correlation was observed between ferritin level and the frequency of inflammatory eye findings (p=0.087). In addition, for each 1 mg/dL increase in C-reactive protein level, the detection of inflammatory eye findings decreased by 1.9% (95% confidence interval: 3.3%-0.4%; p=0.015). It was determined that 7 of 13 patients with inflammatory eye findings died and this was not statistically significant (p=0.810).

Conclusion: Inflammatory examination findings of the ocular surface were detected in 13 (24.5%) of 53 patients treated in the intensive care unit for SARS-CoV-2 infection. Ocular surface examination of patients treated in the intensive care unit due to the SARS-CoV-2 epidemic is important.

Keywords: SARS-CoV-2, chemosis, congestion, intensive care unit

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Introduction

In December 2019, an enveloped RNA virus of unknown origin was reported to be the cause of pneumonia-related deaths in Wuhan, China.[1] Because of its structural similarity to SARS-CoV (severe acute respiratory syndrome coronavirus), the novel virus was named SARS-CoV-2. Within a short time, the World Health Organization announced that coronavirus disease 2019 (COVID-19) was a pandemic.[2,3] Later, there were reports of ocular findings associated with SARS-CoV-2, especially conjunctivitis, and it was shown that the virus could be transmitted through tears.[4,5,6,7]

In this study, we prospectively evaluated the ocular surface examination findings and laboratory data of 53 patients who had a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test result and were treated in the COVID-19 intensive care unit. The results were compared with mortality data.

Materials and Methods

Patients who were hospitalized in the COVID-19 intensive care unit of a pandemic hospital in accordance with predetermined treatment criteria and had a positive RT-PCR test between January 1 and June 30, 2021 were included in the study (Table 1). We prospectively recorded the patients' age, sex, presence of systemic disease, mechanical ventilation support, white blood cell, neutrophil, and lymphocyte counts, and C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin levels. Other than the routine follow-up tests recommended in the Turkish Ministry of Health COVID-19 guideline (https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html), no additional tests were ordered for the study. Necessary measures were taken to prevent SARS-CoV-2 transmission, especially the use of N95 masks. Each patient underwent daily ocular surface examination using a handheld biomicroscope (Portable Slit Lamp, Reichert Inc, NY, USA). In addition, the optic nerve, macula, and vascular arcades of all patients were evaluated using a 90 D Lens (V 90C, Volk Optical Inc, OH, USA) lens due to the risk of developing Valsalva retinopathy and intraretinal hemorrhage or optic neuropathy associated with impaired perfusion. Ethics committee approval was obtained for the study. Written informed consent was obtained from conscious patients and from the first-degree relatives of unconscious patients. The study was conducted in accordance with the Declaration of Helsinki.

The diagnosis of SARS-CoV-2 infection was made by detection of viral RNA using the nucleic acid amplification method by RT-PCR. The SARS-CoV-2 RNA test kit developed in the Microbiology Reference Laboratories-Virology Laboratory of the Turkish Ministry of Health General Directorate of Public Health was used.[8] Diagnostic nasopharyngeal/oropharyngeal swabs and sputum specimens were tested using marked oligonucleotides specific to SARS-CoV-2 target gene regions. The single-step RT-PCR test was evaluated by sending it to an authorized microbiology laboratory.

Statistical Analysis

The data were tested for normal distribution using visual (histogram and probability charts) and analytical methods (Shapiro-Wilk test). Categorical variables were presented as number and percentage, and continuous variables were presented as mean ± standard deviation (SD) or median (25^{th}-75^{th} percentile). Pearson's chi-square test was used to compare categorical variables between independent groups. Fisher's Exact test was performed if the requirements for Pearson's chi-square test were not met (if the expected value in more than 20% eyes was less than 5 or the observed value was less than 2). In comparisons between two independent groups, Student's t-test was used for normally distributed variables and Mann-Whitney U test was used for non-normally distributed variables. In order to evaluate variables associated with inflammatory eye findings and survival, multiple logistic regression analysis was performed with variables that had results with $p<0.05$ and $p<0.200$ in pairwise comparisons. The multiple logistic regression model was established using the backward LR method. Results were evaluated within a 95% confidence interval with an alpha error of 0.05. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software.

Results

Of the 53 patients included in the study, 26 (49.1%) were men and 27 (50.9%) were women. The mean age was 69.9±16.0 (19-94) years. Twenty-six patients (49.1%) received noninvasive ventilation via face mask with reservoir bag, 19 patients (35.8%) received invasive ventilation via high-flow oxygen therapy (HFOT), and 8 patients (15.1%) received invasive ventilation support after endotracheal intubation. Thirty-seven patients (69.8%) had hypertension (HT), 7 (13.2%) had diabetes mellitus (DM), and 21 (39.6%) had chronic obstructive pulmonary

Table 1. Criteria for admission to the COVID-19 intensive care unit

Respiratory rate ≥30/min
PaO_2/FiO_2 <300
SpO_2 <90% or PaO_2 <70 mmHg despite receiving 5 L/min oxygen therapy
Hypotension (SBP <90 mmHg and decrease of >40 mmHg from normal SBP and mean arterial pressure <65 mmHg)
Tachycardia >100/min
Acute kidney injury
Acute liver function test abnormality
Confusion
Acute bleeding diathesis
Immunosuppression
Troponin elevation and arrhythmia
Lactate >2 mmol
Skin findings associated with delayed capillary refill

PaO_2: Partial pressure of oxygen, FiO_2: Fraction of inspired oxygen, SpO_2: Peripheral oxygen saturation, SBP: Systolic blood pressure

disease (COPD). Twenty-six patients (49.1%) survived and 27 (50.9%) died (Table 2). Congestion was detected in 13 patients (24.5%) cases, serous secretion in 6 patients (11.3%), and chemosis in 3 patients (5.7%) (Table 3; Figure 1). On fundus examination, none of the patients exhibited intraretinal hemorrhage, optic neuritis, or Valsalva retinopathy, which are the main findings reported to increase in frequency in COVID-19. The prevalence of inflammatory eye signs was significantly higher among women than men (p=0.031). There was no statistically significant difference in the frequency of inflammatory eye signs between patients who received invasive and noninvasive ventilation (p=0.691). The frequency of inflammatory eye signs did not differ significantly according to survival (p=0.810). The prevalence of inflammatory eye signs increased significantly with age (p=0.011).

No significant relationship was observed between inflammatory eye findings and LDH, white blood cell, neutrophil, or lymphocyte levels (p=0.308, p=0.694, p=0.535, and p=0.374, respectively). In univariate analyses, higher CRP level was associated with a lower prevalence of inflammatory eye signs (p=0.01). In addition, inflammatory eye signs were more frequent among patients with low ferritin levels (p=0.006) (Table 4). However, in multivariate analyses, there was no statistically significant association between ferritin level and the frequency of inflammatory eye signs (p=0.087). In contrast, each 1 mg/dL increase in CRP level was associated with 1.9% lower odds of detecting inflammatory eye signs (95% confidence interval [CI]: 3.3%-0.4%; p=0.015). Each additional year of age increased the risk of inflammatory eye signs by 1.083 times (95% CI: 1.008-1.163; p=0.030) (Table 5).

There was no statistically significant relationship between survival and patient sex or presence of HT, DM, or COPD (p=0.335, p=0.928, p=0.250, and p=0.695, respectively). Older age was associated with significantly higher risk of death (p=0.004). Survival was significantly better among patients for whom respiratory support with noninvasive ventilation via face mask with reservoir bag was sufficient for treatment (p<0.001). No significant difference in survival was observed in patients who received invasive ventilation support with HFOT (p=0.749). All eight patients who received invasive ventilation support after intubation died, which was statistically significant (p=0.004). Seven of the 13 cases with inflammatory eye signs died, which was not statistically significant (p=0.810).

The mortality rate was higher among patients with higher white blood cell and neutrophil counts (p=0.011 and p=0.024, respectively). There was no significant relationship between

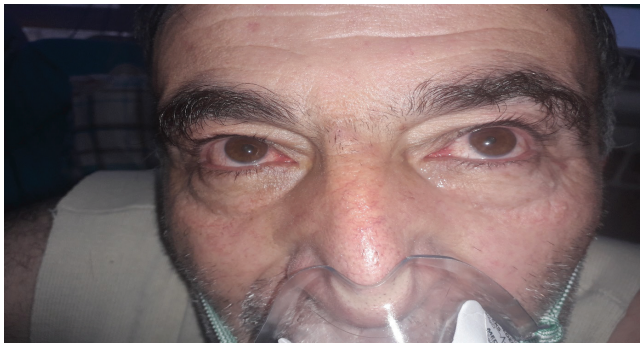

Figure 1. Congestion in a patient being treated in the COVID-19 intensive care unit

Table 2. Sociodemographic and clinical characteristics of the patients

Variable	n (%)
Sex	
Male	26 (49.1)
Female	27 (50.9)
Age (years)	
Mean ± standard deviation	69.9±16.0
Median (min-max)	72.0 (19-94)
Noninvasive ventilation with reservoir mask	
No	27 (50.9)
Yes	26 (49.1)
Invasive ventilation with high-flow oxygen therapy	
No	34 (64.2)
Yes	19 (35.8)
Invasive ventilation by endotracheal tube	
No	45 (84.9)
Yes	8 (15.1)
Hypertension	
No	16 (30.2)
Yes	37 (69.8)
Diabetes mellitus	
No	46 (86.8)
Yes	7 (13.2)
Chronic obstructive pulmonary disease	
No	32 (60.4)
Yes	21 (39.6)
Congestion	
No	40 (75.5)
Yes	13 (24.5)
Chemosis	
No	50 (94.3)
Yes	3 (5.7)
Secretion	
No	47 (88.7)
Yes	6 (11.3)
Survival	
Survived	26 (49.1)
Died	27 (50.9)

min: Minimum, max: Maximum

Table 3. Distribution of inflammatory eye findings

Eye findings	n
Congestion	13
Secretion	6
Chemosis	3
Subconjunctival hemorrhage	2

Table 4. Factors associated with the frequency of inflammatory eye findings			
	Inflammatory eye findings (n=13)	**No inflammatory eye findings (n=40)**	**P**
Sex, n (%) Male Female	 3 (11.5) 10 (37.0)	 23 (88.5) 17 (63.0)	**0.031**[1]
Ventilation type, n (%) Invasive ventilation Noninvasive ventilation	 6 (22.2) 7 (26.9)	 21 (77.8) 19 (73.1)	0.691[1]
Survival, n (%) Survived Died	 6 (23.1) 7 (25.9)	 20 (76.9) 20 (74.1)	0.810[1]
Age (years) Mean ± SD	 77.2±8.8	 67.5±17.2	**0.011**[2]
Lactate dehydrogenase, U/L Mean ± SD	 384.9±91.1	 432.0±156.0	0.308[2]
C-reactive protein, mg/dL Mean ± SD	 86.5±51.2	 154.2±86.8	**0.010**[2]
White blood cells, $x10^3/\mu L$ Median (25^{th}-75^{th} percentile)	 **8.2 (10.7-14.8)**	 **8.6 (11.2-13.7)**	0.694[3]
Neutrophils, $x10^3/\mu L$ Median (25^{th}-75^{th} percentile)	 3.8 (5.9-7.9)	 3.2 (4.9-8.1)	0.535[4]
Lymphocytes, $x10^3/\mu L$ Median (25^{th}-75^{th} percentile)	 0.5 (0.6-0.8)	 0.5 (0.7-0.9)	0.374[3]
Ferritin, ng/mL Median (25^{th}-75^{th} percentile)	 138.5 (237-603.5)	 411 (695-1544.8)	**0.006**[3]

[1]Pearson chi-square test, [2]Student's t test, [3]Mann-Whitney U test, SD: Standard deviation

survival and LDH, CRP, ferritin, or lymphocyte level (p=0.600, p=0.877, p=0.493, and p=0.239, respectively) (Table 6). Logistic regression analysis showed that the risk of death was 40.9 times (95% CI: 6.2-269.9) higher in the group that received invasive ventilation via HFOT or intubation (p<0.001). With each 1000/mm^3 increase in neutrophil count, the risk of death was increased by 1.6 times (95% CI: 1.1-2.3; p=0.015) (Table 7).

Discussion

In the SARS-CoV outbreak of 2003, researchers proved that the coronavirus was transmitted through tears.[9] After the SARS-CoV-2 outbreak that started in 2019, the novel coronavirus was found to have similar infectious properties.[10,11,12,13,14] Wu et al.[15] observed findings such as conjunctival hyperemia, conjunctivitis, chemosis, epiphora, and increased secretion in 12 (31.6%) of 38 patients with positive nasopharyngeal RT-PCR test results. In our study, ocular findings were detected in 13 (24.5%) of 53 patients. Wu et al.[15] reported that two-thirds of the patients in their study were treated with mechanical ventilation in the intensive care unit. In our study, 27 (50.9%) of the 53 patients received mechanical ventilation, and the prevalence of ocular surface findings we detected is similar to that observed by Wu et al.[15]

Zhou et al.[16] reported that they prospectively observed conjunctivitis as an ocular surface examination finding in 8 (6.6%) of 121 patients with positive RT-PCR. However, their study did not include patients treated in the COVID-19 intensive care unit. The rate of inflammatory findings of the ocular surface was higher in our study than that reported by Zhou et al.[16] Inflammatory eye signs may be more common in patients receiving treatment in the intensive care unit.

In another study, conjunctivitis findings were reported in 35 (11.6%) of 301 patients. Of these, 28 patients (9.3%) had conjunctival hyperemia, 15 (5%) had epiphora, and 12 (3.9%) had foreign body sensation. When evaluated together with inflammation markers such as white blood cell, neutrophil, and lymphocyte counts, CRP, and ferritin level, no significant relationship was found between ocular surface examination findings and inflammation markers.[17] In our study, we also observed no link between higher levels of inflammation markers and the frequency of inflammatory signs of the ocular surface.

Xia et al.[6] detected no correlation between illness severity and the frequency of conjunctivitis. However, the results reported by Wu et al.[15] and Guan et al.[18] indicated that the frequency of conjunctivitis increased in severe illness. According to their meta-analysis of a limited number of patients, Liu et al. found no link between the frequency of conjunctivitis and disease severity.[19] In our study, the incidence of inflammatory ocular surface findings was not statistically associated with LDH level, white blood cell count, neutrophil count, or lymphocyte count (p=0.308, p=0.694, p=0.535, and p=0.374, respectively). In addition, multivariate analyses indicated no statistically significant correlation between ferritin level and the frequency of

Table 5. Univariate and multiple logistic regression models of variables associated with the frequency of inflammatory eye findings

	Univariate analysis						Multivariate analysis					
	B	S.E.	Wald	p	OR	95% CI for OR	B	S.E.	Wald	p	OR	95% CI for OR
						Lower / Upper						Lower / Upper
Female (ref: Male)	1.506	0.732	4.236	0.040	4.51	1.074 / 18.929	1.586	0.917	2.992	0.084	4.884	0.81 / 29.46
Age	0.048	0.026	3.438	0.064	1.05	0.997 / 1.105	0.08	0.037	4.733	**0.030**	1.083	1.008 / 1.163
C-reactive protein, mg/dL	-0.013	0.005	5.709	**0.017**	0.987	0.976 / 0.998	-0.019	0.008	5.921	**0.015**	0.981	0.967 / 0.996
Ferritin, ng/mL	-0.002	0.001	4.689	**0.030**	0.998	0.997 / 0.999	-0.001	0.001	2.938	0.087	0.999	0.997 / 1
Constant	-1.506	0.732	4.236	0.040	0.222	0.053 / 0.931	-4.842	2.557	3.586	0.058	0.008	

CI: Confidence interval, OR: Odds ratio

inflammatory signs on ocular surface examination (p=0.087). In fact, with each 1 mg/dL increase in CRP level, the odds of detecting inflammatory signs on ocular surface examination decreased by 1.9% (95% CI: 3.3%-0.4%; p=0.015) (Table 5). We found no other study in the literature in which the risk of detecting signs of ocular surface inflammation decreased with higher CRP level. This suggests that the increase in ocular surface inflammation may have been related to dry eye occurring in the intensive care setting, not due to increased inflammation associated with COVID-19. Studies evaluating patients treated in COVID-19 intensive care units using Schirmer test and fluorescein staining and including larger case series are needed.

In another study of 400 cases, ocular findings were detected in 38 patients (9.5%). Conjunctival injection was reported to be the most common ocular finding. Age, sex, fever, mechanical ventilation, and elevated inflammation markers were not significantly associated with the frequency of ocular findings. Although the prevalence of inflammatory ocular surface findings was lower than in our study, the results were similar in terms of the lack of a relationship between eye signs and elevated inflammation markers or mechanical ventilation.[20] The higher frequency of inflammatory findings on ocular surface examination in our study may be because only patients treated in the COVID-19 intensive care unit were included.

Öncül et al.[21] detected inflammatory eye findings in 28 (7.7%) of the 359 patients in their study. Of these, 294 patients were treated in the ward and 65 were treated in the COVID-19 intensive care unit. Among the 65 intensive care patients, inflammatory eye findings were detected in 4 patients (6.2%). Whereas we included only patients with positive RT-PCR results in our study, Öncül et al.[21] considered it sufficient for patients to be diagnosed based on lung tomography and clinical evaluation as well as by RT-PCR test for SARS-CoV-2. In our study, the prevalence of inflammatory findings on ocular surface examination was 24.5%, which is a higher rate than reported by Öncül et al.[21] Unlike Öncül et al.[21], we defined RT-PCR positivity as a required criterion for the diagnosis of SARS-CoV-2 infection. This may explain the difference in results between the two studies.

In another study conducted prospectively in the intensive care unit before the SARS-CoV-2 pandemic, Öncül and Yektaş[22] observed inflammatory signs such as conjunctivitis and increased secretion that required an ophthalmology consultation in 29 (31.2%) of 93 patients. Johnson and Rolls[23] reported that ocular surface problems were seen in 23-60% of intensive care patients. The higher frequency of ocular surface inflammation findings in the COVID-19 intensive care unit may also be related to the conditions in the intensive care unit. Some of the inflammatory signs observed on ocular surface examination in our study may have been a result of problems such as bacterial conjunctivitis. This prospective study was conducted exclusively with patients in the COVID-19 intensive care unit. Therefore, it differs from many other studies, which may explain why our results are different from previous studies in the literature. Further research with larger case series is needed on this subject.

Table 6. Factors associated with survival			
	Survived (n=26)	**Died (n=27)**	**P**
Sex, n (%) Male Female	 11 (42.3) 15 (55.6)	 15 (57.7) 12 (44.4)	0.335[1]
Noninvasive ventilation via mask with reservoir bag, n (%) No Yes	 5 (18.5) 21 (80.8)	 22 (81.5) 5 (19.2)	<0.001[1]
Invasive ventilation via high-flow oxygen therapy, n (%) No Yes	 25 (73.5) 15 (78.9)	 9 (26.5) 4 (21.1)	0.749[2]
Invasive ventilation via endotracheal tube, n (%) No Yes	 26 (57.8) 0 (0)	 19 (42.2) 8 (100)	0.004[2]
Hypertension, n (%) No Yes	 8 (50) 18 (48.6)	 8 (50) 19 (51.4)	0.928[1]
Diabetes mellitus, n (%) No Yes	 21 (45.7) 5 (71.4)	 25 (54.3) 2 (28.6)	0.250[2]
COPD, n (%) No Yes	 15 (46.9) 11 (52.4)	 17 (53.1) 10 (47.6)	0.695[1]
Inflammatory eye findings, n (%) No Yes	 20 (76.9) 6 (23.1)	 20 (74.1) 7 (25.9)	0.810[1]
Age Mean ± SD	 63.5±17.5	 76±11.8	**0.004**[3]
LDH, U/L Mean ± SD	 409.8±142.3	 430.7±146.5	0.600[3]
Neutrophils, x10^3/µL Mean ± SD	 4.9±2.5	 6.7±3.1	**0.024**[3]
Lymphocytes, x10^3/µL Mean ± SD	 0.7±0.3	 0.7±0.3	0.239[3]
CRP, mg/dL Mean ± SD	 139.4±96.8	 135.8±72.2	0.877[3]
White blood cells, x10^3/µL Median (25th-75th percentile)	 7.5 (9.8-12.4)	 9.3 (12.2-17.7)	0.011[4]
Ferritin, ng/mL Median (25th-75th percentile)	 232.8 (497.5-1137.8)	 287 (573-1577)	0.493[4]

[1]Pearson chi-square test, [2]Fisher's exact test, [3]Student's t test, [4]Mann-Whitney U test, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, LDH: Lactate dehydrogenase, CRP: C-reactive protein

Table 7. Multiple logistic regression model of variables associated with survival							
	B	**S.E.**	**Wald**	**p**	**OR**	**95% CI for OR**	
						Lower	**Upper**
Mask with reservoir bag (ref: Yes)	3.713	0.962	14.906	**<0.001**	40.9	6.2	269.9
Neutrophils, x103/µL	0.453	0.186	5.91	**0.015**	1.6	1.1	2.3
Constant	-0.796	0.978	0.662	0.416	0.451		

CI: Confidence interval, OR: Odds ratio

Study Limitations

During the COVID-19 pandemic, many hospitals have dedicated intensive care units to patients with COVID-19. A similar study with a control group of individuals being treated in a different intensive care unit for reasons other than COVID-19 may yield more accurate results. In our study, patients treated in the COVID-19 intensive care unit were not evaluated for pulmonary involvement by computed tomography, and a positive RT-PCR test was the only criterion considered for COVID-19 diagnosis. A link may be detected between increased inflammation in the lungs on computed tomography and inflammatory eye signs. A study including patients who have negative RT-PCR results but a history of COVID-19 contact and consistent computed tomography findings could yield different results. In addition, conjunctival RT-PCR samples were not obtained from patients with ocular surface findings because the RT-PCR kit available in Turkey can only detect virus in oropharyngeal/nasopharyngeal swab samples. In the future, new studies should be conducted using conjunctival RT-PCR kits. Another limitation of the study is that in the retinopathy screening, patients were only evaluated for findings expected to increase in COVID-19, such as intraretinal hemorrhage, Valsalva retinopathy, and optic neuritis. For example, the frequency of hypertensive retinopathy could be found to be correlated with mortality and ocular findings in COVID-19 intensive care. New studies on this subject are needed. The patients were not evaluated with Schirmer and fluorescein staining tests. New studies can be planned taking into consideration the possible role of dry eye in ocular findings. The new drugs that have recently been introduced due to the SARS-CoV-2 pandemic may also cause inflammatory findings on the ocular surface, thus warranting further investigation.

Conclusion

The results of this prospective study showed that 24.5% of patients treated in a COVID-19 intensive care unit exhibited inflammatory signs such as congestion, secretion, and chemosis on ocular surface examination. Examination of the ocular surface is important in patients receiving intensive care for COVID-19, and ophthalmologists have an important duty in this field.

Ethics

Ethics Committee Approval: Afyonkarahisar Health University of Sciences, 4/12/20-2020/14.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.E.A., Concept: İ.E.A., D.A., Design: İ.E.A., D.A., Data Collection or Processing: İ.E.A., D.A., Analysis or Interpretation: İ.E.A., D.A., Literature Search: İ.E.A., D.A., Writing İ.E.A., D.A.

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Original Article

Short-Term Clinical Results of Preferred Retinal Locus Training

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Abstract

Objectives: This study evaluated acoustic biofeedback training using microperimetry in patients with foveal scars and an eligible retinal locus for better fixation.

Materials and Methods: A total of 29 eligible patients were enrolled in the study. The acoustic biofeedback training module in the MAIA (Macular Integrity Assessment, CenterVue®, Italy) microperimeter was used for training. To determine the treatment efficacy, the following variables were compared before and after testing: best corrected visual acuity (BCVA); MAIA microperimeter full threshold 4-2 test parameters of average threshold value, fixation parameters P1 and P2, and bivariate contour ellipse area (BCEA) for 63% and 95% of fixation points; contrast sensitivity (CSV 1000E Contrast Sensitivity Test); reading speed using the Minnesota Low-Vision Reading Test (MNREAD reading chart); and quality of life (NEI-VFQ-25). In addition, fixation stability parameters were recorded during each session.

Results: The study group consisted of 29 patients with a mean age of 68.72±8.34 years. Median BCVA was initially 0.8 (0.2-1.6) logMAR and was 0.8 (0.1-1.6) logMAR after 8 weeks of preferred retinal locus training (p=0.003). The fixation stability parameter P1 improved from a mean of 21.28±3.08% to 32.69±3.69% (p=0.001) while mean P2 improved from 52.79±4.53% to 68.31±3.89% (p=0.001). Mean BCEA 63% decreased from 16.11±2.27°^{2} to 13.34±2.26°^{2} (p=0.127) and mean BCEA 95% decreased from 45.87±6.72°^{2} to 40.01±6.78°^{2} (p=0.247) after training. Binocular reading speed was 38.28±6.25 words per minute (wpm) before training and 45.34±7.35 wpm after training (p<0.001). Statistically significant improvement was observed in contrast sensitivity and quality of life questionnaire scores after training.

Conclusion: Beginning with the fifth session, biofeedback training for a new trained retinal locus improved average sensitivity, fixation stability, reading speed, contrast sensitivity, and quality of life in patients with macular scarring.

Keywords: Low vision rehabilitation, microperimetry, preferred retinal locus training

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Introduction

Macular diseases affect a significant number of people worldwide. Most are over 60 years old and suffer from age-related macular degeneration (AMD). With increasing life expectancy, quality of life has become an important concern, and investigations aiming to improve or maintain visual performance are increasing.[1]

The human brain contains maps of the retina on the surface of the occipital lobes, called *retinotopic maps*. In patients with macular degeneration, the loss of foveal input leads to deprivation in the cortical regions responsive to foveal stimuli. Consequently, cortical neurons located in the retinotopic position corresponding to the scotoma receive some degree of activity from the unimpaired neurons in the area surrounding the lesion. Over time, these weak connections are gradually reinforced. The system eventually evolves into a new stable state in which every neuron again receives the same amount of activity from the source layer. The brain's ability to adapt its function and structure to recover visual function is called neuroplastic capacity.[2,3] This reorganization of visual cortex has been shown by functional magnetic resonance imaging studies in early childhood foveal vision loss.[4] However, Baseler et al.[5] demonstrated that large-scale remapping does occur in the adult brain. This raises concerns about peripheral reorganization in the retina, especially the macula.

As is known, some patients with foveal scar start to use extrafoveal areas of the retina to compensate within 6 months. This is called eccentric fixation, and the eccentric region of the peripheral macula selected for fixation is called the preferred retinal locus (PRL).[6] As demonstrated in a study by Shima et al.[6], the PRL is not always the area with the highest retinal sensitivity or ability to provide the best visual function and fixation stability. This finding led to the new concept of a trained retinal locus (TRL) selected from among the PRL used for fixation. To determine the TRL, the locus that is closest to the fovea and has the highest retinal sensitivity is preferred to offer the best potential visual acuity (VA).[6,7,8] However, eyes with foveal scars were not able to achieve stable fixation at these selected points, which decreased their quality of vision. To solve this problem, several rehabilitation strategies have been developed to increase fixation stability.[7,8] The biofeedback training technique (BFT) proposed by Nilsson et al.[8] and Fujii et al.[9], which uses a software module incorporated in a microperimeter, appears to be the most promising of these rehabilitation methods.

The BFT system uses audible and visible feedback signals to help patients identify and train the optimal retinal area and improve fixation and related tasks. Patients are asked to perform specific ocular movements to align a selected retinal locus with a visual target. This locus is either the PRL determined by the device software or a new locus determined from among patients' fixation points using special criteria. The latter is called a TRL. Biofeedback audio signals (beeping sounds) aid patients during the oculomotor task by increasing the auditory frequency as the target approaches the desired alignment.[10] This biological feedback causes the intercellular neurotransmitters to increase and establish cerebral links faster than the normal process.[7,11] Additionally, acoustic stimulation increases the patient's conscious attention and prolongs the time that the fixed image of the object is on the retina. It configures the relationship between neurons in the retina and brain. The theory of the remapping phenomenon is based on this explanation.[10,12,13,14]

In the literature, a few studies and case reports have described promising outcomes with BFT. Even oculomotor exercises performed in BFT have been shown to improve fixation stability using either PRL or TRL. However, there is no consensus on the optimal duration, number of training sessions, or effect on patient quality of life.[2,10,15,16,17,18]

Our study aimed to assess the short-term efficacy of BFT on fixation stability. To better understand this effect, we analyzed intersessional changes in fixation parameters. Furthermore, we evaluated the effect of BFT on contrast sensitivity and quality of life in addition to reading speed.

Materials and Methods

This study is based on a non-comparative case series of patients with bilateral macular scarring treated in the retina unit of Selçuk University Faculty of Medicine, Department of Ophthalmology. The study protocol was designed according to the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee for Non-invasive Clinical Research of the Selçuk University Faculty of Medicine. Among the patients with macular disease, those whose disease was inactive for at least 1 year were included. Patients with any other ocular disease that might affect retinal sensitivity or hearing loss were excluded because it could hinder compliance with the training while receiving audio signals from the device. After explaining the purpose and possible consequences of the study, informed written consent was obtained from all subjects.

All patients underwent a complete ophthalmological evaluation, including best-corrected VA measurement with Snellen chart, biomicroscopic examination of the anterior segment and dilated fundus examination. VA values obtained by Snellen chart (in decimal) were converted to logMAR for statistical analysis using the following established formula: $\text{logMAR} = \log^{10} (1/\text{VA})$.

Eligible patients underwent a full-threshold 4-2 test using the MAIA (CenterVue®, Padova, Italy) microperimeter to evaluate localization and fixation stability in a 10-degree area consisting of 37 measurement points. Fixation stability was measured in two ways:

1. Calculating the percentage of fixation points located within a distance of one degree and two degrees, respectively (P1 and P2).[11] If more than 75% of the fixation points were located within P1, the fixation was classified as stable. If less than 75% of the fixation points were located within P1 but more than 75% of the fixation points were located within P2, the fixation was classified as relatively unstable. If less than 75% were located within P2, the fixation was classified as unstable.

2. Calculating the bivariate contour ellipse area (BCEA), which is believed to be the most representative fixation stability parameter. It represents the area of an ellipse that encompasses a given proportion of fixation points based on standard deviations of the horizontal and vertical eye positions during the fixation procedure. BCEA 95% describes the area that includes 95% of retinal loci and BCEA 63% represents the area containing 63% of retinal loci used for fixation.

With improvements in fixation stability, P1 and P2 values are expected to increase while BCEA 95% and 63% decrease.[19,20]

Patients showing eccentric and unstable fixation according to the software were recruited for the study. If both eyes fulfilled the criteria, the eye with lower VA was preferred. The decision to proceed with TRL was based on the locations of the initial and final PRL, which were determined automatically by the microperimeter software, and the location of the scotoma.

The initial PRL was determined after the first 10 seconds of the examination, the point when patients make their strongest effort to hold a steady fixation (labeled with a pink dot in the data). This point determines the center of the MAIA (CenterVue®, Padova, Italy) stimuli grid. The final PRL, labeled with a blue dot in the printout, is found at the end of the MAIA examination and serves as the reference point for calculating fixation stability. Patients with stable fixation will present both PRLs in the same anatomical location, while longer distances between PRLs show more unstable fixation and lower VA. To estimate the TRL, the initial and final PRLs, the BCEA including all fixation points, the size and extent of the scotoma, and location of the fovea are evaluated. Among the fixation points, the one closest to the estimated fovea but the farthest possible distance from the scar in the superior quadrant is preferred. Additionally, to facilitate reading tasks, a fixation locus with horizontal neighbor points and high sensitivity in the superior quadrant is chosen as the TRL.[21]

For eligible patients who had a suitable TRL and were willing to participate regularly in the training program, the average threshold of retinal sensitivity and the values for P1, P2, and BCEA in the full threshold 4-2 test were recorded (Figure 1a, b).

To better determine the effects of the rehabilitation program, contrast sensitivity was tested using the CSV 1000E Contrast Sensitivity Test (VectorVision® Dayton, OH) at 8 feet and reading speed was assessed using the Turkish version of the MNREAD reading chart, with reading glasses under adequate lighting conditions. Reading acuity, critical print size, and maximum reading speed were calculated according to the instructions for the reading cards.[22] Reading speed and contrast sensitivity tests before and after treatment were performed in the same room, in the same ambient lighting, and at the same time of day.

Additionally, the impact of treatment on quality of life was evaluated with the Turkish version of the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25).[23] This questionnaire is composed of 12 groups of questions regarding general health (1 item), general vision (1 item), ocular pain (2 items), near vision (3 items), distance vision (3 items), social functioning (2 items), mental health (4 items), role limitations (2 items), dependency (3 items), driving (2 items), color vision

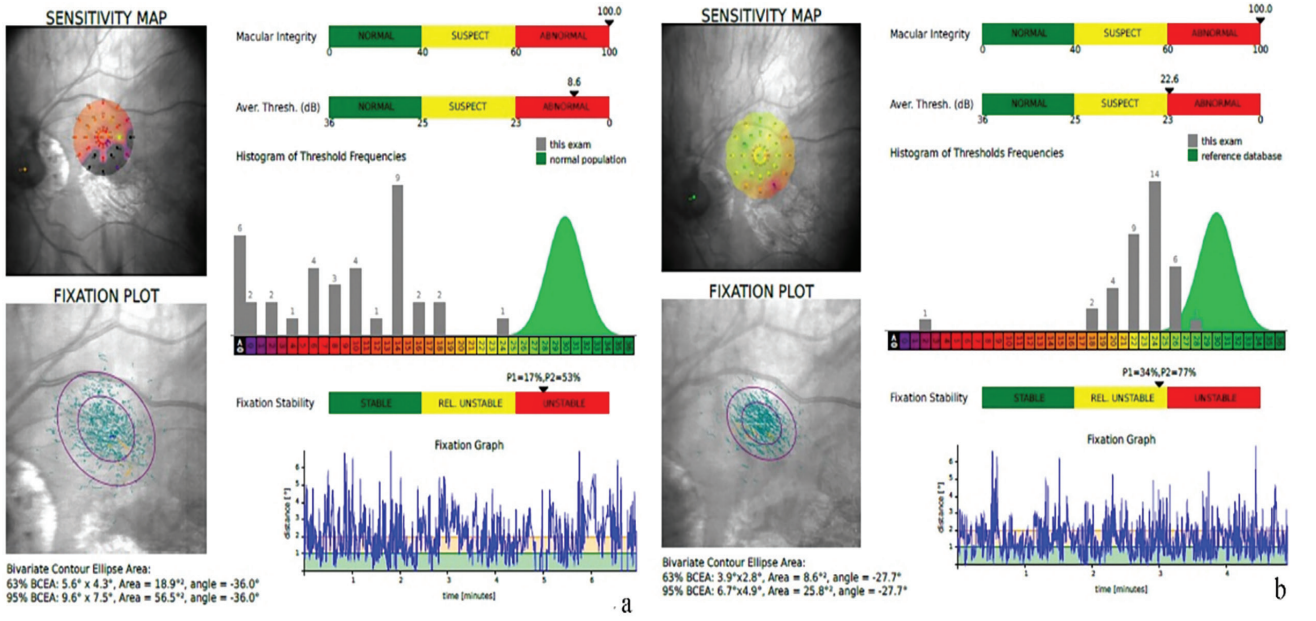

Figure 1. The change in the fixation area used by the patient after training sessions. According to the MAIA (CenterVue®, Padova, Italy) normative studies, the decibel scale is color-coded where green represents normal values, yellow suspect, red abnormal, and black absolute scotomas. (a) The sensitivity map before training demonstrates difficulty in fixation. (b) In the new sensitivity map (after treatment), assessment of the same area demonstrates convergence of the blue fixation points, indicating more stable fixation behavior

(1 item), and peripheral vision (1 item). The points received from these sections and the overall average score was calculated and analyzed. The questions were read to the patients and their scores were recorded by a nurse (S.O.). The total point calculation and data analysis were performed by the first researcher (A.B.O.).

Outcome parameters included best corrected VA; fixation stability parameters P1, P2, and BCEA 63% and 95%; contrast sensitivity; reading speed; and quality of life. P1, P2, BCEA 63%, and BCEA 95% values were recorded at the end of each session for analysis of changes in fixation parameters during training. To analyze changes after training, the parameters were reassessed 1 week after the training program and compared with pretreatment values.

Exercise Techniques

Patients were invited to TRL treatment preferably on the same day and time each week during the 8-week testing period. There is no consensus in the literature about the optimum duration of the training program. Based on experiences in similar studies and to increase the likelihood of adherence to the program, we scheduled 8 sessions once per week for 10 minutes.[18] Patients were allowed to rest for 15 minutes before training. During the 10-minute exercise, patients tried to fix their eyes on the previously determined TRL point. As the patient got closer to the targeted fixation locus, they heard a sound increasing in volume as well as positive comments from the clinician, who was reading from the screen. The patients were also asked to remember the gaze movement performed during the training sessions and try to reproduce the same movement in their daily lives when attempting to focus on a target.

Statistical Analysis

All obtained data were uploaded to the software after proper encoding. The Statistical Package for the Social Sciences version 18.0 (SPSS, Inc., Chicago, IL, USA) Windows software package was used for the statistical analysis. The data were analyzed for normal distribution. Best corrected VA was analyzed with Mann-Whitney U-test; other parameters were analyzed using the parametric paired t-test. Data obtained during follow-up were evaluated using a repeated measures test. If any significant change was detected, the data were analyzed in paired groups using the paired t-test. For all analyses, $p<0.05$ was considered statistically significant.

Results

A total of 29 patients with a mean age of 68.72±8.34 years at enrollment met the selection criteria and agreed to participate in the study. Eighteen (62.1%) of the patients were men and 11 (37.9%) were women. There was no significant difference between male and female patients in terms of age ($p>0.05$). In 27 of the patients, AMD was the etiology of the central scotoma, and trauma was the cause in the remaining 2 patients. Of the AMD patients, 13 had geographic atrophy and 14 had disciform scars. Patients who completed all training sessions are analyzed.

The median value for best-corrected VA was initially 0.8 (0.2-1.6) logMAR and increased to 0.8 (0.1-1.6) logMAR after 8 weeks of PRL treatment. This change was statistically significant ($p=0.003$). Median best-corrected VA in the fellow eye was 0.5 (0.0-1.0) logMAR. The mean average threshold value was 12.96±1.16 dB before training and showed a slight increase to 13.24±1.33 dB, but it was not significant in the statistical analysis ($p=0.900$).

Before training, fixation stability parameters P1 and P2 were 21.28±3.08% and 52.79±4.53%, respectively. After training, the values increased to 32.69±3.69% for P1 ($p=0.001$) and 68.31±3.89% for P2 ($p=0.001$). BCEA 63% was 16.11±2.27 deg^2 before training and decreased to 13.34±2.26 deg^2 after training. Similarly, BCEA 95% decreased from 45.87±6.72 deg^2 before training to 40.01±6.78 deg^2 after training. However, these changes were not statistically significant ($p=0.127$ and $p=0.247$, respectively) (Figure 2). Further subgroup analysis of initial and final VA and fixation parameters P1, P2, BCEA 63%, and BCEA 95%, according to scar etiology (geographical atrophy, disciform scar, or trauma) revealed no statistically significant difference before and after treatment ($p=0.77$, $p=0.67$, $p=0.33$, $p=0.98$, $p=0.46$, $p=0.96$, $p=0.98$, $p=0.87$, $p=0.91$, and $p=0.85$, respectively).

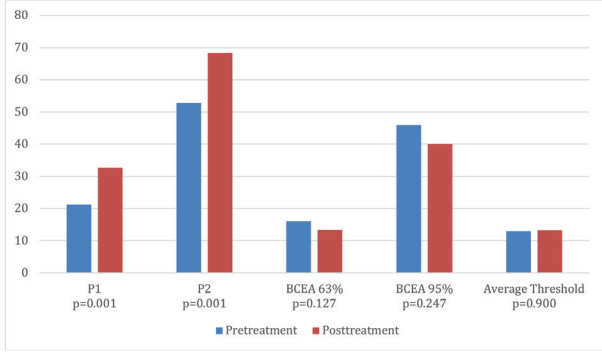

Figure 2. P1 and P2 values were significantly increased in full-threshold 4-2 tests conducted after preferred retinal locus training compared to before training. Despite favorable changes in BCEA 63%, BCEA 95%, and average threshold, they were not statistically significant

BCEA: Bivariate contour ellipse area

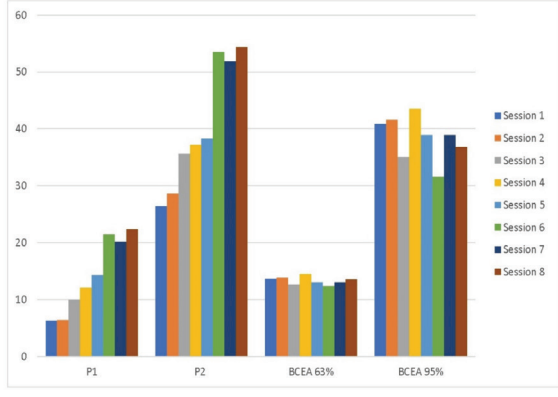

Figure 3. P1 and P2 values recorded over 8 sessions show a significant increase after session 5, while no significant changes were observed in BCEA 63% and BCEA 95% values

BCEA: Bivariate contour ellipse area

The intersession variation of fixation parameters P1 and P2 values showed a consistent rise in each session. Statistical analysis of intersessional change showed statistically significant increases after the fifth session compared to the pre-training value ($p<0.001$). BCEA 63% and BCEA 95% demonstrated fluctuations in each session with no statistically significant difference ($p>0.05$) (Figure 3).

Contrast sensitivity was evaluated at four different spatial frequencies: 3, 6, 12, and 18 cycles/degree. The pre- and post-training values at each frequency demonstrated a statistically significant increase ($p<0.001$, $p<0.001$, $p=0.01$, and $p=0.001$, respectively). For reading speed, the mean values for reading acuity, critical print size, and maximum reading speed (words per minute) changed significantly at the final visit compared to before training ($p<0.001$ for all parameters) (Table 1).

The quality of life questionnaire results showed statistically significant improvement in overall composite scores and all sections except general health and ocular pain. The scores are shown in Table 2.

Discussion

According to data from the World Health Organization (WHO), there are 285 million people with low vision worldwide.[24] Over the years, several rehabilitation methods have been developed for this group of patients. Equipment such as magnifiers, text shifting, or prisms is focused on improving reading skills.[6,25,26] To improve perceptual skills, rehabilitation methods such as training based on eccentric imaging, oculomotor control, and perceptual learning were introduced.[26,27] They enable effective sensitivity improvement through technical training and can be easily implemented during clinical practice because they do not require expensive equipment.[28] Research on integrating perceptual and oculomotor training to induce a new fovea was further developed with the addition of auditory

Table 1. Contrast sensitivity and reading speed before and after treatment

	Pre-treatment (mean ± SD)	Post-treatment (mean ± SD)	p value
Contrast sensitivity			
3 cycles/degree (A)	1.07±0.056	1.19±0.061	p<0.001
6 cycles/degree (B)	1.23±0.051	1.36±0.061	p<0.001
12 cycles/degree (C)	0.91±0.05	1±0.056	p=0.01
18 cycles/degree (D)	0.37±0.04	0.48±0.05	p=0.001
MNREAD reading chart			
Reading acuity	1.05±0.05	0.96±0.06	p<0.001
The critical print size	1.12±0.04	1.07±0.05	p<0.001
Maximum reading speed (wpm)	38.28±6.25	45.34±7.35	p<0.001

SD: Standard deviation, wpm: Words per minute

Table 2. Quality of life questionnaire scores before and after treatment

	Pre-treatment (mean ± SD)	Post-treatment (mean ± SD)	p value
General health	46.552±25.63	48.276±24.93	p:0.480
General vision	30.172±29.41	43.965±28.07	p<0.001
Ocular pain	72.413±19.30	75±20.04	p=0.083
Near activities	30.169±21.29	42.239±21.47	p<0.001
Distance activities	24.699±20.35	31.319±20.97	p<0.001
Social functioning	34.052±24.52	44.396±23.76	p<0.001
Mental health	27.802±18.26	34.482±19.23	p<0.001
Role difficulties	18.534±19.93	23.706±20.41	p=0.001
Dependency	30.170±28.90	34.480±27.52	p=0.001
Driving (n=3)*	58.33±8.33	66.663±8.33	p=0.102
Color vision	34.483±27.88	43.965±26.43	p=0.001
Peripheral vision	28.448±27.32	35.345±24.56	p=0.005
Overall composite score	32.945±17.81	40.795±16.97	p<0.001

SD: Standard deviation, *Only 3 of the patients were driving

feedback.[8] In some studies, additional oculomotor exercises at home following training were shown to increase reading speed and decrease smallest readable font size.[29,30]

This rehabilitation method uses eccentric imaging to look directly at the relatively healthy retina locus to improve visual function. The retinal locus, called a TRL, is in an area advantageous to reading.[31] Nilsson et al.[8] reported initial outcomes for TRL training and found improved reading rates in scotomatous eyes following 5.4 hours of training with scanning laser ophthalmoscope. Watson et al.[32] trained the better-seeing eye and reported that the development of a TRL was easy and fast. In contrast, Baker et al.[4] observed that eyes with more severe foveal scarring were more prone to reorganization. In our study, we also preferred the weaker eye for training, and the patients' improvement after training supported this hypothesis.

Initial trials were performed with basic systems like the AccommotracVision Trainer, Visual Training System (VTS), or the Improved Biofeedback Integrated System (IBIS).[10,33] Significant advancements in rehabilitation methods have been made by developing a software package uploaded to the microperimeter. There are a few studies in the literature reporting the therapeutic outcomes of visual rehabilitation programs containing an auditory feedback mechanism in several disorders, including nystagmus, AMD, glaucoma, anisometropia, amblyopia, retinitis pigmentosa, oculocutaneous albinism, myopic maculopathy, vitelliform dystrophy, posttraumatic macula scarring, and cone dystrophy.[14] These studies differ in several aspects. Some evaluated training the PRL to increase fixation stability, while some identified a TRL and trained to force fixation on that point. In addition, the intensity, frequency, and duration of training were different. Establishing the optimum training program required to transport the central fixation locus to the nearby healthy retinal locus permanently is already a challenge.[34,35]

Two devices currently use this available software training, the MP-1 (Nidek Instruments, Italy) and MAIA (CenterVue®, Padova, Italy). Although the purpose is similar, there are small differences that hinder a head-to-head comparison. The MP-1 does not present objective fixation stability parameters like P1, P2, or BCEA. Typically, reading speed and VA are assumed to be primary outcomes in studies. Vingolo et al.[10] reported improved results in 15 AMD patients who underwent bilateral BFT with the MP-1 device in 10 weekly 10-minute sessions. They claimed that 5 follow-up training sessions every 3 months would maintain visual performance. In 2009, Tarita-Nistor et al.[2] applied BFT using the MP-1 device for 5 sessions lasting 1 hour to relocate the PRL and reported improved fixation stability and better reading performance. In another study, Raman et al.[36] applied BFT to both eyes with myopic maculopathy using the MP-1 device and demonstrated that VA did not change after exercise; only retinal sensitivity and fixation stability improved. The most extensive study with the longest follow-up using MP-1 was conducted by Pacella et al.[33], who reported results for 171 eyes of 99 patients. They applied 16 TRL training sessions and showed improved VA in 76% of the patients. Of those, 19.2% lost the benefits of training after 12 months.

Our study conducted with the MAIA microperimeter resulted in significant improvement in best-corrected VA, average retinal sensitivity, and fixation stability parameters P1 and P2 after 8 sessions of BFT. The initial values were 16.11±2.27 deg^2 for BCEA 63% and 45.87±6.72 deg^2 for BCEA 95%. Normal values for BCEA 95% and 63% in the MAIA microperimeter are 2.40±2.04 deg^2 and 0.80±0.68 deg^2, respectively. BCEA 63% and BCEA 95% have been reported to serve as an accurate, independent parameter with which to evaluate fixation stability.[19] Although not statistically significant, a decline in BCEA 63% and BCEA 95% values were observed at the end of this study. The lack of significance could be explained by the low number of subjects included and fewer training sessions than recent studies, which typically scheduled 10 sessions.[11,12,36-38]

We preferred to train the optimum locus with higher sensitivity, which we believe would enhance plasticity more efficiently. Recent studies support our hypothesis. Morales et al.[7] compared training for the PRL and TRL and suggested that a selected TRL would improve fixation stability more after training. They postulated that spontaneously developed plasticity reflects a compensatory motor pattern rather than true recovery and that selected locus training may enhance plasticity more efficiently. Raman et al.[36] also showed improved fixation stability and retinal sensitivity after TRL training that was maintained at 1-year follow-up. In a study reporting the outcomes of PRL therapy in AMD patients, Vingolo et al.[10] found no statistically significant change in best corrected VA but reported significant improvements in font size and reading rates. Vingolo et al.[37] reported that the P100 latency of visual-evoked potentials (VEP) changed significantly between pre- and post-treatment examinations. However, the effect of this finding on daily life is unknown.

In another study evaluating BFT with the MAIA microperimeter, 9 patients underwent macular hole surgery and 3 BFT sessions lasting 10 minutes each. Within 3 months, the patients showed a statistically significant increase in best corrected VA. Their fixation stability, BCEA 63%, and reading speed also improved but nonsignificantly, like the BCEA 63% values in our study. The investigators attributed the results to the small number of subjects in their study.[39] In our opinion, the low number of sessions may also have influenced the study outcome. Pacella et al.[33] conducted a study with a larger sample size and demonstrated a statistically significant improvement in best corrected VA, reading rate, and fixation behaviors. The etiology of macular scar might be another confounding factor contributing to the different results obtained in various studies. We enrolled patients with disciform scar, geographic atrophy, and traumatic macular scar in this study. However, subgroup analysis demonstrated no statistically significant difference in the short-term evaluation. As macular degeneration is progressive, unlike macular hole or traumatic scar, different long-term

outcomes might be expected with different durations of training.

As the training process is static, assessing function during dynamic situations is essential because they occur in everyday life with moving objects or when performing tasks involving eye movement such as reading. According to our data, the new TRL appeared to improve reading speed, contrast sensitivity, and quality of life. Our study findings should be considered preliminary, as this is the first study on this training method to address contrast sensitivity and quality of life. The data demonstrated statistically significant improvements in contrast sensitivity at all spatial frequencies, a finding consistent with substantial improvement in other parameters (VA, reading speed, and fixation stability). Our results indicated that TRL treatment made positive contributions to visual quality. This promising effect was also observed in two patients with a VA higher than 0.4 logMAR who were enrolled due to unstable fixation parameters and complaints about reading. As their number was limited, a subgroup analysis according to VA level could not be performed. However, these patients showed a 1-line increase in VA and slight improvement in fixation parameters after training, which in turn improved their reading speed and quality of life according to questionnaire scores.

The Turkish version of the NEI-VFQ was used to compare quality of life before and after treatment. Except for general health and ocular pain, the overall scores changed significantly with treatment. Few studies have utilized this questionnaire after PRL treatment. A re-evaluation of the NEI-VFQ-25 questionnaire after exercises revealed statistically significant changes consistent with our study findings.[40] Scuderi et al.[14] implemented BFT for TRL in a patient with Stargardt disease who experienced reduced VA over the previous 3 years. Based on the NEI-VFQ-25 quality of life questionnaire, they observed an increase in VA, reading speed, and overall satisfaction. A meta-analysis conducted by Hamade et al.[41] showed that eccentric viewing training caused the most improvement in reading speed among the low-vision rehabilitation strategies. However, there was no significant effect on the scores for depression.

The total number of BFT sessions required for permanent, stable fixation is unclear. In most studies, the BFT program was designed as 10 sessions of 10 minutes each, although session numbers ranging from 3 to 16 have been reported in the literature.[7,33,39,42] For our study, we preferred a program consisting of 8 sessions of 10 minutes each. This schedule was in response to the difficulty in adhering to hospital visiting rules for AMD patients due to age and poor vision. Based on our follow-up sessions, the changes in the P1, P2, and BCEA showed that fixation stability increased in each session. Changes in the P1 and P2 percentages became significant after the fifth session ($p=0.001$). This finding should be considered when planning a training schedule.

In their study, Estudillo et al.[43] showed improvement in VA, fixation parameters P1 and BCEA 95%, and reading speed after 1 week. They claimed that the short duration of treatment enabled them to attribute the changes directly to the treatment. In our study, we also repeated the assessments 1 week after the last session to determine the real effects of BFT.

Despite promising results, the effect of training duration is unknown. Ratra et al.[38] reported continued effects up to 6 months with a slight reduction in fixation stability. Raman et al.[36] observed that these changes continued during the 1-year follow-up period and suggested that treatment provided permanent results through the mechanism of remapping between retinal neurons and the brain. Morales et al.[7] also showed a slight reduction in fixation parameters after 3 months and scheduled two sets of 12 weeks with 3-month intervals between sets. They suggested that training for more extended periods was needed to achieve permanent results.

We do not plan any long-term follow-up visits because the underlying disease is progressively fibrotic. Any deterioration might be associated with fibrosis instead of the dwindling effects of training. However, repeated training might be useful.

Laterality is another source of bias related to this visual rehabilitation method among studies. Bilateral training was done in some studies. We preferred the worse eye to avoid adverse effects like diplopia. Estudillo et al.[43] preferred the same approach.

Another confounding factor in our study was the selection criteria for the training eye. However, as our subjects were old and had central scotoma, the dominant eye was difficult to determine. We preferred the worse eye with more severe foveal scarring for treatment because it was shown to present better reorganization capacity.[44] The TRL was one of the existing fixation points and the effect of eye dominance was already reflected in the reference microperimetry, which we used to schedule the training. Additionally, treatment outcomes were also assessed monocularly except for the measurement of reading speed and the NEI-VFQ-25 questionnaire. The outcome of both outcome parameters should be evaluated regarding this confounding factor.

With prolonged life expectancy in the modern world, the number of AMD patients is increasing significantly. This increase, in turn, has added to the number of AMD patients with macular scars. Because the disease gives rise to central scotoma, serious problems may arise in patients' daily activities, particularly their reading activity, as reflected in the quality of life questionnaire. A locus with higher sensitivity in the peripheral retina outside of the fovea may provide higher visual quality as a means of adaptation. The goal of BFT is to enable the patient to use that selected area for visual tasks.

Conclusion

Our results demonstrated that patients with macular scar might improve during an 8-session BFT program on the selected TRL and that this adaptation positively affects reading speed, contrast sensitivity, and quality of life in patients with impaired fixation stability. Patients should have good comprehension skills for effective training. To our knowledge, age-related hearing loss is frequent among AMD patients.[45] This fact should be kept in

mind when selecting eligible patients. Our short-term follow-up revealed significant improvement in fixation parameters after the fifth BFT session. The optimum duration and session interval for maintenance of training effects is already a matter of debate that should be addressed in further studies. Etiology of macular scar seems to be insignificant in the short term, but its effects in the long term should be evaluated with regard to the duration of improvement in fixation stability. The need for repeat sessions and frequency of control visits are major issues that should be addressed in the future. However, the effect of TRL training on reading and daily life is promising for low vision rehabilitation.

Ethics

Ethics Committee Approval: Approval was obtained from Selcuk University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee. (14.02.2017 date, 2017/06 number).

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B.O., B.T.Ö., Concept: A.B.O., B.T.Ö., B.B., Ş.Gö., Ş.Ge., S.O., Design: A.B.O., B.T.Ö., B.B., Ş.Gö., Ş.Ge., S.O., Data Collection or Processing: A.B.O., B.T.Ö., B.B., Ş.Gö., Ş.Ge., S.O., Analysis or Interpretation: A.B.O., B.T.Ö., Literature Search: A.B.O., B.T.Ö., Writing: A.B.O., B.T.Ö.

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Original Article

Fixation Stability and Preferred Retinal Locus in Advanced Age-Related Macular Degeneration

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Abstract

Objectives: To evaluate fixation stability and characteristics of the preferred retinal locus (PRL) in patients with advanced age-related macular degeneration (AMD).

Materials and Methods: Sixty-three eyes of 63 patients with AMD who presented to the low vision unit were included in this prospective study. Sociodemographic characteristics, eye examination findings, and reading performance results with the Minnesota Low Vision Reading test were evaluated. Microperimetry was used to evaluate fixation stability and PRL characteristics.

Results: There was unstable fixation in 68% of the eyes, relative stable fixation in 27%, and stable fixation in 5%. The mean PRL-foveal distance was 5.15°±3.31° (range 0.75°-14.2°). PRL-foveal distance was greater in cases with unstable fixation than cases with stable fixation (p=0.023). Distance of the PRL from the lesion margin was not associated with absolute scotoma size or fixation stability (p=0.315, p=0.095, respectively). PRLs were most frequently located in the nasal quadrant (31%), followed by the superior quadrant (26%) of the retina. There was no significant relationship between PRL location and fixation stability (p=0.088). Fixation stability was significantly associated with reading speed (p=0.003).

Conclusion: In advanced AMD, PRL-foveal distance is an important factor in fixation stability. Knowing the factors that affect fixation stability may be important in determining low vision rehabilitation strategies for these patients because of the strong association between fixation stability and reading speed.

Keywords: Low vision rehabilitation, fixation stability, microperimetry, preferred retinal locus, age-related macular degeneration

Introduction

In age-related macular degeneration (AMD), loss of retinal sensitivity at the macula causes central scotoma, thereby reducing visual acuity and fixation stability and leading to loss of central fixation. This causes difficulty in the performance of daily activities such as reading.[1,2] Oculomotor adaptation results in the formation of well-defined "preferred retinal loci" (PRLs) in the healthier regions of the retina that focus on visual targets.[3,4]

Microperimetry devices are currently used to evaluate the properties and stability of PRLs.[5] According to the literature, 77% to 100% of patients with central scotoma develop a PRL,[1,6,7,8] which is most commonly located in the nasal and superior retinal quadrants in AMD,[7,9] and fixation stability was shown to be associated with PRL to fovea and lesion margin distances, lesion size, and distance visual acuity.[1,6,9,10] Studies have also demonstrated a strong correlation between fixation stability and reading speed.[11,12,13,14,15,16,17]

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As reading speed is highly affected by fixation stability, interventions that increase fixation stability are prioritized in modern low vision rehabilitation. Microperimetric PRL training with acoustic and visual stimuli (trained retinal locus; TRL) can increase fixation stability and improve reading speed.[18,19,20] Sahli et al.[19] reported an increase in reading speed and quality of life with TRL training performed with microperimetric biofeedback signals in patients with central scotoma, most of whom had AMD. Therefore, evaluating fixation stability and PRL characteristics is essential in central scotoma.

This study aimed to identify factors associated with fixation stability in advanced AMD and enable our results to be applied in visual rehabilitation to increase reading speed and quality of life. There are few studies in the literature that have analyzed PRL characteristics microperimetrically in such detail, including fixation stability and reading speed, and these studies must also be conducted in languages with different reading directions. Knowing the factors affecting PRL characteristics and stability to increase fixation stability during PRL training with microperimetric acoustic and visual biofeedback signals will guide treatment planning, implementation, and follow-up.

Materials and Methods

This prospective, cross-sectional study was approved by the local clinical research ethics committee (decision no: 26.03.2018/06-363-18). All study procedures were carried out in accordance with the Declaration of Helsinki and informed consent forms were obtained from all participants.

The 63 better-seeing eyes of 63 consecutive AMD patients presenting to the vision research and low vision rehabilitation unit between August 2018 and September 2019 were included in the study. Patients who met the following criteria were included in the study: had best corrected visual acuity (BCVA) of 0.5-1.3 logMAR (Snellen 20/400-20/60) in the better-seeing eye, had atrophic AMD or stable exudative AMD not treated with intravitreal injection in the last 6 months, were over 55 years of age, were a native speaker of Turkish, and for the reading performance test, had completed at least primary school education, had the mental capacity to understand the MNREAD test rules, perform the test, and had no neurological or mental illness that would interfere with reading. Patients who declined to participate, were illiterate, had previously received low vision rehabilitation or TRL training, or were using low vision aids were excluded from the study. Patients with vision-impairing ocular pathologies other than AMD, such as diabetic retinopathy, glaucoma, optic atrophy, and hereditary retinal diseases, and those with systemic diseases that may affect vision, such as diabetes mellitus, were also excluded.

After completing the patients' sociodemographic forms, all patients underwent a detailed eye examination including BCVA assessment, anterior and posterior segment examination, low vision evaluation, MNREAD test, and contrast sensitivity (CS) test. Macular lesion size and vision-related quality of life scores were determined. The patients were asked how long they had not been able to read because of their eye problem and this time was recorded as the "reading interruption" in the data form. This information was obtained from patients and their relatives. The patients' BCVA was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart as logMAR, and reading acuity was tested with MNREAD-TR and recorded in M units. CSV-1000 was used for the CS test. The classical CSV-1000 test is performed at varying spatial frequencies (3, 6, 12, and 18 cycles per degree [cpd]) at a distance of 2.5 meters.[21] However, since our study group was low vision, they had difficulty at the standard test distance and the test distance and cpd values were reduced by half. The size of the macular lesion was calculated by the fundus autofluorescence Image Finder program and recorded as mm^2. Visual quality of life was assessed using the NEI-VFQ-25-TR, which was validated in Turkish by Toprak et al.[22] The questionnaire was administered by the same technician (B.S.) and scores were calculated by the same ophthalmologist (D.A.).

Reading performance was assessed using MNREAD-TR charts, which were validated in Turkish by Idil et al.[23] The charts test near visual acuity as logMAR and M (1M=0.4 logMAR) and include 19 sentences, of which the largest is 8M (1.3 logMAR) and the smallest is 0.12 M (-0.5 logMAR). Four parameters are evaluated: reading acuity (RA), critical print size (CPS), maximum reading speed (MRS), and the reading accessibility index (ACC). RA is the smallest print size that the person can read without significant error, MRS is the fastest reading speed when not limited by print size, and CPS is the smallest print size that can be read at this speed. Assuming the normal MRS is 200, the average reading speed for the top 10 sentences of the MNREAD chart (the print sizes most commonly encountered in daily life) is divided by 200 to obtain ACC (normal=1.0).[24]

MAIA microperimetry (Centervue, Padova, Italy) was used to evaluate fixation stability and PRL characteristics. Fixation stability was determined according to Fuji's clinical classification.[25] This classification is based on the percentage of fixation points within a 1° (P1) and 2° (P2) radius of the foveal center. The presence of 75% of fixation points within the 1-degree area (P1>75%) is regarded as stable fixation. If more than 75% of fixation points do not fall within this 1-degree area but are within the 2-degree area (P1<75% and P2>75%), it is called relatively stable fixation. Fixation is considered unstable when both P1 and P2 are below 75%. Bivariate contour ellipse area is the size (in mm^2) of the elliptical area encompassing 63% (BCEA63) and 95% (BCEA95) of fixational eye movements. Retinal sensitivity is between 0 and 36 decibels. Macular integrity index (MII) is evaluates an individual's responses according to the age-matched mean value for the population. An MII value lower than 40% is considered normal, 40-60% is suspicious, and higher than 60% is regarded as abnormal. P1, P2, BCEA63, BCEA95, and retinal sensitivity are parameters that can be obtained directly from the microperimeter (Figure 1).

Information derived from the microperimetry test results was also used to investigate fixation characteristics. The grid-shaped screen image obtained from microperimetry was printed on A4 paper and the PRL location, PRL distance from the fovea,

PRL distance from the lesion edge, and absolute scotoma size were calculated. A ruler was used for measurements and values calculated in mm were converted to degrees and recorded (1 square in the grid of the microperimeter screen corresponds to 1 degree). If the location of the fovea could not be determined because of advanced AMD, an estimated location of the fovea was marked at 15.5° temporal and 1.3° inferior to the optic disc center.[26] To describe PRL location, the retina was divided into 4 equal quadrants centered on the fovea and PRL location was classified as superior, inferior, temporal, nasal, or central (within 4° of the foveal center) (Figure 2).[9] All measurements were performed by a single ophthalmologist (D.A.) to avoid interobserver variability.

Statistic Analysis

The IBM SPSS Statistics version 20.0 package (IBM Corp, Armonk, NY) was used for statistical analyses. For numerical measurements, the assumption of normal distribution was tested using the Shapiro-Wilk test and comparisons of means between two groups were performed using t-test or Mann-Whitney U test as necessary. Comparisons between multiple groups were performed using one-way analysis of variance or the Kruskal-Wallis test. Bonferroni, Scheffe, and Tamhane tests were used as appropriate for pairwise comparisons between groups. In all tests, $p<0.05$ was accepted as significant.

Results

The study included 41 men and 22 women with a mean age of 77.49±8.56 (58-93) years. The left eyes of 36 patients (57%) and the right eyes of 27 patients (43%) were included. The mean symptom duration was 4.73±4.09 years, daily reading habit was 2.1±2.23 hours, reading interruption was 2.58±3.08 years, vision-related quality of life score was 47.5±11.4, and the near activities subscale score was 29.0±12.4.

The patients' mean distance and near visual acuities were 0.66±0.2 logMAR and 2.63±2.46 M, respectively. AMD was atrophic in 48% of the patients and exudative in 52%; lesion size ranged from 1.110 to 24.568 mm^2 (mean 7.162±4.671 mm^2). CS test results were 10.62±9.49 dB and 4.46±3.93 dB for 1.5 cpd and 3 cpd (low spatial frequencies) and 12.3±11.2 dB and 21.0±15.1 dB for 6 cpd and 9 cpd (medium spatial frequencies), respectively. According to the MNREAD chart, mean RA was 0.86±0.34 logMAR (range, 0.12-1.80 logMAR), CPS was 1±0.35 logMAR (range, 0.32-1.90 logMAR), MRS was 70.2±37.23 words/min (wpm) (range, 19-160 wpm), and ACC was 0.27±0.21 (range, 0-0.69).

Retinal sensitivity, P1, P2, BCEA63, and BCEA95 values were obtained directly from microperimetry. Fixation stability was unstable in 43 eyes (68%), relatively stable in 17 eyes (27%), and stable in 3 eyes (5%) (Table 1). Retinal location of the PRL was nasal in 31%, superior in 19%, inferior in 16%, central in 16%, and temporal in 11% of eyes. In left eyes, the most common location was the nasal quadrant (36%), while in right eyes, the most common location was the superior quadrant (31%). The mean PRL-fovea distance was 5.15°±3.31° (range,

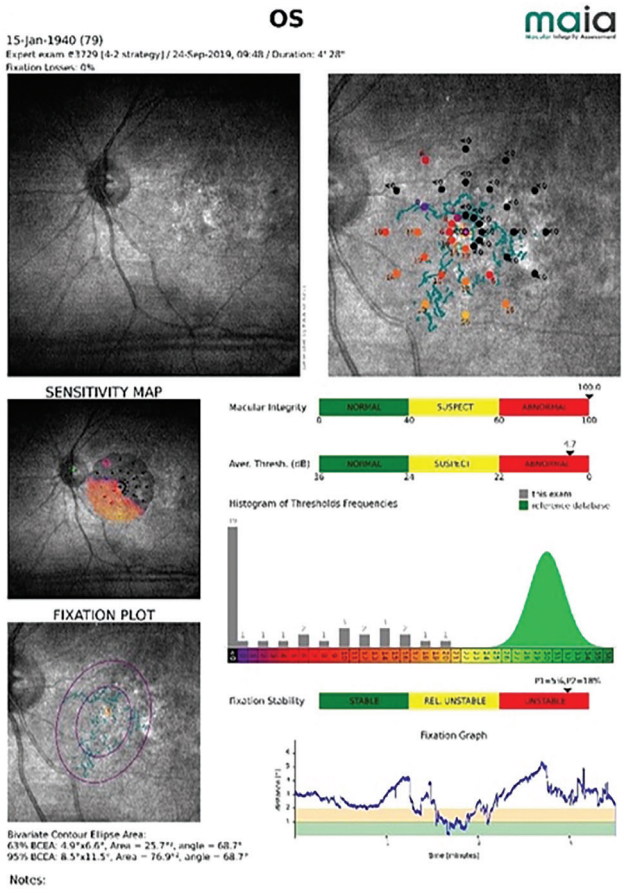

Figure 1. Example of microperimetry output for an eye with AMD
AMD: Age-related macular degeneration

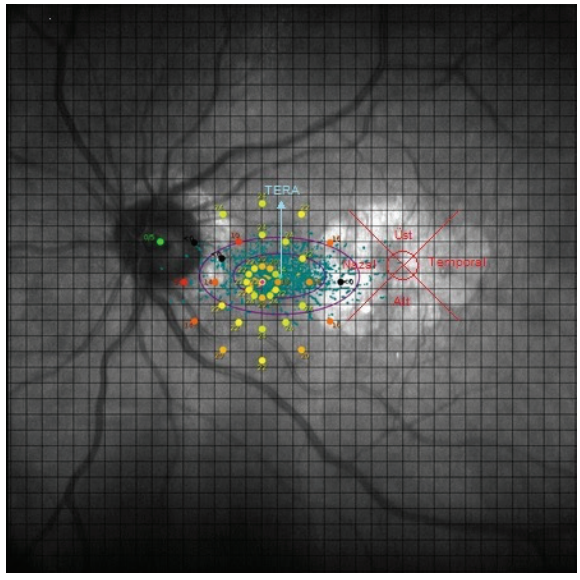

Figure 2. Division of the retina into quadrants centered on the fovea

0.75°-14.2°). The PRL was to the left of the absolute scotoma in 29% of eyes and to the right in 22% of eyes. The mean absolute scotoma size was 16°±15° (range, 0°-62°). Forty-two eyes (67%) had absolute scotoma at the fovea. The results obtained from microperimetry indirectly using special measurements are shown in Table 2.

There was no statistically significant relationship between fixation stability and distance or near visual acuity (p=0.072 and p=0.312, respectively). When the stable and relatively stable fixation groups were combined, distance visual acuity was significantly lower in eyes with unstable fixation compared to those with stable or relatively stable fixation (p=0.041). Reading speed was 148.7±12.7 wpm in the stable fixation group, 80.9±41.1 wpm in the relatively stable group, and 60.5±28.5 wpm in the unstable fixation group. There was a statistically significant relationship between reading speed and fixation stability (p=0.003). In the unstable fixation group, CS values at low (3 cpd) and medium (6 cpd and 9 cpd) spatial frequencies were lower compared to the relatively stable fixation group (p=0.019, p=0.038, and p=0.011, respectively).

There was no significant relationship between fixation stability and the retinal location of the PRL and whether this location was in the right or left eye (p=0.088 and p=0.199, respectively). Fixation stability also showed no statistical association with absolute scotoma size (p=0.095), PRL location relative to the absolute scotoma (p=0.05), or distance of the PRL to the lesion margin (p=0.315). However, distance of the PRL to the fovea was significantly associated with fixation stability (p=0.023) (Table 3).

The PRL was significantly farther from the fovea in eyes with unstable fixation than in eyes with stable fixation (p=0.023). The relationship between PRL-fovea distance and fixation stability is shown in Figure 3.

Table 1. Microperimetry results

		Mean ± SD
MII		99.8±1.6
Mean retinal sensitivity (dB)		10.8±6.5
P1		25.5±20.4
P2		56.2±23.4
BCEA 63		17.3±10.8
BCEA 95		51.6±32.4
		n (%)
Fixation stability	Stable	3 (5)
	Relatively stable	17 (27)
	Unstable	43 (68)

MII: Macular Integrity Index, P1: Percentage of fixation points in a 1° radius circle, P2: Percentage of fixation points in a 2° radius circle, BCEA: Bivariate contour ellipse area, SD: Standard deviation

Table 2. Results derived from microperimetry

		Mean ± SD
PRL-fovea distance (°)		5.15±3.31
PRL-lesion margin distance (°)		1.84±2.66
Absolute scotoma size (°)		16.0±15.0
		n (%)
PRL location	Nasal quadrant	19 (31)
	Superior quadrant	16 (26)
	Inferior quadrant	10 (16)
	Central	10 (16)
	Temporal quadrant	7 (11)
PRL location relative to absolute scotoma	Left of the scotoma	18 (29)
	In the scotoma	14 (22)
	No absolute scotoma	11 (17)
	Below the scotoma	9 (14)
	Right of the scotoma	7 (11)
	Above the scotoma	4 (6)
Foveal absolute scotoma	Yes	42 (67)
	No	21 (33)

PRL: Preferred retinal locus, SD: Standard deviation

Discussion

PRLs that develop through adaptive mechanisms for fixation in advanced AMD are generally extrafoveal and unstable, which are critical factors in reducing reading ability. It has been reported that fixation stability is strongly associated with reading speed,[11-17] and is affected by distance visual acuity, lesion size, and PRL distance to the fovea and lesion margin.[1,6,9,10] In our study, we observed that PRLs were extrafoveal in 85% and unstable in 68% of eyes with advanced AMD, fixation stability was affected by PRL-fovea distance, and there was a strong association between fixation stability and reading speed.

Studies have shown that the PRL, which replaces the nonfunctioning fovea in eyes with central scotoma, is less stable as its distance from the fovea increases.[6,9,10,27] The mean PRL-fovea distance in AMD was reported to be 6.69°±7.4° by Erbezci and Oztürk[9] and 6.25°±2.38° by Sahli et al.,[19] while Fujita et al.[28] reported distances between 5° and 11°. In our study, the mean PRL-fovea distance was 5.15°±3.31° (range, 0.75°-14.2°). This value was determined to be 5.64°±3.41° in the unstable fixation group and 2.04°±0.56° in the stable fixation group, showing that the PRL-fovea distance was greater in eyes with unstable fixation compared to those with stable fixation. We attribute the effect of PRL-fovea distance on fixation stability to the fact that retinal resolution and sensitivity are highest at the fovea. Chung et al.[29] reported that retinal resolution decreased further from the fovea.

Various studies have demonstrated that reading speed decreases with poorer fixation stability.[11-17] In our study, reading speed was 148.7±12.7 wpm in the stable fixation group, 80.9±41.1 wpm in the relatively stable group, and 60.5±28.5 wpm in the unstable group. There was a strong statistical association between reading speed and fixation stability

Table 3. Relationship between ocular parameters and fixation stability				
Characteristic	**Fixation Stability**			**p**
	Stable	**Relatively stable**	**Unstable**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Distance visual acuity (logMAR)	0.50±0.0	0.62±0.23	0.68±0.20	0.072
Near visual acuity (M)	1.2±0.35	3.04±2.98	2.57±2.3	0.312
Lesion size (mm^2)	4963.0±6268.9	6764.9±6518.4	7472.4±3694.4	0.131
Maximum reading speed (wpm)	148.7±12.7	80.9±41.1	60.5±28.5	**0.003**
Low-frequency CS (1.5 cpd) (dB)	10.0±5.0	15.35±13.73	11.26±10.26	0.264
Low-frequency CS (3 cpd) (dB)	10.67±4.62	30.47±19.7	17.91±11.57	**0.019**
Mid-frequency CS (6 cpd) (dB)	5.33±2.31	16.71±13.34	8.58±6.6	**0.038**
Mid-frequency CS (9 cpd) (dB)	3.33±3.18	7.06±5.8	3.51±2.39	**0.011**
Absolute scotoma size (°)	6.33±10.97	11.35±11.45	18.53±15.89	0.095
PRL-lesion margin distance (°)	0±0	1.52±1.24	2.08±3.03	0.315
PRL-fovea distance (°)	2.04±0.56	4.49±3.00	5.64±3.41	**0.023**
	n (%)	**n (%)**	**n (%)**	
Retinal location of PRL				0.088
Inferior quadrant	1 (33)	2 (12)	7 (17)	
Nasal quadrant	0 (0)	6 (35)	13 (31)	
Central	2 (67)	3 (18)	5 (12)	
Superior quadrant	0 (0)	2 (12)	14 (33)	
Temporal quadrant	0 (0)	4 (24)	3 (7)	
PRL location relative to absolute scotoma				0.050
Right	0 (0)	3 (18)	4 (9)	
Left	0 (0)	7 (41)	11 (%26)	
Inside	0 (0)	0 (0)	14 (33)	
Below	1 (33)	1 (6)	7 (16)	
Above	0 (0)	2 (12)	2 (5)	
No absolute scotoma	2 (67)	4 (24)	5 (12)	
PRL: Preferred retinal locus, wpm: words per minute, CS: Contrast sensitivity, cpd: cycles per degree, dB: decibels, SD: Standard deviation				

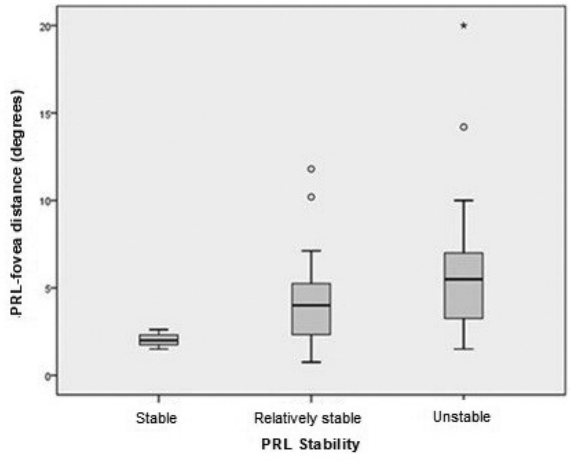

Figure 3. Relationship between fixation stability and PRL-fovea distance (°outlier, *extreme outlier)

PRL: Preferred retinal loci

(p=0.003). Reading function requires good detail detection, which itself requires foveal and stable fixation. Giacomelli et al.[17] stated that improved fixation translated to improved visual capacity. We believe that the decrease in reading speed associated with poorer fixation stability is related to this.

In the literature, single/multiple PRL development in AMD has been reported at different rates (77%-100%),[1,6,7,8] and most are located extrafoveally. Greenstein et al.[6] reported that all patients in their study developed a PRL, of which 73.3% were extrafoveal and 26.6% were foveal in location. In our study, we observed that 98.4% of patients developed a single PRL that was extrafoveal in 84% and foveal in 16% of the eyes. Fixation was unstable in 68%, relatively stable in 27%, and stable in 5% of the cases. We attribute the low fixation stability in our study to the patients having low vision, advanced AMD, symptom duration longer than 6 months, and mostly extrafoveal PRLs. Karaçorlu et al.[30] also observed no stable and central fixation in patients with symptom duration longer than 6 months.

Retinal localization of PRLs is still not fully understood, and in 25% of cases the PRL is not in a favorable location.[31] While there are some studies suggesting that location may be relevant in terms of reading,[7,32] others showed no relationship between PRL location and reading speed.[2,33,34] Evidence indicates that PRLs are usually located to the left of the scotoma.[1,2,7,9,35] However, PRLs can develop in any retinal quadrant.[9,34,35] In AMD, the most common PRL location is the nasal quadrant, followed by the superior quadrant.[7,9,19] Similarly, in our study, we determined that the PRL was located in the nasal retinal quadrant in 31%, superior quadrant in 26%, inferior quadrant in 16%, and temporal quadrant in 11% of eyes, while 16% of PRLs were located centrally. We detected no statistically significant relationship between PRL location and fixation stability. Similarly, Farzaneh et al.[27] found no significant relationship between PRL location on the retina and fixation stability in native Persian-speaking AMD patients.

Erbezci and Oztürk[9] reported that fixation stability was associated with distance BCVA and that fixation in the affected eye became unstable with greater PRL-fovea distance, PRL to lesion margin distance, and lesion size. When we grouped the eyes in our study as stable, relatively stable, and unstable, distance BCVA was not associated with fixation stability. However, when we combined the stable and relatively stable group, a statistically significant relationship emerged. The absence of a statistical relationship initially is likely due to the small number of eyes in the stable fixation group. Similarly, in our study there was no statistically significant relationship between fixation stability and scotoma size or PRL-lesion margin distance, but we observed that scotomas were larger and PRLs further from the lesion margin in eyes with unstable fixation.

Spatial and temporal CS tests in patients with maculopathy have demonstrated moderate to strong correlation between reading speed and CS.[36] In our study, eyes with unstable fixation showed lower CS at low and medium spatial frequencies compared to eyes with relatively stable fixation. This may be related to the higher PRL-fovea distance in this group and the lower retinal sensitivity and resolution in this area of the retina.

Study Limitations

CS tests modified for people with low vision could not be used for our patients because they were not available in our clinic. In addition, as all participants were Turkish-speakers, studies with broader participation in different languages are needed to investigate the effect of PRL location on the retina on fixation stability.

Conclusion

In this study, we observed that fixation stability was affected by PRL distance from the fovea and was strongly associated with reading speed. Given the close relationship between fixation stability and reading speed, awareness of the factors affecting fixation stability in advanced AMD is crucial to restore reading ability in low vision rehabilitation. The results of this study may be both strategically and prognostically useful in the planning and implementation of microperimetric treatment (TRL) to improve fixation stability in low vision rehabilitation centers.

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Ethics

Ethics Committee Approval: This prospective, cross-sectional study was approved by the local clinical research ethics committee (decision no: 26.03.2018/06-363-18).

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Original Article

Evaluation of Optic Disc Perfusion with Optical Coherence Tomography Angiography in Acute Non-arteritic Anterior Ischemic Optic Neuropathy

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Abstract

Objectives: This study aimed to evaluate superficial peripapillary vascularization qualitatively and quantitatively in patients with acute non-arteritic anterior ischemic optic neuropathy (NAION) using optical coherence tomography angiography (OCT-A).

Materials and Methods: Eleven patients with acute NAION and 14 controls were evaluated retrospectively. Complete ophthalmologic examination with best corrected visual acuity, peripheral visual field test, and disc angiography with OCT-A were performed. Quantitative optic disc perfusion indexes were evaluated by the device with automatically segmentation and qualitative comparison of choroidal, retinal, and en-face peripapillary perfusion angiogram images.

Results: In the NAION and control groups, mean age was 57.55±12.34 years and 50.79±4.67 years (p=0.110), the proportion of women was 7/11 (63.6%) and 9/14 (60%), and best corrected visual acuity was 0.95±0.63 and 0.00±0.0 LogMAR (p=0.001), respectively. Visual field defect was present in 10/11 (91%) eyes in the NAION group. In 6 patients, visual field defects were correlated with areas of peripapillary and optic nerve head hypoperfusion. In the patient group, optic nerve head capillary density was significantly decreased (p=0.008) and radial peripapillary capillary density was significantly decreased in all sectors except the inferonasal sector.

Conclusion: In our study, we observed that visual field evaluations were partially correlated with optic nerve head and peripapillary capillary perfusion assessed by OCT-A. Being practical and non-invasive, OCT-A is a useful and up-to-date method for evaluating perfusion in NAION.

Keywords: Non-arteritic anterior ischemic optic neuropathy, optical coherence tomography angiography, OCT-A

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Introduction

Anterior ischemic optic neuropathy (AION) is believed to occur most commonly as a result of acute ischemia in the anterior part of the optic nerve. There are two types, non-arteritic and arteritic.[1] Non-arteritic anterior ischemic optic neuropathy (NAION) is the leading cause of sudden vision loss in the middle-age group. It is painless and generally unilateral, although involvement of the fellow eye may also occur over time. The prevalence of NAION varies by race, particularly in relation to small optic disc size, with a reported incidence of 10.2/100,000 in the United States.[2,3]

The pathogenesis of NAION is known to be associated with impaired blood flow in the posterior ciliary artery (PCA) of the optic nerve head, which results in sudden ischemia in the optic nerve head.[4]

The clinical picture of NAION is often characterized by sudden-onset, painless unilateral vision loss and disc edema with altitudinal visual field defect. This optic neuropathy occurs due to local or systemic predisposing causes.[5] Among the systemic predisposing causes, conditions such as systemic hypertension and diabetes that cause vasculopathy and end organ damage especially increase the risk of developing NAION.[6,7,8] Similarly, causes of decreased optic disc perfusion such as nocturnal hypotension and obstructive sleep apnea syndrome have been associated with NAION.[9,10]

Choroidal perfusion assessed by fluorescein angiography is classically preserved in NAION.[11] However, some studies have demonstrated thinning of the subfoveal or peripapillary choroidal layer in the acute and chronic phases, indicating that a thinner choroid may also be a risk factor.[12,13]

Optical coherence tomography angiography (OCT-A) is a new, non-invasive imaging method that can be used to visualize the microcirculation in the retina and around the optic nerve.[5] Unlike fundus fluorescein angiography, it requires no exogenous contrast agent. OCT-A enables quantitative evaluation of peripapillary retinal, choroidal, and optic nerve head capillary density and flow.[14]

This study aimed to qualitatively and quantitatively evaluate superficial peripapillary vascularization using OCT-A and thereby non-invasively visualize ischemia in patients with acute NAION.

Materials and Methods

Patient Selection and Study Design

This study included 11 patients with a diagnosis of NAION who presented to the University of Erciyes Ophthalmology Clinic between January and July 2019, and 14 healthy volunteers (control group) with completely normal ophthalmological examination findings. The 11 patients presented with sudden-onset painless vision loss for less than 2 weeks on one side (n=11 eyes). Clinical examinations were performed by two different ophthalmologists and the diagnosis was made by excluding other causes of optic neuropathy. All patients underwent neurological evaluation and neurological imaging to exclude central causes. None of the eyes included in the study had a previous diagnosis of NAION. All patients who met the NAION diagnostic criteria and cooperated with the tests were included in the study. Exclusion criteria were: refractive error greater than ±4 diopters, optic disc anomalies, retinopathy, intraocular pressure higher than 21 mmHg and glaucoma diagnosis, use of medications that affect the optic nerve (digoxin, vigabatrin, ethambutol), history of eye trauma and/or retinal surgery, and history of cataract surgery within the last 6 months.

Clinical Examinations

After obtaining past and present clinical history, best corrected visual acuity (BCVA) (assessed with Snellen chart and converted to logMAR equivalent), intraocular pressure measurement, slit-lamp anterior segment examination, relative afferent pupil defect (RAPD) examination with swinging flashlight test, color vision examination with Ishihara test, and fundoscopic examination with 90 D lens were performed. Refraction was measured using an autorefractometer (TonoRef II, Nidek, Japan). C-reactive protein level, erythrocyte sedimentation rate, biochemical markers, and complete blood count were performed to exclude arteritic AION. Orbital and cranial magnetic resonance imaging was performed in all patients to rule out central and retrobulbar etiology. Pattern visual evoked potential (VEP) test was performed (Metrovision Vision Monitor Mon2018F, 2018). Each patient and control subject underwent 30° peripheral visual field test (Octopus-900, Haag-STEIT eyesuite static perimetry, V2.2.0) and disc angiography using OCT-A (RTVue XR Avanti Optovue Inc, Fremont, CA, version 2017.1.0.151).

OCT-A Imaging

All OCT-A measurements were made by the same ophthalmologist at the same time of day (10:00-12:00) to minimize diurnal changes. In OCT-A using the split-spectrum amplitude correlation angiography algorithm, 70,000 A-sections per second were acquired and measurements were evaluated from 4.5x4.5 mm disc images with a tissue axial resolution of 5 µm.[15] Measurements obtained from OCT-A images with signal strength below 6, motion artifacts due to poor fixation, and segmentation errors were excluded from the study.

Quantitative optic disc perfusion values were measured automatically by the device software. The device automatically determined peripapillary vascular density (%) in 10 segments and retinal nerve fiber layer (RNFL) measurements (µm). Qualitative peripapillary perfusion was evaluated by comparing choroidal, retinal, and en-face angiogram images. Optic disc

head and peripapillary measurements were determined for the vitreous/retinal layer over the outer plexiform layer, the radial peripapillary capillary (RPC) layer between the inner limiting membrane and the RNFL, and the choroidal layer under the retinal pigment epithelium (RPE), which were automatically segmented by the software.[16]

Statistical Analysis

SPSS version 22.0 (IBM Corp, Armonk, NY, USA) was used for analyses. Data distribution characteristics were evaluated using the Shapiro-Wilk test. Normally distributed quantitative data were expressed as mean ± standard deviation and categorical data as percentage (%). Independent-samples t-test was used to compare quantitative data that showed normal distribution. Categorical data were compared using chi-square (Fisher's Exact) test. A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Erciyes University Faculty of Medicine Clinical Trials Ethics Committee (approval number: 2019/139).

Results

The study included 11 eyes of 11 NAION patients (group 1) and 14 randomly selected eyes of 14 healthy volunteers (group 2). The mean ages of the groups were 57.55±12.34 and 50.79±4.67 years, respectively (p=0.110). The proportion of women was 63.6% (7/11) in group 1 and 60% (9/14) in group 2. NAION episodes were primary in all affected eyes. Two patients in group 1 had concomitant diabetes and hypertension. No signs of retinopathy were observed in these patients. The demographic data and rates of hypertension/diabetes of the groups are summarized in Table 1.

BCVA was 0.95±0.63 LogMAR equivalent in affected eyes in group 1, compared to 0.00±0.0 in group 2 (p=0.001). In group 1, RAPD was present in 4 (36.4%) of 11 eyes but could not be observed in the 7 eyes with signs of previous optic neuropathy in the fellow eye. Color vision was impaired in 10 (91%) of the 11 eyes. Attenuated wave amplitudes and prolonged P100 latencies were observed on VEP 60'.

Visual field defect was present in 10 (91%) of the eyes (peripheral concentric narrowing in 2 eyes, inferior-hemi scotoma in 4, superior-temporal scotoma in 1, inferior-temporal scotoma in 1, paracentral scotoma in 1, and inferior-nasal scotoma in 1 eye); only 1 eye did not have a localized scotoma but showed reduced sensitivity in the central and temporal regions.

RPC hypoperfusion was defined as dark areas where the capillary network was not visible on OCT-A images. Hypoperfusion in the RPC was not observed in 1 eye and was observed in the optic disc head in 1 eye, in at least 2 quadrants in 4 eyes, in 4 quadrants in 2 eyes, and in 1 quadrant in 3

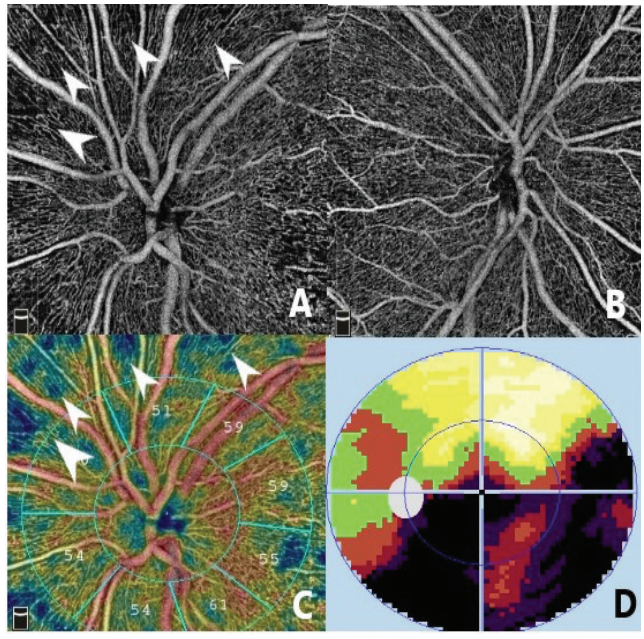

Figure 1. A 49-year-old woman presented with loss of vision in the left eye for 5 days. A) In the optical coherence tomography angiography (OCT-A) radial peripapillary capillary (RPC) cross-section, hypoperfusion is observed in en face images as dark areas in the superior nasal region, indicated by white arrowheads. B) No perfusion defect is observed in the cross-section obtained in the superficial OCT-A section, corresponding to above the outer plexiform layer. C) Color mapping of the vascular density in the RPC layer section indicates reduced perfusion in the blue areas indicated by the white arrowheads. This supports the presence of hypoperfusion consistent with the en face images. D) Visual field shows a scotoma in the inferior-hemi section corresponding to the predominantly inferior hypoperfused region

Table 1. Comparison of selected demographic data and visual field values

	NAION, group 1 (n=11)	Control, group 2 (n=14)	p
Age (years), mean ± SD	57.56±12.34	50.79±4.67	0.110
Sex (female), n (%)	7 (63.6)	9 (60.0)	0.604
DM, n (%)	2 (18.2)	0	-
Hypertension, n (%)	3 (27.3)	0	-
Visual field defect, n (%)	8 (72.3)	0	-

NAION: Non-arteritic acute ischemic optic neuropathy, SD: Standard deviation, DM: Diabetes mellitus

eyes, predominantly in the temporal quadrant. Figure 1 shows a visual field defect corresponding to an area of hypoperfusion detected on OCT-A in a patient with inferior hemiscotoma (Figures 1a-d). Figure 2 shows an inferior-temporal visual field defect corresponding to a hypoperfused area observed on OCT-A imaging in another patient (Figures 2a-d).

In 6 patients, visual field defects corresponded to regions with peripapillary and optic disc head hypoperfusion. One patient exhibited no hypoperfusion. In the other 4 patients, the hypoperfused areas and visual field defects were not correlated.

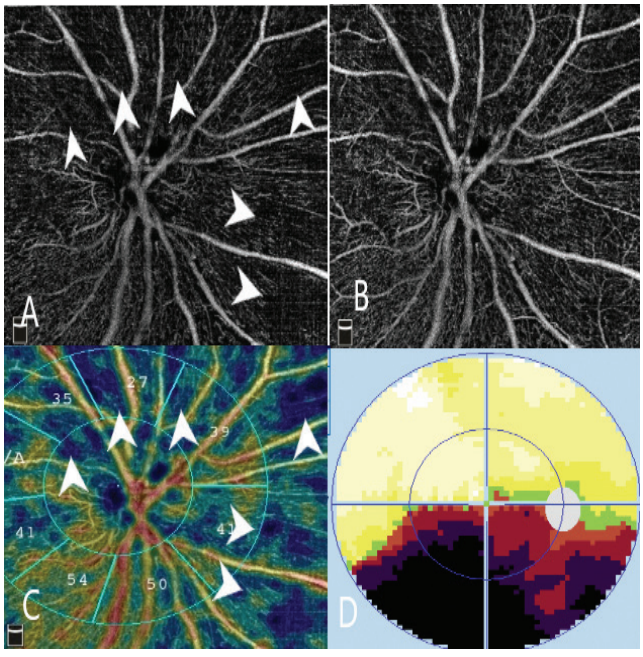

Figure 2. A 60-year-old woman had vision loss in her right eye for 1 week. A) On OCT-A imaging, dark areas consistent with hypoperfusion (white arrowheads) are observed in the RPC layer en face measurement cross-section. B) No disruption of vascular flow is observed in the superficial OCT-A cross-section above the outer plexiform layer. C) The vascular density color map of the RPC layer shows predominantly superior nasal hypoperfused and non-perfused areas corresponding to the dark areas on en face images (white arrowheads). D) Visual field demonstrates scotoma areas in the form of an altitudinal defect in the inferior hemisphere extending temporally, representing the hypoperfused areas

OCT-A: Optical coherence tomography angiography, RPC: Radial peripapillary capillary

In group 1, the RPC appeared mildly dilated and tortuous on OCT-A compared to the control group and unaffected fellow eyes.

In the quantitative analysis of OCT-A measurements, there was a statistically significant difference in RPC densities when the two groups were compared (p=0.005). There was also a significant difference in peripapillary RNFL measurements, with larger values in the patient group (p=0.008). RPC and optic disc head capillary densities were lower in the patient group compared to the control group. When combined, the difference between the groups was significant (p=0.008) while optic disc vascular density measurements were not statistically significantly different (p=0.052). The patients' RNFL, RPC, and optic disc head capillary densities are summarized in Table 2.

In the comparison of RPC density in the 10 different sectors, the patient group had significantly lower values in all sectors except the inferior sector (p=0.115) (Table 3).

Discussion

NAION occurs as a result of sudden ischemia due to impaired PCA circulation in the optic disc head. Two causes are emphasized in its etiology and pathogenesis. The first and most common is non-thromboembolic transient non-perfusion or hypoperfusion of the PCA. This hypotension, which may occur as systemic fluctuation, or sudden intraocular pressure elevations can lead to transient malperfusion of the PCA. The second, less common cause is embolic events in the arteries and arterioles that supply the optic nerve head. NAION resulting from multiple embolisms can cause more severe and permanent vision loss.[4] Kavuncu et al.[17] reported that visual prognosis was worse in older age and those with systemic predisposing factors, while patients with involvement at a younger age had better visual outcomes. In another study, it was found that NAION patients had electrophysiological changes suggestive of axonal loss in the unaffected eye, which the authors defended with the notion that axonal loss caused by ischemia may extend to the optic chiasm and affect the fellow eye.[18]

A study evaluating acute arteritic and non-arteritic AION patients using OCT-A showed that optic disc head and RPC

Table 2. Comparison of peripapillary thickness and optic disc vascular density measurements between the groups

	NAION, group 1 (n=11) Mean ± SD	**Control, group 2 (n=14) Mean ± SD**	**p**
RNFL (µm)	220.64±104.91	116.64±11.60	**0.008**
Peripapillary capillary density (%)	44.65±8.54	53.95±1.68	**0.005**
Optic disc head density (%)	43.90±5.84	48.49±5.32	0.052
All capillary density (%)	43.72±6.18	49.97±2.59	**0.008**

NAION: Non-arteritic acute ischemic optic neuropathy, SD: Standard deviation, RNFL: Retinal nerve fiber layer. Statistically significant values are highlighted in bold

Table 3. Comparison of segmental radial peripapillary capillary density measurements (%) between the groups

Segments	NAION, group 1 (n=11) Mean ± SD	Control, group 2 (n=14) Mean ± SD	p
Superior-hemi	41.7±10.54	53.57±1.89	**0.004**
Inferior-hemi	45.59±9.51	54.30±2.19	**0.013**
Nasal superior	41.17±10.10	50.57±3.33	**0.012**
Nasal inferior	42.39±9.84	51.38±3.44	**0.014**
Inferior nasal	46.16±12.09	52.59±3.41	**0.115**
Inferior temporal	50.60±10.90	61.09±2.79	**0.010**
Temporal inferior	45.27±9.24	54.77±2.79	**0.007**
Temporal superior	47.55±9.99	57.87±1.60	**0.007**
Superior temporal	44.98±11.45	57.75±1.85	**0.004**
Superior nasal	40.17±12.30	50.8±3.94	**0.018**

NAION: Non-arteritic acute ischemic optic neuropathy, SD: Standard deviation. Statistically significant values are highlighted in bold

density was decreased in acute NAION patients compared to healthy controls. In addition, non-perfusion areas in the optic disc head detected by indocyanine green angiography and fundus fluorescein angiography were correlated with the non-perfusion areas seen on OCT-A, and it was concluded that OCT-A evaluation provided useful information in the diagnosis of NAION.[19] In another study, qualitative OCT-A evaluation of the optic disc head in NAION revealed increased capillary tortuosity and dilation, predominantly in the hypoperfused areas, in more than half of the patients. The authors suggested this could be explained by the hypothesis of venous insufficiency in the optic disc head secondary to temporary hypoperfusion or venous infarction.[20] In the literature, it has been reported that eyes with NAION have greater involvement in the temporal quadrant due to choroidal watershed zone damage.[14,21] Sharma et al.[5] observed increased capillary tortuosity in patients with acute NAION and attributed it to transient venous insufficiency. In our study, quantitative RPC segmental measurements were significantly reduced in all sectors except the inferonasal sector. In qualitative peripapillary OCT-A evaluations, hypoperfusion was not observed in 1 patient but was detected in 1 or more quadrants (including the temporal quadrant) in 8 patients, consistent with the literature. However, the decrease in capillary density measured by OCT-A may also be a result of edematous compression of the optic disc or secondary signal attenuation due to the shadowing effect of the fluid (edema, hemorrhage). One study demonstrated that in patients with decreased peripapillary flow densities, low flow persisted in repeated OCT-A measurements after resolution of optic disc edema.[5] In our OCT-A evaluation, we found that RNFL values were higher in the patient group than the control group, contrary to the literature. A previous study showed that in animal models of ischemic optic neuropathy, more severe optic nerve ischemia in the acute phase leads to more optic disc edema and vision loss.[22] Measured RNFL values may have been higher due to the fact that our patient group had optic disc edema associated with acute NAION.

In our study, we determined that visual field assessments were partially correlated with optic disc head and RPC perfusion evaluated by OCT-A, with one patient having no hypoperfusion area detected on OCT-A and no detectable visual field defect. Six patients had predominantly inferior visual field defects that were consistent with the hypoperfused optic disc head and peripapillary quadrants. However, four patients' visual field defects did not correspond to the areas of hypoperfusion observed in RPC images on OCT-A scans. Rougier et al.[23] reported poor correlation between OCT-A measurements and visual field in their study, observing close correlation between the hypoperfused area and visual field defect pattern in only one patient. They argued that visual field defects were associated with changes in PCA flow rather than peripapillary flow. Ling et al.[24] evaluated optic disc perfusion and determined that visual acuity and visual field defects were correlated with hypoperfusion detected on OCT-A. In another study, visual field defects were reported to be significantly correlated with optic disc vascular density, vascular tortuosity, and RNFL thicknesses.[25] Gaier et al.[26] concluded that the pattern of visual field defect in patients with acute and non-acute NAION correlated with associated regions of reduced patent capillary density. Consistent with the literature, we found that BCVA was lower in the patient group in our study.

OCT-A is a current, practical, and non-invasive method that can be easily applied to support the diagnosis of NAION and is

useful in the qualitative and quantitative assessment of retinal and choroidal vascularization.

Study limitations

This study has certain limitations. One of these is the small number of patients included in the study. In addition, we could not perform manual segmentation due to the absence of the most recent version of Angiovue in the Optovue software. Therefore, calculations were based on the inner and outer segments determined automatically by the device. Other limitations were the small measurement area and limited evaluation of the peripapillary area, and the fact that scans were not repeated after edema resolution to rule out possible RPC circulatory impairment caused by obstruction, which can also cause optic disc edema.

Conclusion

The results of this study indicate that optic disc head and superficial peripapillary microcirculation are impaired in acute NAION. The partial correlation between detected microvascular changes and visual field defects reveals an important structural and functional relationship.

In summary, OCT-A is a current, rapid, and non-invasive method for the assessment of the peripapillary microcirculation in NAION patients. Controlled randomized studies with larger patient numbers are necessary to more clearly demonstrate the relationship between visual field defects and the microcirculatory impairments detected by OCT-A.

Ethics

Ethics Committee Approval: The study was approved by the Erciyes University Faculty of Medicine Clinical Trials Ethics Committee (approval number: 2019/139). **Informed Consent:** Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.K.S., D.G.S., H.A., Concept: H.K.S., D.G.S., H.A., Design: H.K.S., D.G.S., H.A., Data Collection or Processing: H.K.S., D.G.S., Analysis or Interpretation: H.K.S., D.G.S., H.A., Literature Search: H.K.S., D.G.S., H.A., Writing: H.K.S., D.G.S., H.A.

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Original Article

Treatment of Nanophthalmos-Related Uveal Effusion with Two- vs. Four-Quadrant Partial-Thickness Sclerectomy and Sclerotomy Surgery

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Abstract

Objectives: To report visual and anatomical outcomes following two- or four-quadrant partial-thickness sclerectomy and sclerotomy surgery to treat nanophthalmos (NO)-related uveal effusion (UE).

Materials and Methods: Consecutive patients with NO-related UE were treated with four-quadrant or two-quadrant (for those with associated glaucoma) partial-thickness sclerectomy and sclerotomy surgery. Axial length, extent of UE, preoperative, postoperative, and final best corrected visual acuity (BCVA), time to retinal reattachment, and rates of retinal reattachment and recurrence were noted.

Results: Fourteen eyes of 10 patients with NO-related UE were operated. Retinal detachment (RD) involved mainly the peripheral retina in 7 (50%) eyes, macula in 2 eyes (14.2%), both macula and peripheral retina in 4 eyes (28.6%), and the whole retina in 1 eye. Eleven eyes had four-quadrant surgery, and 3 eyes with associated glaucoma had two-quadrant surgery. External subretinal drainage was performed in one patient who had total RD. The mean preoperative logMAR BCVA of 1.50±0.53 increased significantly to 0.92±0.49 after surgery (p=0.002). Resolution of RD could be achieved with two-quadrant surgery in only 1 of 3 eyes. In the other 2 eyes, retinal reattachment was achieved after a secondary surgery for the remaining two quadrants to complete four-quadrant sclerectomy. Final outcome was total reattachment of the retina in 11 eyes (78.6%), partial reattachment in 1 eye (7.1%), and recurrence of macular detachment in 2 (14.3%) eyes.

Conclusion: Quadrantic partial-thickness sclerectomy and sclerotomy surgery seems effective for treating UE in eyes with NO. Two-quadrant surgery may be tried for mild UE associated with glaucoma to preserve the superior quadrants for future possible glaucoma surgeries, but secondary surgery for the superior quadrants may be needed. External drainage of subretinal fluid may be an option in severe cases to achieve quicker resolution.

Keywords: Nanophthalmos, partial sclerectomy, sclerotomy, uveal effusion, exudative retinal detachment

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Introduction

Nanophthalmos (NO) comes from the Latin word *nanos*, which means "dwarf." NO is thought to result from developmental arrest of the globe. In contrast to microphthalmos, which is frequently complicated by developmental defects of the fetal fissure and coloboma of the iris, choroid, and retina, the nanophthalmic eye is typically reduced in volume with a normal-sized crystalline lens, resulting in a high lens to eye volume ratio.[1]

The incidence of NO was reported to range from 0.002% to 0.017% in a British cohort.[2] Clinical features include a deep-set globe within a small orbit with narrow palpebral fissures, short axial length (<20.5 mm), axial hypermetropia (+8.00 to +20.00), a shallow and crowded anterior chamber, and thickened sclera.[3,4] The thickened and abnormal sclera causes angle-closure glaucoma and posterior segment problems such as uveal effusion (UE), macular hypoplasia, chorioretinal folds, pseudopapilledema, and retinal pigment epithelium (RPE) hyperpigmentation.[5]

UE may develop spontaneously or after an uncomplicated anterior segment surgery such as cataract surgery.[6] Different theories regarding the pathophysiology of UE have been speculated, including vortex vein compression, choroidal permeability changes, and decreased scleral permeability.[7] Gass[8] proposed that subretinal fluid may be absorbed transsclerally instead of through vortex veins and suggested that UE develops not as a result of vortex vein compression, but because the thickened and abnormal sclera blocks transscleral fluid absorption. He also suggested that when the sclera is thinned with sclerectomies, effusion may regress. It was reported that resorption of the subretinal fluid could be achieved with sclerectomies alone in a group of patients with UE.[9] Vortex vein decompression, partial-thickness sclerectomy, partial-thickness sclerectomy with mitomycin C (MMC), partial-thickness sclerectomy with incision or punch sclerostomy, and subretinal fluid drainage are some of the reported procedures to treat this condition.[10]

However, glaucoma is another significant problem encountered in eyes with NO.[11] When partial-thickness sclerectomy and sclerotomy surgery is performed in four quadrants, glaucoma surgery would be very problematic and aggressive when needed later in life because of the scarred conjunctiva. Therefore, an inferior two-quadrant surgery in eyes with glaucoma may be a good option to protect the superior quadrants from surgical damage.

The aim of our study was to report visual and anatomical outcomes after two- or four-quadrant partial-thickness sclerectomy and sclerotomy surgery for the treatment of NO-related UE.

Materials and Methods

This retrospective, non-comparative, consecutive interventional case series included patients with NO-related UE. The design of the study was approved by the local ethics committee of the university. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and all participants gave written informed consent. The patients' records were reviewed to obtain complete ophthalmic examination findings including best corrected visual acuity (BCVA), slit-lamp examination, intraocular pressure (IOP) measurement, fundus examination, optical coherence tomography (OCT), and axial length (AL) measured with A-scan ultrasonography. Patients with glaucoma underwent inferior two-quadrant, and all others underwent four-quadrant partial-thickness sclerectomy and sclerotomy surgery.

Surgical technique (Figure 1): All surgeries were done by three experienced retinal surgeons (S.O., M.C.O., and M.H.) under retrobulbar anesthesia. Briefly, the technique involved the creation of rectangular partial-thickness (two-thirds to three-quarters) sclerectomies measuring approximately 6x4 mm (depending on the size of the globe) in the two inferior quadrants or all four quadrants. The anterior boundary was the rectus muscle insertions, the posterior boundary was the vortex vein ampulla to avoid its intrascleral course, and the lateral boundary was the rectus muscles, leaving a very narrow strip of sclera blocked by the muscle mass. The superior oblique muscle insertion area was spared in the superotemporal quadrant to avoid damage. First, a partial-thickness scleral incision was made to delineate the extent and depth of the scleral dissection (Figure 1a). Partial-thickness scleral flaps approximately 80-90% of the original thickness were dissected and removed (Figure 1b,c). A linear sclerotomy was created in the center of the sclerectomy area to determine the thickness of remaining scleral until the choroid is seen (Figure 1d). No attempt was made to drain the subretinal fluid (except in 1 eye) or decompress the vortex veins.

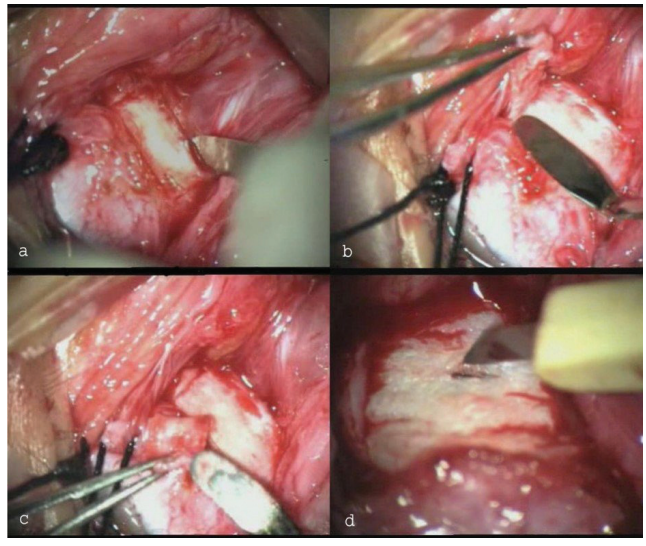

Figure 1. a) Partial-thickness rectangular scleral incision is made to delineate the scleral dissection. b, c) Dissection of the scleral flap to be removed. d) Linear sclerotomy in the center of the sclerectomy area

Surgery was performed only in the inferior two quadrants in 3 eyes of 3 patients with known glaucoma to preserve the superior conjunctiva and sclera for glaucoma surgery that may be needed in the future. Drainage of subretinal fluid was performed only in 1 eye with the most severe UE using a 20-gauge MVR knife after cauterizing the choroid in the superotemporal quadrant. The eye was infused with balanced salt solution (BSS) through a limbal incision during external drainage.

Postoperative control visits were performed at 2 weeks, 1, 3, 6, and 12 months, and every 6 months thereafter. Outcomes were classified as total reattachment of the retina if the effusions had resorbed entirely within 3 months, partial reattachment if there was a reduction in the subretinal fluid over 3 months, and unsuccessful if the fluid collections failed to improve within 3 months of surgery. A secondary surgery with superior quadrant sclerectomies was suggested to patients who underwent primary inferior two-quadrant sclerectomy if resolution of the subretinal fluid was not observed in the first 3 months postoperatively. Reoperation with mitomycin C (MMC) was performed in eyes that underwent primary four-quadrant sclerectomy if subretinal fluid increased during follow-up.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS for Windows version 20 (IBM Corp., Armonk, NY, USA). Values were summarized using mean ± standard deviation or median (minimum-maximum) according to data distribution. Categorical variables were presented as number (n) and percentage (%). Wilcoxon test was used to compare preoperative and postoperative BCVA. A value of $p \leq 0.05$ was considered statistically significant.

Results

Fourteen eyes of 10 patients were included in the study. Demographic features of the patients are shown in Table 1. There were 7 male patients and 3 female patients, and the mean age was 32.7±14.1 (14-64) years. Four of the 10 patients had bilateral surgery. The mean AL of 14 eyes was 15.1±2.7 mm (10.2-20.1 mm). The mean refractive error was +15.0±3.9 diopters (D) (+8.00-+18.25 D). Nine right eyes and 5 left eyes underwent surgery. Seven (50.0%) of 14 eyes had peripheral retinal detachment (RD), 1 patient had bilateral (14.3%) severe (highly elevated) localized macular RD with pigmentary retinopathy, 4 of 14 eyes (28.6%) had both macular and peripheral RD, and 1 eye had total RD. Four of 14 eyes (28.6%) had glaucoma. Two patients had pseudophakia with piggyback IOLs (operated elsewhere), and one of them underwent pars plana vitrectomy (PPV) and intravitreal silicone oil tamponade surgery for macular hole later (Table 1). Case 1 and 2 were brother and sister whose father also had NO (case 10).

Eleven eyes had four-quadrant surgery, and 3 eyes with known glaucoma (case 5, case 6, and case 10) had two-quadrant surgery. Case 5 gradually resolved within 12 weeks with only two-quadrant surgery. Case 6, however, showed a transient partial resolution and required a second operation at postoperative 4 months to complete four-quadrant surgery, which resulted in total resolution of the subretinal fluid within 3 months. Case 10 also needed surgery in the other two quadrants at postoperative 8 months. This patient had highly elevated retinoschisis in the temporal peripheral retina, sparing the macula, which was demarcated with laser photocoagulation later following total resolution of the UE. The median follow-up after the surgery was 32.5 months (range 5-96 months). Final outcome was total reattachment of the retina in 11 eyes (78.6%), partial reattachment in 1 eye (7.1%), and recurrence in 2 eyes (14.3%). The mean time to resolution after surgery was 8.4±7.1 weeks (range 1-20 weeks).

The mean preoperative BCVA in logarithm of the minimum angle of resolution (logMAR) units was 1.50±0.53, which significantly increased to 0.92±0.49 logMAR postoperatively at the end of follow-up ($p=0.002$). BCVA improved in 12 eyes (85.7%) and remained stable in 2 eyes (14.3%).

Case 3: A 14-year-old boy presented with BCVA of 20/400 with +17.00 D correction bilaterally. He had bilateral highly elevated macular detachment with peripheral pigmentary retinopathy. Following bilateral four-quadrant partial-thickness sclerectomy and sclerotomy surgery, BCVA improved to 20/200 in both eyes with an evident subjective increase in visual quality within 5 months. Fundus examination and OCT demonstrated reduction in macular detachment height with partial resolution of submacular fluid. However, his vision deteriorated again to the preoperative level with an increase in macular UE height at 9 months. Episcleral scarring was thought to be the reason for the clinical worsening. Thus, he was reoperated with MMC as suggested by Akduman et al.[12] The sclera was seen to be surprisingly thickened with fibrosis during the second surgery and was resected in the same way as in the first surgery. During postoperative follow-up, the subretinal fluid decreased minimally (not as much as after the first surgery).

Case 6: A 36-year-old woman had BCVA of 20/400 in her right eye and 20/60 in her left eye with +15.00 D correction and AL of 16.2 and 16.4 mm, respectively. She had previously undergone YAG laser iridotomy for narrow-angle glaucoma elsewhere. IOP was 14 mmHg without medication. She had foveal and peripheral RD in the right eye and peripheral limited RD in the left eye. We opted to perform two-quadrant (inferior) partial-thickness sclerectomy and sclerotomy surgery for the right eye to preserve the superior quadrant for the possible future need for glaucoma surgery. RD regressed partially during the first postoperative month but recurred over the next 4 months.

Table 1. Demographic and clinical features of the nanophthalmos patients

Case #	Age/ Sex	Eye/Axial Length (mm)	Preoperative BCVA	Quadrants	BCVA at 3 months	Peripheral (P) / Macular (M) RD	Subretinal Fluid Resorption Time (Weeks)	Retinal Reattachment	BCVA Before Second Surgery	Second Surgery	Other Ocular Features	Follow-up Time (Months)	Final BCVA
1	24/M	OD/13.3	20/400	4	20/100	M+P	2	(+)		-		60	20/100
	26/M	OS/12.8	20/200	4	20/100	P	2	(+)		-		36	20/100
2	26/F	OS/14.1	20/400	4	20/200	P	3	(+)		-		96	20/100
3	14/M	OD/10.5	20/400	4	20/200	M	-	(-)	20/200	Sclerectomy surgery with MMC	Pigmentary retinopathy	10	20/200
	14/M	OS/10.2	20/400	4	20/400	M	-	(-)	20/400	Sclerectomy surgery with MMC	Pigmentary retinopathy	10	20/200
4	21/M	OD/16.3	CF (1m)	4	CF (1m)	P	20	(+/-)	CF (1m)	PPV and intravitreal silicone oil tamponade surgery for macular hole	Pseudophakic RD	96	CF (1m)
5	51/F	OD/20.1	CF(1m)	2	20/60	M+P	12	(+)		-	Glaucoma	72	20/60
6	36/F	OD/16.2	20/400	2	20/200	M+P	12	(+)	20/400	Sclerectomy in other two quadrants	Glaucoma	50	20/60
	39/F	OS/16.4	20/60	4	20/50	P	5	(+)			Glaucoma	5	20/50
7	31/M	OD/14.4	CF (10 cm)	4	CF (1m)	P	4	(+)		-	Aphakia, Previous lensectomy,	24	CF (1m)
8	32/M	OD/17.2	LP	4	20/200	Total	1	(+)	20/200	PPV-lensectomy and secondary scleral fixated IOL implantation with modified Yamane technique	Retina was at the back of the lens, Subretinal fluid was drained, Lens subluxated during primary surgery	20	20/100
	32/M	OS/17.6	20/500	4	20/200	M+P	16	(+)		-	Amblyopia	29	20/200
9	48/M	OD/16.4	HM	4	20/200	P	4	(+)		-	After uncomplicated cataract surgery	10	20/100
10	64/M	OD/16.6	20/200	2	20/200	P	20	(+)	20/400	Sclerectomy in other two quadrants	Glaucoma, Retinoschisis	36	20/200

M: Male, F: Female, OD: Right eye, OS: Left eye, HM: Hand Motions, LP: Light Perception, CF (1m): Counting fingers at 1 meter, CF (10 cm): Counting fingers at 10 centimeters, BCVA: Best-corrected visual acuity, RD: Retinal detachment, PPV: Pars plana vitrectomy MMC: Mitomycin C

Another surgery was performed on the other two (superior) quadrants, which resulted in regression of the UE starting in the first postoperative days and total resolution at 12 weeks. Her BCVA improved to 20/60 in the right eye during the 50-month follow-up period. Three years later, the peripheral RD in the left eye progressed, and a four-quadrant (instead of two-quadrant) surgery was preferred because of our experience with her right eye. UE regressed totally in 5 weeks, and her BCVA improved to 20/50 in the left eye within 5 months of follow-up.

Case 8: A 32-year-old man presented with complaints of reduced vision in his right eye for 1.5 years and in his amblyopic left eye for 5 years. His BCVA was only light perception in his right eye, which used to be the better eye, and 20/500 in his left eye with +8.00 correction, and AL was approximately 17 mm bilaterally. He had leukocoria and the retina was at the back of the lens in his right eye (Figure 2a), and his left eye showed subtotal foveal and superior peripheral RD (Figure 2b). The right eye was thought to be inoperable, and a four-quadrant partial-thickness sclerectomy and sclerotomy surgery was performed on his left eye. Following surgery, UE regressed on postoperative day 1 and total reattachment was observed at 1 year (Figure 3). BCVA improved to 20/200 in the left eye. Eight months later, the patient requested treatment for his right eye and underwent four-quadrant partial-thickness sclerectomy and sclerotomy with subretinal fluid drainage for his right eye. After drainage of the subretinal fluid, the globe was repressurized with BSS through a limbal incision during the surgery. The retina moved posteriorly with drainage, but so did the crystalline lens. The retina totally reattached starting on postoperative day 1. The dislocated lens in the vitreous cavity was removed with PPV/lensectomy, and scleral-fixated IOL implantation was done using the modified Yamane technique in the right eye (Figure 4a). At last follow-up at 29 months, the retinas were totally reattached bilaterally and BCVA was 20/100 in the right eye and 20/200 in the left eye (Figure 4b).

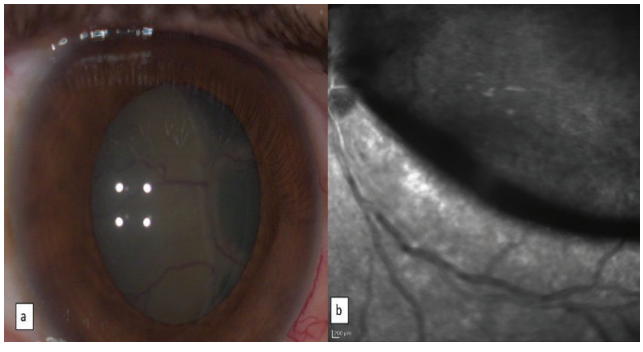

Figure 2. Case 8 had leukocoria with the retina at the back of the lens in his right eye (a) and subtotal foveal and peripheral exudative detachment in his left eye (b)

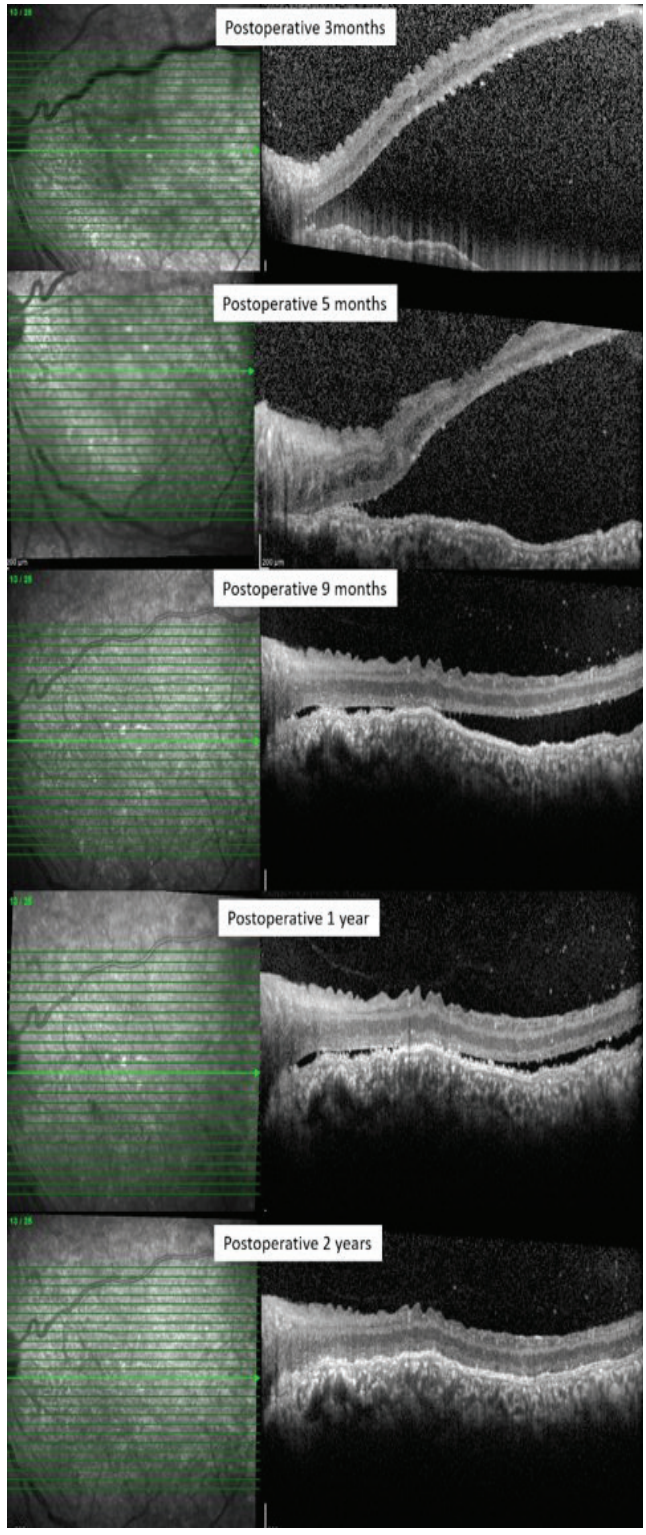

Figure 3. Spectral domain optical coherence tomography scans of the left eye of case 8 revealed gradual resolution of the exudative RD with total reattachment at 2 years

RD: Retinal detachment

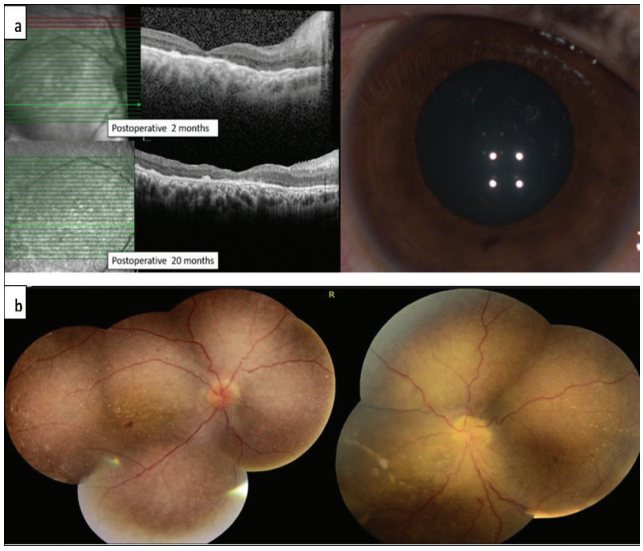

Figure 4. a) Spectral domain optical coherence tomography scans of the right eye of case 8. Note that the retina was totally reattached following four-quadrant scleral window surgery with drainage of subretinal fluid starting from the first postoperative visit in the right eye and remained attached through the entire follow-up period. b) Fundus images of both eyes of patient 8 showing resolution of the exudative RD and total reattachment during 20-month follow-up

RD: Retinal detachment

Discussion

In the present study, a final retinal reattachment rate of 78.6% was achieved, followed by a functional improvement in BCVA in 85.7% using a modified Gass technique in patients with NO-related UE.

Gass[8] was the first to suggest the four-quadrant sclerectomy and sclerostomy procedure to treat eyes with UE. He reported total resolution of the supraciliochoroidal and subretinal fluid with this technique within 3 months. Johnson and Gass[9] reported a series of 23 eyes of 20 patients with idiopathic UE syndrome (UES) operated with a similar technique where UE resolution was seen within 6 months in 96% of the eyes after one or two procedures, with stable or improved final VA in 91% of the eyes.

The success rate in the present study was lower than that reported by Johnson and Gass.[9] This may be because our cases were all extreme NO-related UE in very small eyes (mean AL 15.1 mm), in contrast to Gass' series, which were all idiopathic UES. It is important to note that surgery for UE in nanophthalmic eyes has more complications, recurrence, and disappointing results.[11,13]

Many authors have modified the technique in different ways, with varying success rates. Jackson et al.[14] reported a multicenter series of 10 patients with idiopathic UES treated with a modified Gass technique with deeper sclerectomies (full-thickness or deep enough to visualize the choroid and allow fluid to leak through the sclera), with a 50% success rate. Uyama et al.[15] modified the technique to an inferior two-quadrant subscleral sclerectomy with scleral flap and treated 19 eyes of 16 patients with UE. Of the 6 eyes with NO-related UE in their series, reattachment was achieved in 4 (66.6%), and the remaining 2 eyes needed a secondary procedure in the superior quadrants to achieve reattachment, as in cases 6 and 10 in the present series. Another modified technique involving full-thickness sclerotomy without sclerectomy resulted in resolution of subretinal fluid in 4 of 5 eyes with UE, 3 of which were associated with NO.[16] Mansour et al.[17] described an extensive circumferential partial-thickness (90% depth) scleral excision technique very similar to our technique in 8 eyes of 5 patients with NO-related UE and reported rapid resolution of the effusion. Intravitreal anti-VEGF injection was also suggested recently to increase the efficacy of partial-thickness sclerectomy surgery for intractable UES.[18]

Recurrences and repeated surgeries for UE have been reported due to sclerectomy closure.[13,17] Johnson and Gass[9] reported recurrences in 23% of their cases, all of which resolved spontaneously or with an additional operation to remove scar tissue from the sclerectomy sites and reopen the sclerostomies. Jackson et al.[14] reported a total of 19 operations in 14 eyes with idiopathic UES, where 4 eyes required multiple operations. It was suggested that episcleral and scleral scarring might lead to closure of the scleral windows after surgery, and topical application of MMC might prevent such scarring at the sclerectomy site.[12,19] We suppose that episcleral scarring was the cause of recurrence of macular detachment in case 3 in the present study. However, a second surgery with MMC did not help to control the macular UE in this case. Our hypothesis for the limited response in this patient was the lack of healthy RPE to pump subretinal fluid out because of the pigmentary retinopathy.

The treatment of NO-related UE can be difficult. It is suggested that choroidal inflammation might be an underlying reason for UE.[20] However, the results of studies on corticosteroid therapy for the treatment of UE are not promising.[7,21,22] Other medical therapies such as topical non-steroidal anti-inflammatory drugs, topical prostaglandin analogs, and systemic carbonic anhydrase inhibitors have been reported only in a few case reports.[22,23]

It is well known that glaucoma is very prevalent in eyes with NO, most commonly angle-closure glaucoma with progressive shallowing of the anterior chamber that narrows the angle and causes pupillary block.[24] The incidence of angle-closure glaucoma in NO was reported to be 69.2% in a high-hyperopia database.[25] In the management of angle closure in these eyes, laser iridectomy and argon-laser peripheral iridoplasty can be performed. When laser treatments are ineffective, glaucoma filtering surgeries may be needed.[24]

When surgical treatment for UE is needed in nanophthalmic eyes, it may be logical to preserve the superior quadrants for future possible glaucoma surgeries, especially when there

is already known glaucoma. We believe that two-quadrant sclerectomies can yield successful results in early, mild cases with limited peripheral UE and longer AL (as in case 5). However, it may not be sufficient in severe cases with bullous extensive UE, where it may be necessary to complete the surgery in all four quadrants to obtain the same favorable outcome, as in cases 6 and 10 in this study.

External transscleral subretinal fluid drainage is usually avoided in these cases due to fear of complications like choroidal hemorrhage during choroid puncture because the choroid may be highly congested secondary to blocked transscleral drainage caused by the thickened sclera in these eyes. However, we tried this in the most severe case (patient 8, right eye), in which the retina was behind the lens and vision was at the level of light perception. Although expectations were extremely low, very favorable and unexpected anatomical and functional outcomes were achieved. This approach was recently described in two other cases in the literature, with similar results and no complications.[26] Therefore, external drainage of subretinal fluid can be performed in addition to sclerectomies for very advanced, highly bullous UE and might lead to a quicker and better response.

Study Limitations

A limitation of our study was the small number of cases, especially in the two-quadrant surgery group, which is basically because of the low overall incidence of NO and associated UE with glaucoma. However, strengths of the study were the unique modified technique, being the largest single-center study on the surgical treatment of NO-related UE with relatively long-term follow-up, and the emphasis on two-quadrant surgery to preserve the superior quadrants for future possible glaucoma surgeries in eyes with glaucoma.

Conclusion

In conclusion, scleral thinning surgeries are effective for the treatment of NO-related UE. Our results supported the effectiveness of the four-quadrant extensive sclerectomy technique. However, two-quadrant surgery might be successful in mild cases with glaucoma to preserve the superior quadrants for future glaucoma surgery. External transscleral drainage of subretinal fluid may be an option in severe cases to achieve quicker resolution.

Ethics

Ethics Committee Approval: Gazi University Faculty of Medicine Clinical Research Ethics Committee (date: 07.12.2020, decision no: 821)

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.Ö., M.C.Ö., M.H., Concept: Ş.Ö., D.Y.Y., Design: Ş.Ö., Data Collection or Processing: Ş.Ö., D.Y.Y., M.H., M.C.Ö., Analysis or Interpretation: Ş.Ö., M.C.Ö., Literature Search: D.Y.Y., M.H., Writing: M.H., D.Y.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Clinical Features of Untreated Type 2 Macular Telangiectasia and Efficacy of Anti-Vascular Endothelial Growth Factor Therapy in Macular Neovascularization

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Abstract

Objectives: To compare best corrected visual acuity (BCVA), central macular thickness (CMT), and central choroidal thickness (CCT) in patients with type 2 macular telangiectasia (MacTel 2) and a control group and to evaluate the efficacy of intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment in MacTel 2 patients with macular neovascularization (MNV).

Materials and Methods: We conducted a retrospective chart review of consecutive MacTel 2 patients who underwent a full ophthalmologic examination including BCVA and dilated fundus examination with slit-lamp biomicroscopy, fluorescein angiography, and optical coherence tomography imaging at baseline and follow-up visits. BCVA, CMT, and CCT were compared between all identified patients (n=26) and a control group (n=30). A subgroup analysis was performed among eyes with MNV (n=7) before and after treatment.

Results: CMT and CCT were significantly lower in the MacTel 2 group compared to the control group. Forty-one treatment-naive eyes without MNV proliferation showed no significant change in BCVA, CMT, or CCT during follow-up. Eight eyes of 7 MacTel 2 patients developed MNV during follow-up. All of the patients were treated with intravitreal anti-VEGF.

Conclusion: It is important to closely follow MacTel 2 patients for MNV development. To avoid adverse effects, we prefer to monitor patients who have not yet developed MNV. Patients with proliferative MacTel 2 with decreasing visual function may benefit from intravitreal anti-VEGF treatment.

Keywords: Macular telangiectasia, macular neovascularization, anti-VEGF treatment

Introduction

Idiopathic juxtafoveal telangiectasia (IMT) is associated with foveal thinning, crystalline deposits in the macula, telangiectatic vascular changes with leakage, and macular neovascularization (MNV).[1] Gass and Blodi[2] classified IMT into stages and groups. Of the three groups, type 2 is the most common.[3] Macular telangiectasia type 2 (MacTel 2) is an acquired bilateral disease that causes reduced visual acuity and metamorphopsia, occurring most commonly in middle-aged men and women.[4] Although it has been shown that luteal pigment loss may be involved in the pathogenesis of the disease,[5] Müller cell dysfunction is known to play critical role in the pathogenesis.[6] Visual loss may occur due to atrophy of the foveal photoreceptors and foveal structural changes.[2,3,4,5,6] MNV may occur in some patients and can cause

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serious visual deterioration.[2,7] Various therapeutic approaches have been used in patients with MacTel 2 complicated with MNV, including laser photocoagulation,[8] photodynamic therapy,[9] transpupillary thermotherapy,[10] intravitreal triamcinolone,[11] and anecortave acetate.[12] Recently, anti-vascular endothelial growth factor (anti-VEGF) therapy has become the preferred treatment option.[13,14]

The aim of our study was to compare best corrected visual acuity (BCVA), central macular thickness (CMT), and central choroidal thickness (CCT) in MacTel 2 and a control group and to evaluate the efficacy of intravitreal anti-VEGF therapy in MacTel 2 patients with MNV.

Materials and Methods

This retrospective study included a series of consecutive patients with MacTel 2 who were examined between January 2012 and December 2019 in our ophthalmology department. Eyes with ocular pathology causing decreased vision, such as diabetic retinopathy or age-related macular degeneration, were excluded from the study. MacTel 2 patients with at least 6 months of follow-up were included in the study. An age-matched control group was selected from healthy patients with no systemic disease. This study was approved by Baskent University Institutional Review Board (project no:19/63) and informed consent was obtained from each subject.

Forty-nine eyes of 26 MacTel 2 patients and 60 eyes of 30 healthy control patients were included in the study. All patients underwent a full ophthalmologic examination including dilated fundus examination with slit-lamp biomicroscopy, BCVA, color fundus photography, fluorescein angiography (FA; Zeiss Visucam 500), and optical coherence tomography (OCT; Heidelberg Engineering, Heidelberg, Germany) imaging at baseline and follow-up visits. The clinical criteria for the diagnosis of MacTel 2 included small intraretinal crystalline deposits, parafoveal graying of the retina, and presence of pigment clumps and right angle venules.[1] Parafoveal telangiectatic capillaries observed in the mid-arteriovenous phase and late phase leakage surrounding the fovea is diagnostic in FA. Submacular neovascular membrane was confirmed on OCT imaging and FA. Signs of MNV include increased CMT on OCT, presence of retinal hemorrhage, or decline in visual acuity from baseline.

BCVA, CMT, and CCT were compared between all identified patients (n=26) and the control group (n=30). A subgroup analysis was performed among eyes with MNV (n=7) before and after treatment.

Statistical Analyses

Statistical analysis of the data was performed using SPSS version 23.0 package program (IBM Corp, Armonk, NY). Categorical measurements were summarized as number and percentage, continuous measurements as mean and standard deviation (or median and minimum-maximum where necessary). Chi-square test or Fisher test statistic was used to compare categorical variables. Data distribution was checked for comparison of continuous measurements between groups; Mann-Whitney U test was used for non-normally distributed and Student's t test for normally distributed parameters. Wilcoxon test was used to compare values before and after treatment. The statistical significance level was 0.05 in all tests.

Results

There were 23 women and 3 men in the MacTel 2 group and 30 women in the control group. The mean age of the MacTel 2 group was 65.54 years (range 53-83, median 65) and that of the control group was 61.86 years (range: 47-77, median: 62). There was no statistically significant difference in age and gender between the groups. Mean follow-up time was 33.6 months (range: 6-72).

CMT and CCT were significantly lower in the MacTel 2 group compared to the control group (Figures 1 and 2). Mean CMT was 243.55 µm (range: 161-318, median: 241) in the MacTel 2 group and 263.58 µm (range: 225-295, median: 263) in the control group (p=0.0001). Mean CCT in the MacTel 2

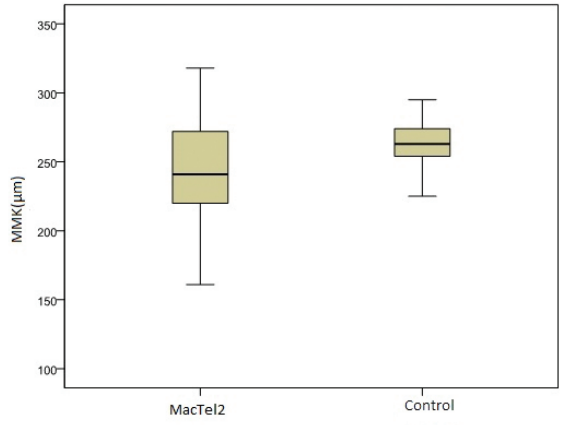

Figure 1. Central macular thickness (CMT) was significantly lower in the MacTel 2 group compared to the control group (p=0.0001)

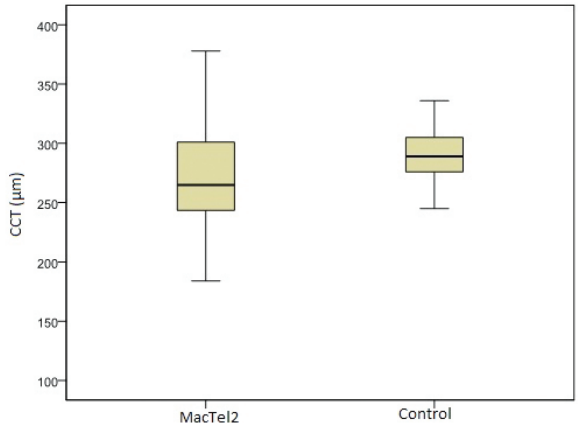

Figure 2. Central choroidal thickness (CCT) was significantly lower in the MacTel 2 group compared to the control group (p=0.014)

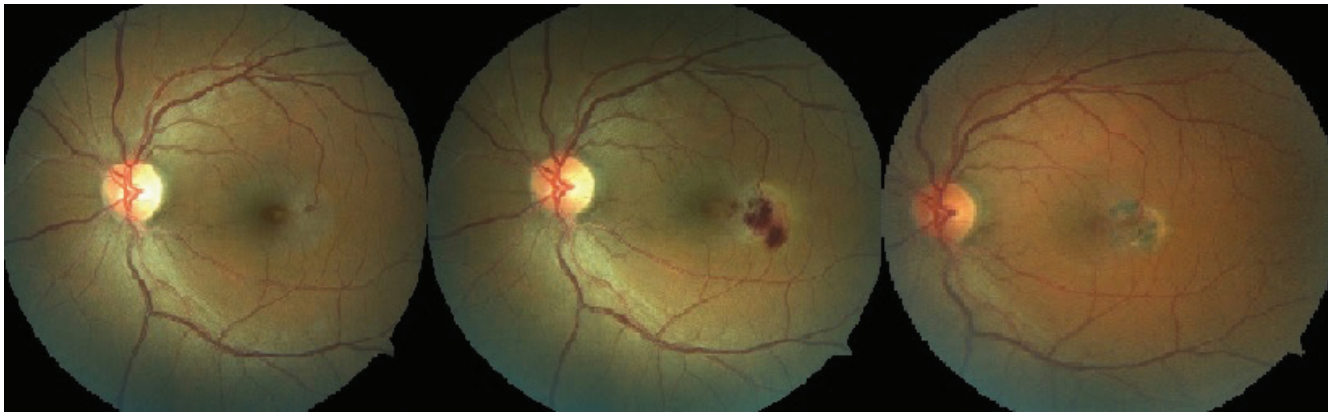

Figure 3. Fundus photograph of the left eye of a 53-year-old female patient showed temporal parafoveal foci of retinal pigment epithelium hyperplasia with foveal pigmentary change (left image). She presented to the clinic with acute vision loss 1 year after the diagnosis (middle image) due to retinal hemorrhages and choroidal neovascularization. The right image was taken after 3 doses of anti-VEGF treatment and shows regression of the macular neovascularization

and control groups was 273.04 µm (range 184-378, median 265) and 289.83 µm (range: 245-336, median: 289), respectively (p=0.014).

The 41 treatment-naive eyes without MNV showed no significant change in BCVA (p=0.058), CMT (p=0.304), or CCT (p=0.062) during follow-up.

Eight eyes of 7 MacTel 2 patients developed MNV during follow-up (Figure 3). All of the patients were treated with intravitreal anti-VEGF injection. Six eyes were treated with intravitreal ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA) and two were treated with aflibercept (Eylea; Regeneron, Tarrytown, New York) (Figure 4a-c). CMT and CCT decreased slightly after treatment but not significantly. Mean CMT before treatment was 252.33 µm (range 216-297, median 250.16) and after treatment 237.33 µm (range 215-254, median 237.33) (p=0.123). Mean CCT before treatment was 279.12 µm (range 210-325, median 285.5) and after treatment 262 µm (range 235-288, median 262) (p=0.123). Best corrected visual acuity improved in 5 eyes, decreased in 2 eyes, and remained the same in 1 eye.

Discussion

MacTel 2 is a neuroretinal degenerative condition with vascular involvement, telangiectasia, and deeper retinal vessel proliferation.[2,7,15] Müller cells play a role in its pathogenesis.[6,15,16] Spectral-domain OCT reveals hyperreflective spots in the external parafoveal retinal layers in the absence of FA findings. These hyperreflective spots are due to nonspecific neurodegenerative development.[17] Late FA leakage occurs before capillary dilation.[2] Gass and Oyakawa[16] also emphasized in their study that retinal fluorescein dyeing occurs before capillary dilation. Central vision loss may occur as a result of photoreceptor atrophy without macular edema.[15] The primary impairment in MacTel 2 is in Müller cells or parafoveal neural cells. The disease does not involve the deep external retinal juxtafoveal capillaries.[15] Late FA leakage is not due to increased retinal vascular permeability but

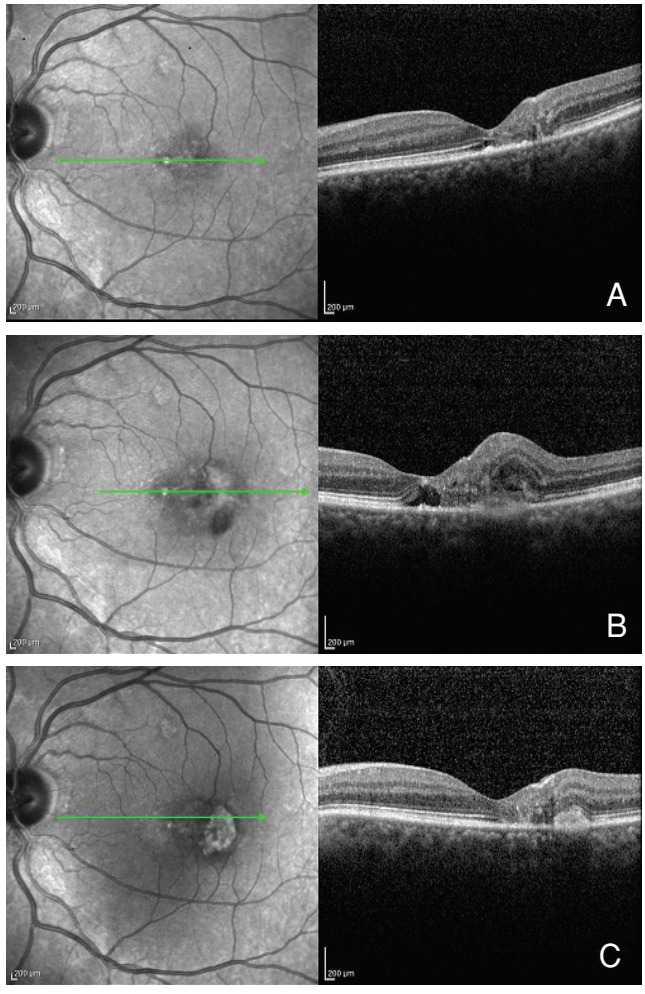

Figure 4. Optical coherence tomography and fundus photographs of the same MacTel 2 patient showing small intraretinal crystalline deposits (A). During follow-up, the patient's vision decreased due to macular neovascular membrane with active choroidal neovascularization (B). After intravitreal anti-VEGF therapy, her macular lesion regressed and the fluid resolved, with improved visual acuity (C)

is a result of damaged retinal cells, intracellular dye diffusion, and extracellular matrix staining.[16,18] Clinicopathologic studies have shown that rod and cone photoreceptors in the central macular area are preserved, whereas Müller cells are reduced.[6]

In patients who develop MNV, the role of VEGF molecules in the pathogenesis continues to be controversial. Yanuzzi et al.[7] proposed that endothelial cell degeneration may be the triggering factor of a vasogenic mechanism without ischemia and inflammation. Some investigators suggested that endothelial cell degeneration may be initiated by Müller cell dysfunction.[19,20] Green et al.[21] emphasized that retinal hypoxia due to endothelial degeneration and capillary structural disruption may increase angiogenesis and VEGF release. Spaide et al.[22] mentioned that retinal-choroidal anastomoses were commonly observed in eyes with MacTel 2 without MNV using projection-resolved OCT angiography. This study suggests MacTel 2 is more than just a neurodegenerative disease with secondary abnormalities, as the choroid may be involved in the disease process.

Although some authors have stated that choroidal thickness did not differ between eyes with MacTel 2 and age-matched healthy subjects,[23,24] in our study we determined that CMT and CCT were lower in the MacTel 2 group compared to the control group in long-term follow-up. This may be due to the neuroretinal degenerative nature of the disease, and MacTel 2 may also include abnormalities involving the choroid, though these are likely minor in comparison to the predominant retinal changes.[22,25] Eight eyes (16.3%) of 7 patients developed MNV. CCT and CMT were reduced in all eyes after anti-VEGF treatment (mean 1.87 injections, range 1-3, median 2). In 5 eyes, vision improved by more than 2 lines.

In another study including 25 eyes of 20 patients with MNV membrane secondary to MacTel type 2, patients received an average of 8.4 injections over 3 years of follow-up.[13] Intravitreal anti-VEGF monotherapy appears to be safe and effective in MacTel 2 patients who develop MNV.

MacTel 2 patients without MNV in our series received no treatment and showed no statistically significant change in BCVA, CMT, or CCT during follow-up. It was reported previously that intravitreal anti-VEGF therapy for macular telangiectasia without MNV was effective in reducing macular thickness but did not improve visual acuity.[26,27,28,29] A recent study indicated that anti-VEGF treatment might even have an adverse effect on the retinal neurodegenerative process in patients with nonproliferative MacTel 2 because of VEGF's role in the maintenance of cones and Müller cells.[30]

Study Limitations

The most important limitations of our study are that it was retrospective and included a small number of patients.

Conclusion

Patients with MacTel 2 must be closely monitored for the development of MNV. To date, there is no evidence for effective treatment of nonproliferative MacTel 2.[30,31] We prefer follow-up without treatment for patients who have not developed MNV to avoid potential adverse effects. Intravitreal anti-VEGF therapy may be beneficial for patients with proliferative MacTel 2 and declining visual acuity.[31]

Ethics

Ethics Committee Approval: Baskent University Medicine Faculty (KA 19/63).

Informed Consent: Obtained.

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Authorship Contributions

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Original Article

Effects of Upper Eyelid Surgery on the Ocular Surface and Corneal Topography

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Abstract

Objectives: To evaluate the effect of upper eyelid surgery on ocular surface and corneal topography.
Materials and Methods: Patients who underwent upper eyelid blepharoplasty and/or blepharoptosis repair were evaluated prospectively. Tear film break-up time (TBUT), Schirmer tests, corneal staining pattern, Ocular Surface Disease Index questionnaire, corneal topography, and autorefractor parameters were measured preoperatively and at 1 day, 1 week, 1 month, 3 months, and 6 months postoperatively.
Results: Thirty-two eyes of 20 patients (9 male, 11 female) were included in the study. The mean age was 44.8±18.9 years (range: 8-74). Patients were divided into the following 3 groups according to the type of surgery performed: upper eyelid blepharoplasty (group 1), upper eyelid blepharoplasty and levator advancement ptosis surgery (group 2), and levator advancement ptosis surgery (group 3). There was a significant decrease in Schirmer test results at 6 months in groups 1 and 2 but no change in group 3. TBUT values were decreased at 1 week in group 3 ($p=0.028$) and returned to baseline at 1 month. Corneal punctate staining was detected at 1 day and 1 week in all groups. On corneal topography, group 3 showed a significant change in K2 values (0.3 diopters) at 1 month ($p=0.006$). There was no statistically significant change in autorefractor measurements postoperatively compared to preoperative values ($p>0.05$).
Conclusion: Depending on the type of surgical procedure performed, blepharoptosis repair and upper eyelid blepharoplasty can lead to dry eye of varying severity that may persist at postoperative 6 months.
Keywords: Blepharoptosis, dry eye syndrome, corneal topography, blepharoplasty

Introduction

Blepharoptosis and dermatochalasis are common upper eyelid diseases that cause anatomic and functional impairment. Although upper eyelid surgery provides successful anatomic results, dry eye and irritative symptoms can also develop postoperatively.

Upper eyelid surgery can lead to postoperative dry eye symptoms by affecting other anatomical structures in the eyelid, such as the lacrimal gland, auxiliary tear glands, meibomian glands, and the orbicularis muscle, thereby negatively impacting tear production. Studies have reported that upper eyelid blepharoplasty and blepharoptosis repair cause dry eye symptoms and ocular irritation symptoms in patients postoperatively, but these symptoms regress within a few days or a few weeks after surgery.[1,2,3,4]

Pressure exerted by the eyelids causes flattening of the peripheral cornea and steepening in the central cornea, which can

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result in alterations in with-the-rule astigmatism.[5] It is known that hemangioma, gold implants, and lesions such as dermoid cysts in the eyelids can affect the shape of the cornea.[5] Studies have also evaluated the effects of upper eyelid surgery on corneal topography.[6,7,8,9,10,11]

The aim of the present study was to evaluate the early and late effects of different surgical interventions for blepharoptosis and dermatochalasis on the ocular surface and corneal topography.

Materials and Methods

This prospective study included 32 eyes of 20 patients with no previous surgical history or concomitant ocular disease who underwent surgery for ptosis and/or dermatochalasis in the oculoplastic surgery clinic of the İstanbul University Department of Ophthalmology between April 2014 and June 2014.

All patients in the study provided informed consent and ethical approval was obtained from the faculty ethics committee.

The patients underwent a full ophthalmologic examination including best corrected visual acuity, intraocular pressure measurement, biomicroscopic examination, and fundus examination.

Surgical technique was selected according to the patients' levator function (LF) and the coexistence of dermatochalasis with ptosis. LF was determined by asking the patient to look up and down while pressing on the brow and measuring the excursion of the upper eyelid margin. A distance ≤5 mm was regarded as poor, 6-11 mm as fair, and ≥12 mm as good LF.[12] Frontal suspension surgery was planned for patients with poor LF, and levator resection was planned for patients with fair to good LF (>5 mm). Upper eyelid blepharoplasty was performed alone or in combination with levator resection in patients with dermatochalasis depending on whether they had concomitant ptosis.

In terms of dry eye, patients were evaluated using anesthetized and unanesthetized Schirmer tests, tear film break-up time (TBUT), corneal staining pattern according to the Oxford scale, and the Ocular Surface Disease Index (OSDI) questionnaire. OSDI scores of 0-12 were interpreted as the absence of ocular surface disease, 13-22 as mild, 23-32 as moderate, and 33-100 as severe ocular surface disease.[13]

Schirmer tests were performed by placing Schirmer strips (Tearstrip, Contacare, India) in the outer third of the lower lid fornix, with and without topical anesthesia (Alcaine 0.5%, Alcon, Turkey), and measuring the distance wetted in millimeters after 5 minutes. Results of ≤10 mm/5 min for the unanesthetized Schirmer test and ≤5 mm/5 min for the anesthetized Schirmer test were considered abnormal.[14]

Corneal and conjunctival staining patterns were graded using the Oxford scale by asking the patient to blink several times after staining the ocular surface with a fluorescein strip (Fluostrips, Netherlands). Staining was rated as absent (0), minimal (1), mild (2), moderate (3), marked (4), or severe (5) according to the Oxford scale.[15]

TBUT was measured after instilling fluorescein dye as the time between the last blink and the first break in the dye on the cornea under biomicroscopic examination at x10 magnification with cobalt blue filter.[16] A TBUT <5 s was interpreted as suggestive of dry eye.[17]

Autorefractometry and corneal topography (Oculus Pentacam HR) measurements were obtained to measure the patients' refractive changes. The mean of 3 autorefractometer readings was recorded. Corneal topography was evaluated in a single measurement with high scan quality obtained after the patient blinked twice. All assessments and complete ophthalmological examination were performed preoperatively and repeated at postoperative 1 day, 1 week, 1 month, 3 months, and 6 months.

The patients were divided into 3 groups according to the surgery performed: upper eyelid blepharoplasty (group 1), upper eyelid blepharoplasty and levator resection (group 2), and levator resection (group 3). Within each group, ocular surface and refractive changes at postoperative 1 day, 1 week, 1 month, 3 months, and 6 months were evaluated by comparing with preoperative values. Changes in refractive values of 0.2 D or greater were considered clinically significant because they may cause noticeable visual complaints.[5]

Statistical Analysis

All results were statistically analyzed using SPSS software (version 21.0, IBM Corp, Armonk, NY, USA). Results were compared using the nonparametric Friedman test, and those with significant results in the Friedman test were evaluated by post-hoc analysis. In the statistical analysis, p values of <0.05 were regarded as significant, <0.001 as highly significant, and >0.05 as insignificant.

Results

Thirty-two eyes of 20 patients were included in the study. There were 11 female patients and 9 male patients, and the mean age was 44.8±18.9 years (range, 8-74). Twelve patients underwent bilateral surgery and 8 underwent unilateral surgery.

According to the surgery performed, 12 eyes were included in group 1, 8 eyes in group 2, and 12 eyes in group 3.

Table 1 shows the comparison of pre- and postoperative unanesthetized Schirmer test values within the groups. In group 2, values were lower at all postoperative visits compared to preoperative values, with statistically significant decreases at postoperative 1 day, 1 week, and 6 months (p=0.006, p=0.025, and p=0.003, respectively). There were no significant postoperative changes in groups 1 or 3 (p>0.05).

The comparison of the groups' pre- and postoperative anesthetized Schirmer test results is shown in Table 2. In group 1, there was no significant change compared to preoperative measurements, although the change between postoperative 1 day and 3 months was statistically significant (p=0.008). In group 2, all postoperative values were lower than preoperative values, with significant decreases at 1 day, 1 month, and 6 months (p=0.013, p=0.008, and p=0.001, respectively). In group 3,

we detected no significant difference between preoperative and postoperative measurements (p>0.05).

Changes in corneal punctate staining patterns according to the Oxford scale observed in the operated eyes are shown in Table 3. Corneal punctate staining was not observed in any eye preoperatively, while eyes in all groups exhibited corneal punctate staining of varying severity according to the Oxford scale at postoperative 1 day and 1 week. In group 2, corneal punctate staining persisted at 6 months.

Table 4 shows the comparison of preoperative and postoperative TBUT values within the groups. There was no statistically significant change in postoperative TBUT compared to preoperative values in groups 1 and 2. In group 3, TBUT was significant decreased at postoperative 1 week when compared with preoperative values (p=0.028) but returned to the preoperative level at postoperative 1 month.

Table 5 shows the comparison of preoperative and postoperative OSDI scores within the three groups. Although none of the patients were diagnosed with dry eye preoperatively, their preoperative OSDI questionnaire scores indicated mild, moderate, and severe ocular surface disease in 3, 3, and 9 patients, respectively, while the other 5 patients had no ocular surface disease. Postoperative OSDI scores decreased in group 1 but not significantly (p>0.05), while significantly decreases were observed in groups 2 and 3 at postoperative 6 months compared to preoperative values (p=0.005 and p=0.012, respectively).

Table 1. Comparison of pre- and postoperative unanesthetized Schirmer test results (mm/5 min) within the surgical groups

Unanesthetized Schirmer test	Group 1 mean ± SD	p value	Group 2 mean ± SD	p value	Group 3 mean ± SD	p value
Preop	24±8	0.053	18±3	0.001	22±8	0.732
Postop 1 day	22±7.7		11±5.2[a]		25±10.4	
Postop 1 week	19±8		9±6[b]		23±9	
Postop 1 month	23±8		11±6		23±7	
Postop 3 months	19±9		11±6		20±6	
Postop 6 months	25±9		11±6[c]		18±8	

Preop: Preoperative. Postop: Postoperative. SD: Standard deviation
[a]The difference between preoperative and postoperative 1 day values was significant in post-hoc analysis (p=0.006).
[b]The difference between preoperative and postoperative 1 week values was significant in post-hoc analysis (p=0.025).
[c]The difference between preoperative and postoperative 6 months values was significant in post-hoc analysis (p=0.003).

Table 2. Comparison of pre- and postoperative anesthetized Schirmer test results (mm/5 min) within the surgical groups

Unanesthetized Schirmer test	Group 1 mean ± SD	p value	Group 2 mean ± SD	p value	Group 3 mean ± SD	p value
Preop	20±6	0.041	15±3	0.001	13±7	0.716
Postop 1 day	17±6.2		6±5.6[b]		14±7.2	
Postop 1 week	14±7		8±6		15±8	
Postop 1 month	16±7		8±5[c]		17±7	
Postop 3 months	13±6[a]		10±4		14±7	
Postop 6 months	16±6		6±6[d]		11±7	

Preop: Preoperative, Postop: Postoperative, SD: Standard deviation
[a]The difference between postoperative 1 day and 3 months values was significant in post-hoc analysis (p=0.008).
[b]The difference between preoperative and postoperative 1 day values was significant in post-hoc analysis (p=0.013).
[c]The difference between preoperative and postoperative 1 month values was significant in post-hoc analysis (p=0.008).
[d]The difference between preoperative and postoperative 6 months values was significant in post-hoc analysis (p=0.001).

Table 3. Change in corneal punctate staining patterns in the surgical groups (n = number of eyes)

Corneal punctate staining	Group 1 (n=12)	Group 2 (n=8)	Group 3 (n=12)
Preop	0	0	0
Postop 1 day	1	5	3
Postop 1 week	2	6	3
Postop 1 month	0	4	0
Postop 3 months	0	4	1
Postop 6 months	0	3	0

Preop: Preoperative, Postop: Postoperative

When autorefractometric spherical values were examined, none of the groups showed a significant change in postoperative spherical values compared to preoperative values (p>0.05). In group 1, spherical values were decreased at 1 week (mean 0.88±0.71 D) and increased at 3 months (mean 1.25±0.73 D) when compared with preoperative values (mean 1±0.70 D), with a significant difference between 1 week and 3 months (0.37 D change, p<0.05).

"The postoperative autorefractometric cylindrical values of the surgical groups are shown in Table 6. Compared to preoperative values, autorefractometric cylindrical values showed changes of 0.25 D starting from postoperative day 1 in group 1, at postoperative 1 week and 1 month in group 2, and at postoperative 1 day in group 3, but the differences were not statistically significant (p>0.05). Cylindrical axis values increased by 10° or more at postoperative 1 month in group 1, at 6 months in group 2, and starting from 1 week in group 3, but the differences were not statistically significant (p>0.05).

The surgical groups' postoperative keratometric values (K1, K2) on corneal topography were compared with preoperative values. Compared to preoperative values, K1 changed by 0.2 D or more at postoperative 1 day in group 1, from postoperative 1 month in group 2, and at postoperative 1 month in group 3, but the differences were not statistically significant (p>0.05). K2 values in groups 1 and 2 did not change by 0.2 D or more or show any statistically significant differences. In group 3, K2

Table 4. Comparison of pre- and postoperative tear film break-up time (TBUT) measurements within the surgical groups

TBUT (s)	Group 1 mean ± SD	p value	Group 2 mean ± SD	p value	Group 3 mean ± SD	p value
Preop	10±3	0.086	6±3	0.074	8±2	**0.001**
Postop 1 day	9.5±2.8		4.5±2.9		6.5±3.3	
Postop 1 week	10±4		5±4		5±2[a]	
Postop 1 month	10±3		5±4		8±2	
Postop 3 months	9±3		6±3		9±2	
Postop 6 months	10±2		6±4		8±2	

Preop: Preoperative, Postop: Postoperative, SD: Standard deviation
[a]The difference between preoperative and postoperative 1 week values was significant in post-hoc analysis (p=0.028).

Table 5. Comparison of pre- and postoperative Ocular Surface Disease index (OSDI) scores within the surgical groups

OSDI score	Group 1 median (min-max)	p value	Group 2 median (min-max)	p value	Group 3 median (min-max)	p value
Preop	23.9 (2.1-68.1)	0.208	53 (8.3-58.3)	**0.021**	32.3 (0-77.3)	**0.024**
Postop 1 day	4.2 (0-79.5)		56.3 (4.2-64.6)		19.5 (4.6-63.6)	
Postop 1 week	3.1 (0-84.1)		35.3 (6.3-77.1)		14 (0-68.2)	
Postop 1 month	13.5 (0-83.3)		20.4 (2.1-70.1)		12.5 (0-50)	
Postop 3 months	17.7 (2.1-79.2)		28.4 (0-70.8)		15.9 (0-40.9)	
Postop 6 months	6.3 (2.1-95.5)		12.5 (2.1-64.6)[a]		9.5 (0-40.9)[b]	

Preop: Preoperative, Postop: Postoperative, SD: Standard deviation
[a]The difference between preoperative and postoperative 6 months values was significant in post-hoc analysis (p=0.005).
[b]The difference between preoperative and postoperative 6 months values was significant in post-hoc analysis (p=0.012).

Table 6. Comparison of pre- and postoperative autorefractometric cylindrical values within the surgical groups

Cylindrical values (D)	Group 1 mean ± SD	p value	Group 2 mean ± SD	p value	Group 3 mean ± SD	p value
Preop	-0.50±1.12	0.284	-1.13±0.28	0.777	-0.88±0.73	0.716
Postop 1 day	-0.75±1.08		-1.13±0.49		-1.13±0.91	
Postop 1 week	-0.75±1.08		-0.88±0.30		-0.88±1.23	
Postop 1 month	-0.75±1.04		-0.75±0.53		-0.88±0.64	
Postop 3 months	-0.75±1.19		-1.13±0.52		-0.75±0.47	
Postop 6 months	-0.75±1.23		-1±0.40		-0.75±0.74	

D: Diopters, Preop: Preoperative, Postop: Postoperative, SD: Standard deviation

values changed by 0.2 D or more compared to preoperative values starting at postoperative 1 week, with a statistically significant difference (0.3 D) at postoperative 1 month compared to the preoperative values (p=0.006).

Discussion

Upper eyelid blepharoplasty and blepharoptosis repair are known to cause dry eye symptoms and ocular irritation findings in the postoperative period.[1,2,3,4]

Black et al.[18] determined that there was a temporary reduction in eyelid sensation after upper eyelid surgery and attributed this decrease to damage to the trigeminal nerve branches that receive sensation from the upper eyelid during incision and dissection. In addition to direct nerve damage, it is also known that ocular surface sensation can be diminished because of proinflammatory cytokines and opioid peptides, which increase as a result of inflammation.[19,20] Reduced ocular surface sensation results in decreased tear production.[19]

In a study evaluating ocular surface sensation and tear production in patients who underwent upper eyelid blepharoplasty or blepharoptosis repair, Kim et al.[3] reported that ocular surface sensation was reduced in all patients at postoperative 1 day and returned to preoperative values at 1 month. Contrary to other studies, they observed an increase in Schirmer test results at postoperative 1 month. Yan et al.[21] also reported an increase in Schirmer 1 and noninvasive TBUT measurements 1 week after upper eyelid blepharoplasty in young patients. Unculu et al.[4] prospectively evaluated dry eye parameters in 11 patients who underwent transcutaneous levator resection and found a significant decrease in Schirmer 1 test values at postoperative 1 month.

In the present study, we detected no significant change in postoperative Schirmer test results in the group that underwent only levator surgery. The statistically significant decrease observed in the blepharoplasty group suggests a mechanism associated with the orbicularis muscle. Orbicularis muscle excision is believed to weaken the orbicularis muscle, reduce the blinking reflex, and decrease corneal sensation and tear secretion due to damage to trigeminal nerve branches, resulting in a decrease in basal and reflex tears. Zloto et al.[22] performed upper eyelid blepharoplasty without orbicularis muscle excision and observed no change in objective and subjective dry eye parameters when preoperative and postoperative tests were compared. This supports the hypothesis regarding the role of the orbicularis muscle in the development of dry eye. In addition, the decrease in Schirmer test values observed at postoperative 1 day may be associated with a reduction in corneal sensitivity caused by proinflammatory cytokines and opioid peptides.

In previous studies with short-term postoperative follow-up, it was reported that dry eye findings appeared in the early postoperative period but resolved within a few weeks or months.[1,21,23] Demirok et al.[24] evaluated late Schirmer test, TBUT, and OSDI values in 81 patients who were followed for at least 6 months after upper eyelid blepharoplasty and compared them with preoperative values. They reported no change in Schirmer test and OSDI scores but a statistically significant decrease in TBUT values at postoperative 6 months and beyond. However, no change in TBUT values was observed after upper eyelid blepharoplasty in two studies by Shao et al.[23] and Soares et al.[25] Unculu et al.[4] also detected no change in TBUT after levator resection surgery.

In contrast to these studies, we found that TBUT was significantly decreased at postoperative 1 week and returned to preoperative values after postoperative 1 month in the group that underwent only levator surgery. We thought that TBUT, which is associated with tear film stability, may have been temporarily reduced as a result of decreased blinking reflex, insufficient blinking, and transient meibomian gland dysfunction caused by perioperative local anesthetics and postoperative inflammation, but this effect was not observed in all groups.

Unlike previous studies, the patients in our study were followed up at regular intervals until postoperative 6 months, and the significant reduction in Schirmer test results and corneal punctate staining at postoperative 6 months demonstrated that dry eye findings persisted in the postoperative long term.

A study by Vold et al.[26] showed that patients with dermatochalasis developed subjective dry eye symptoms that regressed after upper eyelid blepharoplasty. Yan et al.[21] reported that the postoperative OSDI scores of patients who underwent upper eyelid surgery changed significantly postoperatively, independent of dry eye findings. Similar to the study conducted by Vold et al.[26], we observed in this study that none of the patients had preoperative dry eye signs, but their OSDI scores suggested the presence of subjective dry eye symptoms. In our study, the decrease in OSDI scores at postoperative 6 months in the combined surgery and levator surgery groups was not correlated with Schirmer test results, consistent with the study by Yan et al.[21], and we thought the decrease in OSDI may have been related to postoperative patient satisfaction.

Studies have also evaluated the effects of upper eyelid surgery on corneal topography.[5,6,7,8,9,10,11,27] In a study by Zinkernager et al.[5], patients undergoing surgery for dermatochalasis or ptosis were divided into three groups according to the surgery performed: ptosis repair by levator surgery, blepharoplasty performed with skin-only removal, and blepharoplasty with skin and fat pad removal. At postoperative 3 months, they detected astigmatic changes of 0.19 D in the blepharoplasty with fat pad reduction group and 0.25 D in the ptosis repair by levator surgery group, while no statistically significant change was detected in the astigmatic axis. In the study, astigmatic changes of 0.2 D or greater were considered clinically significant because based on the authors' experience, changes of this magnitude could affect visual acuity and be noticed by the patient.

In a study by Brown et al.[27] evaluating blepharoplasty and ptosis surgeries, patients in the ptosis group had a mean change of 0.6 D, with 30% having changes greater than 1 D. In the blepharoplasty group, keratometry showed a mean change of 0.55 D, and only 11% of patients had a change greater than 1 D.

Mean astigmatic change after upper eyelid blepharoplasty was reported as 0.22 D in a study by Altin Ekin et al.[8] and 0.15 D in a study by Simsek et al.[9] Savino et al.[7] examined corneal topographic changes after ptosis surgery and found a change of 0.15 D in mean keratometry values, 0.26 D in astigmatism, and 10° in mean axis values. On the other hand, Dogan et al.[10] reported detecting postoperative changes only in K2 values after upper eyelid blepharoplasty, with no changes in other keratometric values.

Unlike other studies, we evaluated autorefractometric measurements in addition to corneal topography in the present study. We detected no significant postoperative changes in autorefractometric spherical and cylindrical values compared to preoperative values. As observed by Dogan et al.[10] in patients undergoing upper eyelid blepharoplasty, the only significant difference in corneal topography was a change of 0.3 D in K2 values at postoperative 1 month in the group undergoing levator surgery, but this change did not persist at postoperative 3 and 6 months. Similar to the studies by Dogan et al.[10] and Nalcı et al.[11], we detected no other significant postoperative changes in other keratometric values.

Previous studies have suggested that upper eyelid surgery changes the pressure exerted by the eyelid on the cornea and that the resulting change in cornea shape may cause refractive changes.[5,7,8] However, as these patients were evaluated at a single postoperative visit, it is not clear whether the refractive changes persisted at later visits. Şimşek et al.[9] assessed corneal topography at postoperative 1 and 3 months and detected astigmatic changes at both time points. In our study, patients were followed up until postoperative 6 months, and although the group undergoing levator surgery showed a change at postoperative 1 month, we observed no astigmatic changes at subsequent visits, leading us to conclude that upper eyelid surgery did not permanently alter corneal topography. As studies have yielded different results regarding the effect of upper eyelid surgery on corneal keratometric values, further studies with larger patient groups are needed.

Study Limitations

Although we prospectively evaluated the effects of different upper eyelid surgeries on corneal topography and the ocular surface, prospective studies with larger patient samples are needed because of the small number of patients included in this study. In addition, although our follow-up period was longer than in previous studies, even longer postoperative follow-up to evaluate whether dry eye findings are temporary would further contribute to the literature.

Conclusion

Depending on the surgical procedure performed, ptosis surgery and upper lid blepharoplasty can lead to dry eye of varying severity that may persist at postoperative 6 months. Assessment of corneal topography in patients who underwent upper eyelid surgery showed that levator surgery could cause temporary refractive changes, whereas upper eyelid blepharoplasty was not associated with postoperative keratometric change.

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Ethics

Ethics Committee Approval: Approval for the study was obtained from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine. (approval number: 09, date: 09.05.2014).

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Authorship Contributions

Surgical and Medical Practices: N.A.C., B.Y., Concept: N.A.C., B.Y., Design: N.A.C., B.Y., Data Collection or Processing: N.A.C., Analysis or Interpretation: N.A.C., B.Y., Literature Search: N.A.C., Writing: N.A.C.

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Review

The Effects of Space Radiation and Microgravity on Ocular Structures

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Abstract

Long-term exposure to microgravity and space radiation leads to physiological and pathological changes in human biology. Pathological neuro-ocular changes are collected under the name spaceflight-associated neuro-ocular syndrome. This review examines studies on the effects of microgravity and space radiation on the ocular structures and their results. In addition, we discuss treatment methods and hypotheses to reduce the effects of microgravity and space radiation on biological structures.
Keywords: Space radiation, microgravity, spaceflight-associated neuro-ocular syndrome, artificial gravity

Introduction

The space race began on October 4, 1957, when the Soviet Union (USSR) launched the artificial satellite Sputnik 1, followed soon after by the first animal and manned flights. At present, space studies continue on the International Space Station (ISS), which was built by joining modules brought together in a collaborative project by the United States National Aerospace Agency (NASA), Russian Federal Space Agency (Roscosmos), European Space Agency (ESA), Canadian Space Agency (CAS-ASC), and Japan Aerospace Exploration Agency (JAXA). The ISS is an artificial satellite in low Earth orbit that can be inhabited by humans. Thanks to the ISS, the number of long-duration spaceflights such as low orbit flights and Moon missions is increasing. This has also increased the number of people exposed to space conditions. Space studies have revealed several problems that affect human biology, such as low gravity, lack of atmosphere, galactic cosmic rays (GCR), and solar energetic particles (SEP).[1] Microgravity (MG) and space radiation constitute a major part of these problems. Solutions to these and many other problems are necessary to enable human beings to explore the solar system and beyond.

GCR and SEP are an important problem affecting manned space missions. GCR consist of high-energy protons, high-energy ions, neutrons, gamma and x-rays, and secondary particles formed as a result of particles colliding with spacecraft and human tissues. These rays cause molecular bond breaks and mutations in DNA, resulting in cell damage, tumors and tissue degeneration, cataract, heart disease, central nervous system damage, and acute radiation syndrome.[2] The effects of radiation on human tissues can be investigated by examining dosimetric results in people with occupational radiation exposure on Earth and those participating in space missions, as well as radiation dose information obtained from robotic exploration tools sent to planets for research purposes. However, all of these are indirect assessments. It should be noted that the detectors are silicone

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in structure. The annual radiation dose limit for people with occupational radiation exposure on Earth is 50 millisievert (mSv).[3] Although the ISS is slightly protected by Earth's magnetic field, the level of radiation exposure for humans in the station was measured as approximately 200 mSv per year.[4] According to data obtained by the radiation assessment detector on the Curiosity space probe sent to Mars, the approximate dose of radiation exposure incurred during the roundtrip flight to Mars (2x180 days) and 500 days on the Mars surface was calculated as 1.01 Sv.[5] Radiation exposure on the surface of Mars is greater than on Earth because Mars has a thin atmosphere and no global magnetic field to deflect energy-laden particles. According to results obtained in the Chinese Chang'e 4 robotic mission to the Moon's Von Kármán crater, the daily GCR dose on the Moon's surface was found to be 2.6 times higher than the daily exposure on the ISS.[6] Epidemiological data indicate that exposure to 1 Sv of radiation increases the likelihood of cancer development by 5.5%.[4] In this case, long-duration deep space missions are many times over the current physiological limits. Therefore, solutions must be developed to protect crew members from space radiation.

Table 1 shows the upper limits for space radiation exposure of tissues and organs determined by the International Commission on Radiological Protection.[7]

Effects of Space Radiation on the Eye

Phosphenes

Astronauts in the Apollo program, a crewed lunar landing project conducted between 1961 and 1975, noticed flashes of light (phosphenes) in their eyes during deep space missions. Flashes of light have also been reported by astronauts working on the ISS. Research revealed that these phosphenes were the result of GCR and SEP stimulating the retina, optic nerve, and occipital cortex.[8,9,10] Similar phosphenes are seen in ocular oncology and in radiotherapeutic interventions applied to the head and neck region.[11] In addition, cosmic rays entering at certain angles can interact with the vitreous and cause bright blue phosphenes through the Cherenkov effect.[12] While few astronauts have seen this type of phosphene, the more commonly seen phosphenes are those that appear as moving or static white dots or lines.[13,14] Chemical luminance due to radiation-induced lipid peroxidation around photoreceptors has been shown to form bioluminescent photons.[15]

Cataract Development

Mutations in the genes that control the transparency of the intraocular lens[16] lead to the development of apoptosis cataracts in the germinal zone cells that provide crystalline lens transparency.[17] Due to the high radiation doses involved in deep space travel, studies are being conducted on the effects of low- and high-dose radiation exposure on the crystalline lens. According to results from phase 2 of the two-phase, 5-year NASA Study of Cataract in Astronauts (NASCA), cortical cataract progression rate was associated with space radiation dose. However, there was no relationship between space radiation and nuclear or posterior subcapsular cataract.[18]

In a cohort study in which radiologic technologists exposed to low-dose radiation (<100 mGy) were followed for an average of 12.4-13.1 years, it was determined that the risk of cataract development increased but not the risk of cataract surgery.[19] Cortical cataract can cause glare and reduce visual acuity. Therefore, further studies with longer follow-up periods are needed to understand the effects of space radiation on cataract development.

Effects of Microgravity on Ocular Tissues

Gravity is a natural phenomenon that causes one object to move toward another. Despite the general belief that space is devoid of gravity, some degree of gravity is present everywhere in space. Gravity is the force that keeps the Moon in orbit around the Earth, the Earth in orbit around the Sun, and the Sun in its place in the Milky Way galaxy. The ISS orbits the Earth at a distance of 400 km and a speed of approximately 27,743 km/h. At this altitude, gravity is 90% of that present on the Earth's surface. The reason the ISS does not crash to the Earth despite being subjected to 90% of Earth's gravity is the high speed at which it travels in orbit. As all objects in Earth's orbit are in a state of continuous free fall, the effect of gravity is not felt. However, internal stress caused by tidal forces is not zero, as this only happens in the complete absence of gravity. The term MG refers to a free-fall state with very small tidal effects associated with gravity.

Due to the high cost of conducting all biological studies in an MG environment, various methods are used to create a similar environment on Earth. These methods include dry immersion, wet immersion, unilateral lower-extremity limb suspension, head-down tilt (HDT), supine bed rest, and Einstein's elevator, with HDT believed to best simulate the MG-induced cephalad fluid shift.[20]

Table 1. NASA and ESA dose limits

Organ	30 days	1 year
Central nervous system	500 mGy	1000 mGy
Eye	0.5 Sv	1 Sv
Circulatory system	250 mGy-Eq	500 mGy-Eq
Blood-forming organs	0.25 Sv	0.5 Sv
Skin	1.5 Sv	3 Sv

NASA: National Aeronautics and Space Administration, ESA: European Space Agency, mGy: milligray, Sv: sievert

MG has serious adverse effects on human physiology. The cardiovascular and musculoskeletal systems are particularly affected. On Earth, blood pressure is higher in the legs and feet because of gravity. However, hydrostatic pressure disappears in the MG environment. As a result, arterial pressure equalizes throughout the body. In addition, within a few minutes of MG exposure, approximately 2 liters of blood shifts from the lower part of the body to the cephalic region.[21] At 1*g*, cephalic arterial pressure is lower (approximately 70 mmHg), while the blood pressure in the feet is higher (approximately 200 mmHg). In the early stage of adaptation to the MG environment, redistribution causes an increase in central blood volume. As a result, blood pressure in the upper parts of the body increases, heart rate decreases due to stimulation of neck baroreceptors, vasodilation is observed, and mean arterial pressure decreases.[22] In addition, MG causes facial edema, diuresis, reduced plasma volume, osteoporosis, sarcopenia, and kidney stones.[21,23,24]

Another important problem caused by MG is vision problems detected in astronauts participating in space flights. This phenomenon increases as the duration in space increases. Changes in visual function in astronauts were first reported in the Mercury, Gemini 5, and Gemini 7 missions, and research on the cause of this problem was immediately undertaken because of its impact on astronauts' health and missions.[9]

Some astronauts who participated in long-duration spaceflights had neuro-ocular structural and functional changes such as decreased visual performance, increased hypermetropic refractive error (+0.5 to +1.75 D), papillary edema, cotton-wool spots, posterior globe flattening and choroidal folds on orbital magnetic resonance imaging (MRI) and ultrasound (US), and retinal nerve fiber layer thickening on optical coherence tomography (OCT).[25] The condition involving these findings was later named spaceflight-associated neuro-ocular syndrome (SANS). Here again, we would like to point out that cases referred to as SANS were observed in people who had returned to Earth after spaceflight and were examined at a gravitational force of 1*g*. As the signs were similar to those of terrestrial idiopathic intracranial hypertension (IIH), lumbar puncture (LP) was performed and demonstrated borderline elevation in cerebrospinal fluid (CSF) pressure.[25] However, the reported intracranial pressure values were the result of LP performed some time after the astronauts returned to Earth. This may actually make an elevated intracranial pressure seem lower. Therefore, research is being done on methods that can be applied and provide CSF pressure measurement in space.

Although there are some similarities between IIH and SANS, there are also differences between the two conditions. For example, none of the astronauts reported complaints of pulsatile synchronized tinnitus, diplopia, or chronic headache. Although some astronauts described a mild headache thought to be associated with space adaptation syndrome, these headaches are not similar to those seen in IIH. In addition, none of the astronauts had a history of obesity or the use of drugs that cause elevated intracranial pressure. While cotton wool spots are seen around the optic nerve in IIH, they can also be widely distributed on the retina in SANS. Papillary edema associated with IIH is bilateral, whereas in SANS it is unilateral or bilateral and markedly asymmetric.[26] On orbital US, OCT, MRI, and computed tomography, posterior globe flattening and CSF accumulation in the subarachnoid space are more prominent in SANS than in IIH.[26,27,28] Posterior globe flattening is accompanied by choroidal folds. A study examining the types of folds seen in IIH showed that choroidal folds the least common.[29] However, choroidal folds are frequently seen in SANS. The choroidal folds seen in SANS may be associated with anterior deformation (toward the vitreous) of the peripapillary retinal pigment epithelium/Bowman's membrane layer due to optic disc edema or, as Newell hypothesized, increased choriocapillaris layer thickness and adhesions between the choriocapillaris and Bruch's membrane.[30] We believe this is why the choroidal folds cannot regress despite resolution of the optic disc edema.

Various studies have demonstrated an increase in intraocular pressure with acute exposure to simulated and actual MG environments.[31,32] Later in flight it was observed that intraocular pressure approached normal, pre-flight levels. Causes of this increase in intraocular pressure following acute exposure may include increased choroidal thickness, increased episcleral venous pressure, and narrowing of the anterior chamber angle.[33,34,35,36] The reduction in intraocular pressure with chronic exposure may be attributable to an increase in compensatory aqueous humor drainage and a decrease in aqueous humor synthesis due to dehydration.[34,37]

Theories Regarding the Pathogenesis of SANS

The first proposed theory is that intracranial pressure is increased due to the displacement of blood from the legs to the cephalic region during long-duration space flights. On Earth, CSF is secreted from the choroid plexus and drains into low-pressure cervical venous vessels. Although vascular autoregulation stabilizes cerebral and optic nerve head artery diameters, cerebral and jugular venous distension has been demonstrated in HDT and MG environments.[38] A Doppler study conducted in the MG environment showed retrograde internal jugular venous flow, which was reported to predispose to thrombus formation.[39] Reduced drainage of CSF into the venous system due to spaceflight and cerebral venous expansion and CSF displacement into the intracranial compartment may increase intracranial pressure, and this pressure increase may be transferred to the optic nerve sheath and lead to optic nerve sheath expansion. This can result in axoplasmic flow stasis and globe flattening, which also occurs in terrestrial IIH. The modest increase in CSF pressure (28-28.5 cmH_2O) observed in some astronauts may support this hypothesis. Other risk factors for elevated CSF pressure are resistance exercises, increased carbon dioxide (CO_2) level in the environment, high salt consumption, and vascular hyperpermeability due to low levels of folate, which regulates nitric oxide (NO) release associated with defects in the vitamin B-12-dependent 1-carbon transfer pathway.[40,41]

There are several findings that may contradict the hypothesis of MG-induced CSF pressure elevation. No astronauts have

experienced chronic severe headache, temporary vision obscurations, or diplopia. Although typical headache symptoms are common in terrestrial IIH, complaints of headache are less common in ISS astronauts and the pain differs from that described in IIH. Temporary vision obscuration occurs at a rate of 68% in terrestrial IIH, whereas no such complaint has been reported in SANS to date. Similarly, diplopia can be seen in 30% of patients with terrestrial IIH but has never been observed in SANS.[42]

Patients with terrestrial IIH usually exhibit bilateral papillary edema; unilateral papillary edema occurs at a rate of only 3-10%.[42,43] In a study of 5 astronauts who participated in long-duration spaceflight, it was observed that optic disc edema was frequently asymmetrical (asymmetric in 1 astronaut, unilateral in 2 astronauts, and symmetric in 2 astronauts). In another study, an astronaut who developed unilateral disc edema because of a previous spaceflight was reported to develop optic disc edema again on the same side in the following spaceflight.[44] If disc edema was caused by venous stasis associated with cephalad fluid shift in MG, the edema would be expected to resolve quickly once back in Earth gravity (1*g*). However, it has been shown that in some cases this edema persisted for 6 months after returning to Earth, while changes seen on OCT lasted for 630 days.[27] As in terrestrial IIH, there is no marked increase in CSF pressure in SANS. In addition, while optic atrophy develops as a result of long-term papillary edema in IIH, optic atrophy after papillary edema has not yet been reported in SANS. Another proposed theory is the compartmentalization theory.[25,45] According to this theory, optic disc edema, optic nerve sheath expansion, and other findings of SANS develop due to changes in the intraorbital part of the optic nerve, independent of increases in CSF pressure. The cul-de-sac-like anatomical junction between the intracranial subarachnoid space and the orbital subarachnoid space may cause disruption of CSF flow in the MG environment during spaceflights. Chronic cephalad fluid shift in MG might disrupt intraorbital CSF flow. Impaired orbital CSF drainage can lead to optic nerve compartment syndrome due to CSF accumulation in the optic nerve sheath within the orbit.[25,27] Cases of optic nerve meningocele/dural ectasia are also thought to be associated with congenitally disordered CSF circulation in the orbital section of the optic nerve and subarachnoid space.[46,47] The findings are strikingly similar to SANS.

Another hypothesis involves MG-induced flow imbalance in the glymphatic system of the optic nerve head.[48,49] The hypothesis regarding insufficient lymphatic drainage in the optic nerve head due to MG was proposed by Thornton and Bonato. According to this hypothesis, optic nerve edema and optic nerve sheath expansion in astronauts are thought to be the result of blocked optic nerve lymphatic flow. MG-induced lymphatic obstruction may block CSF drainage in the subarachnoid space and cause a localized pressure increase in the optic nerve. Elevated pressure in the subarachnoid space may alter the translamina cribrosa pressure gradient, directing Bruch's membrane angle toward the vitreous and resulting in compression of the lymphatic pathways and blockage of the lymphatic drainage in the prelaminar region. As a result, various degrees of papillary edema can be seen without an increase in intracranial pressure.[50] Further studies should be conducted in MG environments to examine the role of the ocular glymphatic system in SANS.

Measures to Reduce These Effects

What options does someone have if they develop a visual impairment in space? Would this jeopardize the mission, especially on long-duration flights like to Mars? This possibility is prompting space agencies to work on this issue. There are a number of proposed solutions to mitigate space-related problems encountered before landing on journeys to Mars and beyond. Some of the suggested solutions related to MG, which is the most important of these problems, are as follows:

The simplest way to create artificial gravity is through centrifugal artificial gravity using centrifugal force. The gravity (*g*) created by centrifugal force can be calculated with the formula, $g = \omega^2 \times r$, where ω is the angular velocity and r is the radius of the circle traveled. For a person subjected to centrifugal force, the gravitational force applied along the head-to-foot axis (Gz) is not uniform like the Earth's gravitational force. The strength of the Gz force varies according to the distance of the body parts from the center. The same effect could be produced by rotating the spacecraft, but this approach would not be logical because it would cause motion sickness in astronauts due to Coriolis forces.[51] The length of the arm that creates the centrifugal force will affect the spin rate; a shorter rotational radius requires faster rotation, which causes motion sickness. Therefore, it would be logical to extend the radius and reduce the rotation rate.[52] To avoid these adverse effects of centrifugal artificial gravity systems, linear artificial gravity systems (Turbolift) are also being designed.[53] After understanding the effect of artificial gravity on human physiology, the necessary dose and duration of artificial gravity therapies should be calculated.

Another alternative method is to apply lower body negative pressure (LBNP). The LBNP suit is designed to be worn over the lower abdomen and legs at regular intervals while in space to redirect blood into the lower body through negative pressure. Macias et al.[54] observed that applying 25 mmHg of negative pressure to the lower extremities reversed the increases in intraocular and intracranial pressure induced by simulated MG (HDT). Another method employed to reduce the effects of MG-induced cephalad fluid shift is venoconstrictive cuffs. Similar to LBNP, their aim is to reduce venous return from the legs to the heart.[22] However, we believe it would be more physiologically sound to ensure that pressure applied to prevent venous return is distributed across the entire vessel.

To increase tolerance to orthostatic hypotension caused by 1.2*g* exposure during the return from space to Earth, studies are being carried out on anti-G suits used by combat pilots, which apply positive pressure to the lower extremities and lower abdomen.[55]

Some researchers recommend the use of acetazolamide for symptomatic cases of optic disc edema during spaceflight.

However, it should be noted that this drug predisposes to dehydration and kidney stone development and has an intraocular pressure-lowering effect.[56]

In terms of radiation, conventional shields of reasonable thickness provide effective protection against SEP during space missions, whereas thicker passive shields or active electromagnetic shields should be used for high-energy GCR. However, these methods are not practical. If shields of insufficient thickness are used, secondary particles created by the interaction of GCR with the atoms in the shield pose an additional health risk to the crew. Therefore, studies on methods that can reduce the effects of GCRs for long-duration space missions are essential.

In addition to aluminum for passive protection against GCR, methods such as using shields containing high hydrogen, carbon (graphite), or boric acid (boron), placing lunar regolith in the body of the spacecraft, or storing spacecraft fuel around the body can be used.[2,57,58] Studies are also being conducted on the feasibility of storing water and liquid waste between flexible metals as a radiation shielding method.[58,59] After the Lunar Reconnaissance Orbiter detected low magnetic fields regions on the Moon's surface, the possibility of establishing colonies and facilities there is being evaluated.

Dietary countermeasures against the harmful effects of reactive oxygen species formed by GCR include the use of antioxidants and drugs such as vitamin A, vitamin C, omega-3, and ferric- and hexacyanoferrate-containing Radiogardase (Prussian blue).[60,61,62]

Conclusion

Further research is needed to increase human resilience to the conditions of space. Attempting to improve our understanding of the physiopathology of SANS and the effect of radiation on tissues will not only help people traveling in space, but also elucidate the physiopathology of diseases seen on Earth. The mechanisms of optic nerve supply and CSF circulation around the optic nerve are still unclear. The MG environment has demonstrated what can happen when fluid dynamics are altered. These studies will enable us to better understand the fluid and tissue dynamics of the optic nerve and develop novel approaches to optic nerve diseases.

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Case Report

Surgical Management of Corneal Hydrops: Case Series

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Abstract

Descemet's membrane (DM) rupture/detachments have traditionally been treated conservatively, with limited efficacy and a long rehabilitation period that significantly affects patients' vision and quality of life. Although there are no established gold standards for the timing and nature of treatment, with this series of 4 cases we aimed to highlight the importance of the current optimal intervention methods. The first two patients were treated with anterior chamber injection of isoexpansile 14% C3F8 due to acute hydrops associated with keratoglobus in the first case and keratoconus in the second case. The third patient had keratoglobus and chronic hydrops complicated by multiple stromal clefts detected on anterior segment optical coherence tomography, and the fourth patient had a chronic broad DM detachment which occurred after cataract surgery. Both of these patients were treated with intracameral C3F8 injection together with corneal compressive sutures. In all four cases, DM reattached completely and effectively with surgical intervention. Surgical management of DM rupture/detachment with intracameral gas injection and compressive corneal sutures seems to provide fast symptomatic relief and less healing-related corneal scarring with better visual rehabilitation, and may alleviate the need for corneal transplant surgery in this group of patients.

Keywords: Descemet's membrane detachment, Descemet's membrane rupture, acute hydrops, Descemetopexy, 14% isoexpansile C3F8, corneal compression sutures

Introduction

Descemet's membrane (DM) integrity problems such as ruptures or detachments manifest with loss of vision due to corneal edema and DM folds. Rupture of the DM has been reported in association with keratoglobus, keratoconus, congenital glaucoma, intraocular surgeries, prolonged and complicated labor with forceps, Terrien marginal degeneration, *Acanthamoeba* keratitis, and rarely spontaneously.[1,2,3,4,5]

Acute corneal hydrops is characterized by a rupture in the DM in the setting of corneal ectasia, which results from stretching of the DM leading to its rupture, allowing aqueous to enter the corneal stroma and epithelium. Corneal hydrops is relatively uncommon and is estimated to occur in 2.6-2.8% of patients with keratoconus. With a male preponderance, the mean age at onset of corneal hydrops is around 25 years.[6] Although the development of acute hydrops in keratoconus is well described, acute hydrops secondary to keratoglobus is rare in the literature.

On the other hand, Descemet's membrane detachment (DMD) mainly occurs in association with intraocular surgeries, particularly cataract surgery. Possible mechanisms by which DMD develops during intraocular surgeries have been reported as shallow anterior chamber; complicated or repeated surgeries; inadvertent insertion of instruments or inadvertent injection of saline and viscoelastic between the corneal stroma and DM; anteriorly located and shelved incisions; and the use of dull blades.[7,8]

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Complete spontaneous resolution of edema associated with DM separation may take months, with variations from 5 to 36 weeks.[6] In some cases, prolonged edema may lead to inflammatory reaction and neovascularization, affecting the prognosis of subsequent transplantation procedures.[9] Although DM integrity problems spontaneously resolve, severe visual symptoms or vision loss and long disease duration negatively influence quality of life and cause significant visual morbidity.

Conventional treatments for DM integrity problems, such as patching or bandage contact lens, tarsorrhaphy, cycloplegia, or hypertonic ophthalmic solutions, are of limited efficacy. Shaw[10] attempted corneal cauterization and thermokeratoplasty for faster resolution of corneal edema. Hirst and Dejuan[11] presented a technique using tissue adhesives and viscoelastic agents. Macsai and Lemley[12] described onlay epikeratoplasty with a donor corneoscleral button. More recently, Hussin et al.[13] described a novel technique, non-expansile (14%) perfluoropropane (C_3F_8) gas tamponade "descemetopexy," which currently seems to be the most widely used technique. Rajaraman and associates[14] combined the use of intracameral gas and compression sutures in corneal hydrops with stromal clefts and reported it to be an effective and safe treatment modality in the presence of large gaping tears and stromal clefts. Mohebbi et al.[15] indicated that combined intracameral gas injection and approximation sutures provided rapid recovery with very rare complications for the treatment of acute corneal hydrops. Zhao et al.[16] reported superior clinical outcomes using compression sutures with intracameral air injection versus thermokeratoplasty in the management of acute corneal hydrops. Our purpose in this report was to present a case series of 4 eyes with DM integrity problems and describe our approach to management.

Case Reports

Case 1

A 47-year-old woman presented with 6-day history of blurred vision and pain in the left eye. Corrected distance visual acuities (CDVA) were 20/200 in the right eye and counting fingers at 50 cm in the left eye. Anterior segment examination revealed keratoglobus bilaterally and acute hydrops with central corneal edema in the left eye (Figure 1a). Pentacam HR (Oculus Optikgerate GmbH, Wetzlar, Germany) anterior segment tomography revealed keratoglobus with a maximum keratometry measurement (KMax) of 75.7 diopters (D) and thinnest corneal thickness (TCT) of 160 µm in the right eye. Anterior-segment optical coherence tomography (AS-OCT, Visante, Carl Zeiss Meditec, Dublin, CA) revealed a giant DMD centrally (Figure 1b). Intracameral injection of an isoexpansile mixture of 14% C_3F_8 (gas diluted with air) was performed in the operating room after anterior chamber paracentesis. Three injections were done in a period of 2 months to completely reattach the DMD, and complete resolution of edema took 3 months. The decision to reinject was made when corneal edema increased and DMD enlarged on AS-OCT.

At 1-year follow-up examination, CDVA was 20/200 in the left eye. A slight stromal scar was observed, and the DM remained attached (Figure 1c). TCT was 138 µm. After genetic consultation, a diagnosis of brittle cornea syndrome was made with detection of a *ZNF469* mutation. Other systemic findings of the patient were sensorineural hearing loss, metacarpal hypoplasia, and subluxation of various joints (Figure 1d).

Case 2

A 60-year-old man with keratoconus and no history of ocular surgery presented with blurred vision and pain for 7 days. CDVA was counting fingers at 50 cm in the right eye and 20/100 in the left eye. On slit-lamp examination, acute hydrops with bullous edema was observed in the right eye (Figure 2a). Pentacam HR showed a KMax value of 48.7 D and TCT of 465 µm in the left eye. On AS-OCT, a break in the DM with DMD was visible below the area of edema (Figure 2b). A single intracameral injection of an isoexpansile mixture of 14% C_3F_8 was performed and the edema had resolved at 2-week follow-up. At 3-month follow-up examination, CDVA was 20/125 and a faint central corneal scar with complete resolution of stromal edema was observed on slit-lamp examination (Figure 2c,d). Pentacam HR revealed a KMax value of 64.8 D and a TCT of 396 µm in the right eye.

Case 3

A 44-year-old man presented with complaints of blurred vision, photophobia, and pain in the right eye for 3 months. CDVA was counting fingers at 15 cm in the right eye and 20/40 in the left eye. Anterior segment examination showed acute hydrops with prevalent corneal edema in the right eye and a very thin ectatic cornea in the left eye (Figure 3a). Pentacam HR indicated keratoglobus with a KMax value of 61.9 D and TCT of 500 µm in the right eye. AS-OCT revealed a wide

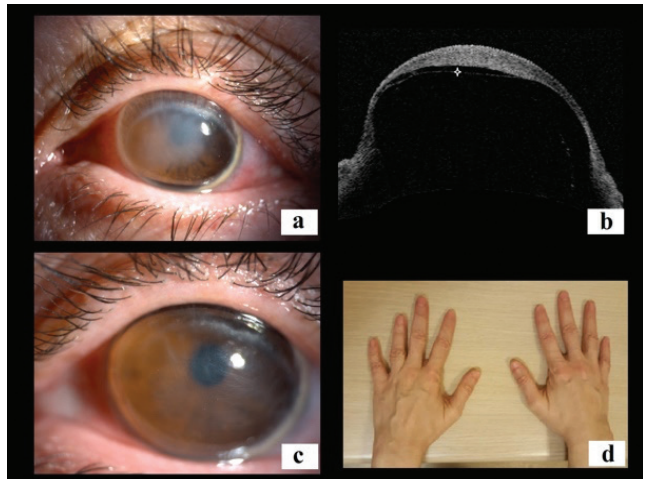

Figure 1. Case 1: Slit-lamp photos of a patient with brittle cornea syndrome showing acute hydrops with central corneal edema in the left eye (a). On anterior segment optical coherence tomography (AS-OCT), central corneal edema and Descemet's membrane detachment was observed (*) (b). Three months later, clearing of the corneal cloudiness with only slight stromal scarring was observed on slit-lamp examination (c). Hypoplasia of the fourth and fifth metacarpals was apparent in both hands (d)

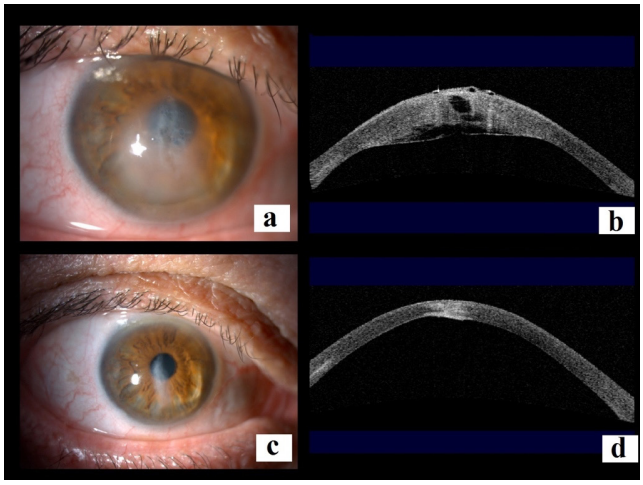

Figure 2. Case 2: Slit-lamp photos of a keratoconus patient showed acute hydrops and microcystic edema in the right eye (a). On anterior segment optical coherence tomography (AS-OCT), Descemet's membrane (DM) rupture was visible below the area of edema (b). At 3 months after C_3F_8 administration, central corneal scar with complete resolution of stromal edema was observed

central separation of the DM from the corneal stroma, most severe temporally, with multiple stromal clefts (Figure 3b). An intracameral injection of 0.2 mL isoexpansile (14%) C_3F_8 and seven compression sutures were applied simultaneously for the large gaping DM tear. On day 10 after the intervention, the edema was decreased and the cornea regained much of its clarity (Figure 3c). AS-OCT demonstrated complete reattachment of the DM (Figure 3d). Resolution of edema took 4 weeks. At 1-year follow-up examination, CDVA was 20/70 in the right eye. On slit-lamp examination, neither corneal edema nor neovascularization was observed, and AS-OCT showed the DM remained attached and the clefts had collapsed entirely (Figure 3e,f).

Case 4

An 88-year-old man who underwent cataract surgery in the left eye 1 year earlier at another clinic and had progressive visual deterioration since then was referred to our clinic for a corneal transplant. At initial examination, CDVA was 20/40 in the right eye and counting fingers at 10 cm in the left eye. Anterior segment examination revealed a very cloudy and thick cornea, obscuring the anterior chamber view. AS-OCT revealed a wide separation of the DM from the stroma (Figure 4a). An intracameral injection of 0.2 mL isoexpansile (14%) C_3F_8 was performed together with 11 compression sutures simultaneously and resolution of edema took 4 weeks. At the 3-month follow-up examination, CDVA was 20/200 in the left eye, the bullous edema had resolved completely, and the DM was attached as confirmed with AS-OCT (Figure 4b,c).

Discussion

We presented four cases of DM rupture/detachment and their management. As causative factors, two of the four patients

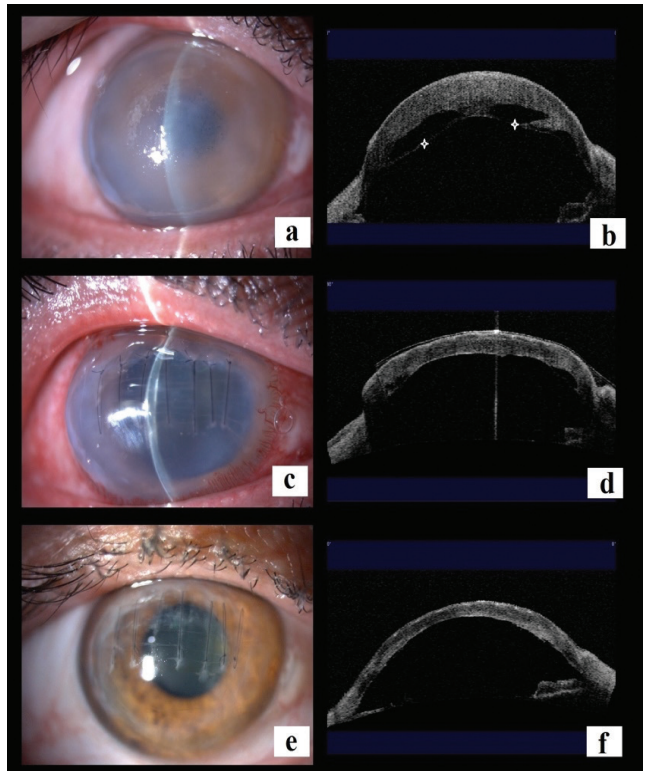

Figure 3. Case 3: Slit-lamp photos of the patient with acute hydrops and severe epithelial and stromal edema in the right eye (a). Anterior segment optical coherence tomography (AS-OCT) revealed widespread corneal edema and Descemet's membrane detachment (DM) (*) and DM rupture complicated with stromal clefts (b). At 10 days after C3F8 infection together with full-thickness corneal compression sutures, the corneal haze had subsided and AS-OCT showed complete reattachment of the DM to the stroma and reduction in corneal steepness (c,d). At 1-year follow-up, the cornea was clear and the DM remained attached (e,f)

had keratoglobus, one had keratoconus, and the last patient had undergone cataract surgery. Only intracameral C_3F_8 injection was performed in the first two cases; the third case with chronic DM rupture complicated with intrastromal clefts and the fourth case with chronic DMD were effectively managed with intracameral C_3F_8 injection and compression sutures.

Descemetopexy with repeated injections of intracameral air or gas can accelerate the resolution of corneal edema by acting as a mechanical barrier preventing the entry of aqueous humor into the stroma and acting as a tamponading agent.[17] Miyata et al.[18] reported that corneal edema persisted for an average of 20 days in patients managed with intracameral air injection versus 65 days in patients who received no treatment for acute hydrops in keratoconus. As air is absorbed in a short period of time, Panda et al.[19] reported descemetopexy with injection of 0.1 mL of an isoexpansile concentration of 20% SF_6 as an alternative. The authors reported earlier and more effective resolution of corneal edema compared to conservative management, with complete resolution achieved at 4 weeks in the SF_6-injected group compared to 12 weeks in the conservative treatment group. Whereas undiluted C_3F_8 expands to 4 times its initial volume in 4 days inside the anterior chamber, the 14% nonexpansile

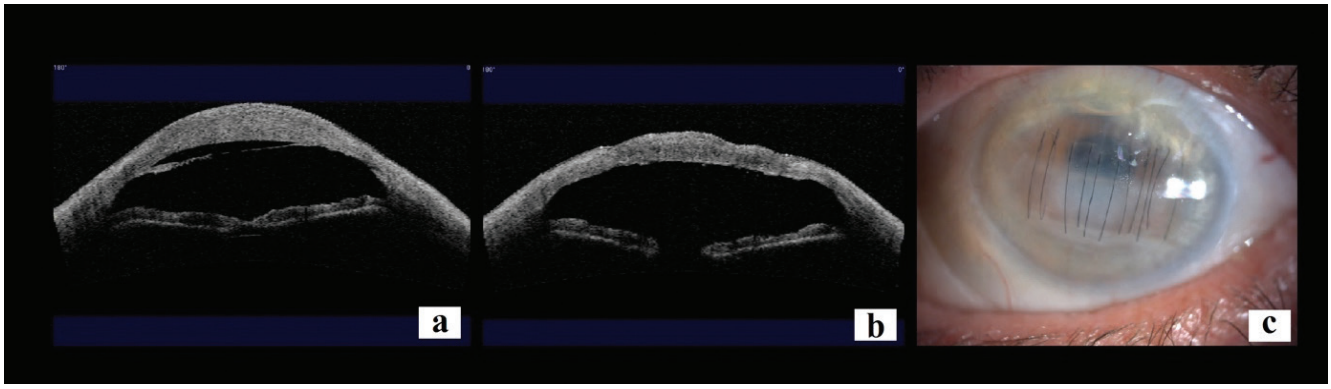

Figure 4. Case 4: Anterior segment optical coherence tomography (AS-OCT) at presentation 12 months after phacoemulsification showed corneal edema and Descemet's membrane detachment (DM) (a). At 3-month follow-up, central corneal scarring was observed without edema. On AS-OCT, the DM was totally attached and anterior corneal surface irregularities were noted (b,c)

dilution of the gas persists in the anterior chamber for 6 weeks, and is therefore considered to be a safe and effective modality for early resolution of corneal edema in eyes with acute hydrops.[20] In one study, descemetopexy with 1.8% sodium hyaluronate was also used to unscroll and reattach recalcitrant DMD.[21]

The use of intracameral C_3F_8 with full-thickness corneal compression sutures to bring the edges of the DM tear together was also proposed.[14] Suturing together with intracameral gas injection decreases the amount and number of gas fillings needed and reduces the complications associated with isoexpansile gases such as pupillary block glaucoma, endothelium toxicity, and cataract formation.[22]

An AS-OCT study of cases involving acute hydrops described two stages of resolution: DM reattachment and endothelial migration. When DM breaks, it retracts or coils. First, the DM has to reattach to the posterior stroma; the time for this stage depends on the depth of the DMD. Afterward, endothelium has to migrate to the gap between the broken DM edges and synthesize a new DM; the time required for this depends on the scale of the DM break. Injection of C_3F_8 can hasten DM reattachment to the posterior stroma in the first step but not the second.[23] In contrast, compression sutures can hasten both the first and second steps, probably by bringing the DM and stroma together and holding the edges of the tear in close apposition, thus enabling endothelial cells to rapidly seal and cover the lesion.

Acute corneal hydrops complicated by intrastromal cleft formation is considered a risk factor for delayed resolution, persistent edema, corneal perforation, and the development of stromal neovascularization.[24] Corneal stromal neovascularization may decrease the long-term survival of a penetrating graft because of increased risk of rejection. Hydrops with clefts generally requires multiple intracameral gas applications. The clefts are usually connected to the anterior chamber by small gaps through which intracameral gas can easily enter into the corneal clefts. For this reason, compressive sutures with or without gas injection may be a better approach to treat acute corneal hydrops complicated by clefts.[25]

Eyes with wide DMD require more time for resolution of corneal edema, even with descemetopexy.[23] Whereas localized and narrow separation of DM from the stroma following phacoemulsification typically resolves spontaneously, wide DMDs demand early recognition and timely intervention to achieve the best visual outcomes. If the DMD is wide, folded, or curled, or persists for a long time as in our third and fourth cases, surgical unfolding of the DM with full-thickness corneal sutures together with gas injection usually recommended.

In conclusion, we aimed to highlight the importance of the current optimal intervention methods in patients who suffer from DM ruptures or detachments. Although there are no established gold standards for the timing and nature of treatment, ophthalmologists should consider multiple factors when making management decisions, such as the location and duration of the detachment and tear, and the degree of anteroposterior separation from the posterior stroma. Descemetopexy with gas tamponade is an easy and effective treatment approach that can hasten the healing process and improve visual acuity. However, in complicated cases such as those with corneal clefts and chronic or large DMD, using compressive sutures with intracameral gas injection seems to be a better approach. Overall, surgical management of DM rupture/detachment can provide faster symptomatic relief and less healing-related corneal scarring with better visual rehabilitation and may alleviate the need for corneal transplant surgery in these patients. Further comparative studies with more patients are required to demonstrate the safety and efficacy of these procedures.

Informed Consent: Written informed consent was obtained from patients.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Ö.U., Concept: G.Ö., Ö.Ö.U., Design: G.Ö., Data Collection or Processing: G.Ö., Analysis or Interpretation: G.Ö., Ö.Ö.U., Literature Search: G.Ö., Writing: G.Ö., Ö.Ö.U.

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Case Report

Diffuse Corneal Edema after Uneventful Pterygium Surgery: Toxic Anterior Segment Syndrome or Toxic Keratopathy?

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Abstract

A 29-year-old woman was referred to our department for corneal edema after uneventful pterygium excision surgery with conjunctival autografting. She was prescribed topical dexamethasone and showed a complete response within 2 weeks of treatment. Specular microscopic examination revealed severe endothelial cell loss in the operated eye. Mild corneal haze causing a decrease in vision (20/50) was observed in long-term follow-up. This steroid-responsive complication was linked to two possible etiologies: mild toxic anterior segment syndrome or povidone-iodine (PVP-I) corneal toxicity. Surgeons should be careful during pterygium surgery to completely clear PVP-I and avoid any penetration into the anterior chamber to prevent possible serious complications. When diffuse corneal edema is encountered after pterygium surgery, intense steroid treatment should be prescribed as in the present case.

Keywords: Pterygium, povidone iodine, toxic anterior segment syndrome, toxic keratopathy

Introduction

Pterygium is a wing-shaped fibrovascular proliferation of conjunctiva over the cornea, mostly on the nasal side. Its prevalence was reported to be between 3% and 30% in different countries.[1] The bare sclera technique or using a conjunctival or conjunctivolimbal autograft or amniotic membrane graft with suturing or fibrin glue are among the possible surgical strategies for pterygium and have different recurrence rates.[2] To prevent recurrence, antimitotic agents such as mitomycin C (MMC) can be applied during surgery or as postoperative eye drops.[2] However, MMC may have toxic effects on the cornea, including corneal epithelial toxicity or edema and scleral melting, with increased risk at higher dosage.[3]

Although rare, some minor complications such as wound dehiscence, Tenon's granuloma, and conjunctival cyst might develop after surgical excision of pterygium. However, diffuse corneal edema similar to toxic anterior segment syndrome (TASS) has not been reported in the literature.

Here, we report a case of diffuse corneal edema resembling toxic keratopathy or TASS after uneventful pterygium surgery involving a sutured conjunctivolimbal autograft with no antimitotic agent (e.g., MMC) and discuss the possible etiologies.

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Case Report

A 29-year-old woman presented with corneal edema after an uneventful pterygium excision surgery with conjunctival autografting. Best corrected visual acuity (BCVA) was counting fingers at 3 meters in her right eye (RE) and 20/20 in her left eye (LE). In the slit-lamp examination, diffuse corneal edema and Descemet folds were observed together with an intact graft which was upside down; conjunctiva was hyperemic in the RE (Figure 1a). Her fundus could not be examined because of corneal edema. She had been prescribed topical moxifloxacin, dexamethasone, eye lubricant, and 10% NaCl solution 3 times a day for 1 week before referral to our department.

The surgeon who performed her operation was contacted to determine the technique and ocular disinfection method he used. He stated that he applied 5% povidone-iodine (PVP-I) (diluted in balanced salt solution) for 3 minutes and then washed the eye for preoperative antisepsis. He did not report the use of any antifibrotic agent such as MMC during the surgery. The autograft taken from the superior area had been secured to the excised nasal area with 8.0 vicryl sutures. He reported corneal edema on the first postoperative day. She had been operated by the same surgeon at the same hospital using the same technique on her LE 1 year earlier with no complications.

Specular microscopic imaging showed that the healthy eye had 2882 cells/mm^2, the RE was not clear enough to obtain a good result as depicted in the anterior segment optical coherence tomography (OCT) image (Figure 2a). The patient was prescribed topical dexamethasone (Maxidex®, Alcon, USA) every hour, moxifloxacin (Vigamox®, Alcon, USA) 3 times a day, and eye lubricant (Refresh®, Allergan, USA) 4 times a day. After observation of a 3-mm epithelial defect on the nasal cornea after the first day of treatment, the topical dexamethasone regimen was changed to 4 times a day, a bandage contact lens (Purevision HD, Bosch & Lomb, USA) was applied, and oral vitamin C (1 g/day) was added. After one week of treatment, a dramatic decrease in the corneal edema was observed. Descemet folds, conjunctival hyperemia, and epithelial defect disappeared. The bandage contact lens was removed and topical moxifloxacin was stopped. The corneal edema disappeared totally after 2 weeks of this treatment (Figure 1b) and the BCVA increased to 20/50. After 1 year of follow up, specular microscopy showed the endothelial cell density in the RE was 1001 cells/mm^2 (coefficient of variation [CV]: 36; hexagonality [HEX]: 46%) and that of the LE was 2880 cells/mm^2 (CV: 38, HEX: 67%). BCVA in her RE was still 20/50. Corneal stromal vascularization and corneal haze on the nasal side were observed at the last visit (Figure 1c,d) with no corneal edema (Figure 2b).

Discussion

Although minor complications can sometimes be observed after pterygium surgery, in this case we observed diffuse corneal edema. We suspected TASS or endothelial toxicity (toxic keratopathy) due to the use of PVP-I, MMC, or any solution used perioperatively as possible etiologies. However, MMC was not used during or after the surgery.

TASS is postoperative anterior segment inflammation with diffuse corneal edema that can occur after any interventions involving contact with the anterior chamber. Substances that can cause TASS include residual disinfection or sterilization solutions, preservatives in medicines, or bacterial endotoxins.[4] Intense topical steroid therapy is indicated for this syndrome. In terms of TASS, although we did not observe any anterior segment reaction, we might have examined the patient at a stage when the reaction was suppressed but the corneal edema persisted. The patient's complete response to 2 weeks of steroid treatment supports this possibility.

PVP-I at a concentration of 0.025% did not show any toxic effect on human corneal endothelium in vivo when used to treat

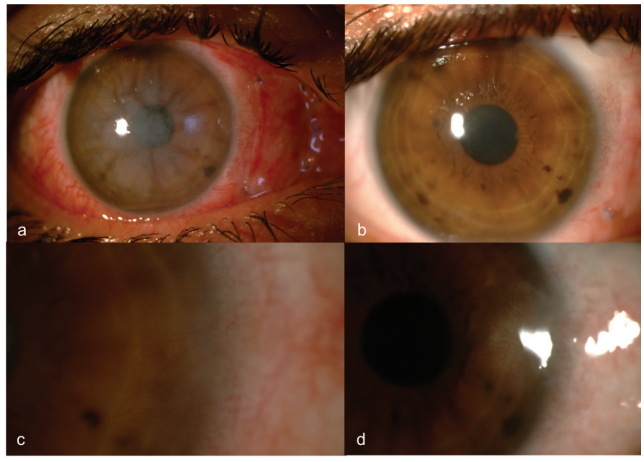

Figure 1. Biomicroscopic images of the patient showing conjunctival hyperemia and corneal edema together with the autograft at initial presentation (a), resolution of the corneal edema after 2 weeks of treatment (b), and development of corneal stromal vascularization (c) and corneal haze (d) on the nasal side after 1 year of treatment with low-dose topical steroid

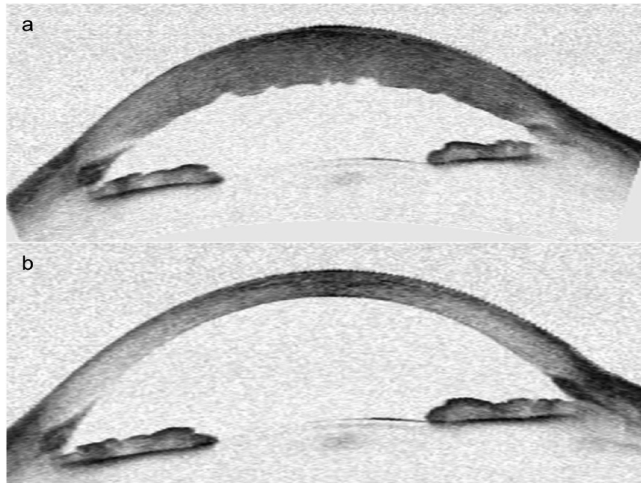

Figure 2. Anterior segment optical coherence tomography images of the patient showing diffuse corneal edema and Descemet folds at initial presentation (a) and regression of the corneal edema after 2 weeks of steroid therapy (b)

postoperative endophthalmitis.[5] However, a single drop of 5% PVP-I was shown to exert toxic effects on the corneal endothelium of healthy rabbits when injected into the anterior chamber.[6] It was also shown to cause endothelial toxicity when injected at a concentration of 1% into bovine corneal endothelium.[7] In their study on rabbit eyes, Jiang et al.[8] postulated that although 5% PVP-I does not cause endothelial toxicity through an intact cornea when instilled on the ocular surface, it may penetrate when the epithelial layer is damaged. Therefore, 5% PVP-I in our patient might have penetrated through the excised pterygium area to cause endothelial toxicity, since that area was devoid of corneal epithelium. The lower endothelial cell count in that eye supports this possibility. Epithelial debridement has been linked to an increased penetration of some molecules such as riboflavin.[9] However, further studies are necessary to investigate the penetration of PVP-I after corneal epithelial debridement. In addition, there is no report on humans or animals showing that corneal edema secondary to the endothelial toxicity of PVP-I responds to topical steroid therapy. Although our patient showed a complete response after 2 weeks of topical steroid, corneal haze and stromal vascularization developed and persisted for 1 year despite low-dose steroid treatment.

Residual liquid disinfectants such as alcohol, glutaraldehyde, or chlorhexidine on surgical instruments might be responsible for toxic keratopathy or TASS.[10] However, the surgeon who performed the procedure reported that none of these agents was used for disinfection or sterilization.

In conclusion, here we report a unique case of diffuse corneal edema secondary to uneventful pterygium surgery. We attribute this steroid-responsive complication to two possible conditions: mild TASS or PVP-I-induced corneal toxicity. During pterygium surgery, caution must be taken to clear all PVP-I. Further studies investigating the penetration of different concentrations of PVP-I and determining the concentration that causes corneal endothelial toxicity or toxic keratopathy should also be performed to understand its pharmacokinetics in damaged cornea.

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: C.A., B.M., O.K., A.Ö., Concept: C.A., B.M., O.K., A.Ö., B.T.A., A.A., Design: C.A., B.M., O.K., A.Ö., B.T.A., A.A., Data Collection or Processing: C.A., B.M., O.K., A.Ö., B.T.A., A.A., Analysis or Interpretation: C.A., B.M., O.K., A.Ö., B.T.A., A.A., Literature Search: C.A., B.M., O.K., A.Ö., B.T.A., A.A., Writing: C.A., B.M., O.K., A.Ö., B.T.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Dramatic Improvement of Severe Cicatricial Ectropion after Discontinuing Long-Term Erlotinib Therapy in a Patient with Lung Cancer

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Abstract

There is no consensus on the choice of systemic and ophthalmic treatment for patients who develop ocular toxicity with erlotinib in the few cases reported previously. Various ocular complications related to erlotinib have been reported, with one of the most serious being corneal perforation. Our patient was at risk of potential corneal perforation because of severe cicatricial ectropion and diffuse punctate corneal epitheliopathy. Therefore, erlotinib treatment was temporarily discontinued with the approval of the oncology department and the patient was closely followed. She was prescribed steroid eye ointment, single-use preservative-free artificial tears, and eye lubricant gel to protect the ocular surface. On day 4 of treatment, the patient's findings were significantly improved. After 1 week, the cicatricial ectropion had dramatically improved and the patient's complaints were completely resolved. To our knowledge, there is no case report of a patient with both ocular toxicity after long-term use that shows dramatic improvement with drug cessation, and severe cicatricial ectropion affecting the entire lower eyelid. Here, we described a patient who used erlotinib for 3 years due to non-small cell lung cancer and developed severe cicatricial ectropion which improved dramatically within one week of temporarily discontinuing erlotinib and discussed the possible reasons. Although ocular complications with erlotinib are usually encountered early in treatment, it should be kept in mind that erlotinib-related ocular complications may also arise with long-term use.

Keywords: Ectropion, cicatricial ectropion, ocular toxicity, lung cancer, erlotinib, long-term erlotinib

Introduction

Erlotinib is a tyrosine kinase inhibitor that specifically targets epidermal growth factor receptor (EGFR).[1] It is frequently used in the treatment of lung cancer and may cause ocular toxicity.[1,2,3,4] Ocular complications range widely from mild dry eye syndrome to corneal perforation that requires corneal transplantation.[1,2,3,4] It is reported in the literature that erlotinib-related ocular complications usually occur early in treatment (within the first 6 weeks) and resolve slowly (after 6 weeks).[1,2,3,4] To our knowledge, there is no case report of a patient with both ocular toxicity after long-term use that shows dramatic improvement with drug cessation, and severe cicatricial ectropion causing eversion of the entire lower eyelid. Furthermore, there is no consensus regarding the choice of systemic and ophthalmic treatment in patients who develop ocular toxicity with erlotinib in previous studies.[1,2,3,4] Here, we described a patient who used erlotinib for 3 years due to non-small cell lung cancer and developed severe cicatricial ectropion which improved dramatically within one

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week of temporarily discontinuing erlotinib, and we discussed the possible reasons.

Case Report

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. This case report is in compliance with the ethical principles outlined in the Declaration of Helsinki.

A 70-year-old woman was referred from the oncology clinic to our ophthalmology clinic due to complaints of burning, stinging, pain, and dryness in both eyes and outward turning of both lower eyelids (Figure 1A). Her history was significant for non-small cell lung cancer, for which she had been using erlotinib (150 mg/day) for 3 years.

On ophthalmologic examination, visual acuity was 0.8 in both eyes. Diffuse punctate epitheliopathy was detected in both corneas. Diffuse hyperemia and madarosis in the tarsal conjunctiva of both lower eyelids and severe cicatricial ectropion affecting the entire lower eyelid were observed (Figure 1A, 2A). The patient also had diffuse dry, scaling skin and desquamation on her face (Figure 1A).

The patient was at risk of potential corneal perforation because of severe cicatricial ectropion and diffuse punctate corneal epitheliopathy. Therefore, erlotinib treatment was temporarily discontinued with the approval of the oncology department and the patient was closely followed in the ophthalmology clinic. She was prescribed a steroid eye ointment (hydrocortisone acetate; Cortimycine, Abdi İbrahim, Istanbul, Turkey) to be used 4 times a day on the lower eyelids to treat the ectropion. Single-use preservative-free artificial tears (polyvinyl alcohol; Refresh, Allergan, Westport, Ireland) every hour and an ophthalmic gel (carbomer; Lipotears, Bausch & Lomb, Aubenas, France) 4 times a day were also prescribed to protect the cornea. On day 4 of treatment, the patient's findings had improved significantly (Figure 1B). After 1 week, her cicatricial ectropion was dramatically improved, her eyelashes were starting to grow back, and her ocular complaints were completely resolved (Figure 1C, 2B).

Discussion

Various ocular complications related to erlotinib have been reported, with corneal perforation being among the most serious.[1-4] Corneal perforation can result in irreversible vision loss despite treatment by corneal transplantation. In a healthy person, EGFR may be expressed in the epithelial tissues of the cornea and conjunctiva and can be found in tears.[1] Therefore, EGFR inhibition may negatively impact the ocular surface and cornea. In addition, ectropion may cause incomplete eye closure and exposure keratopathy. The simultaneous occurrence of these conditions, as in our patient, may increase the risk of corneal perforation.

In their series of five patients, Saint-Jean et al.[1] reported erlotinib-related (150 mg/day) ectropion in only one patient after 1 month of treatment, and the ectropion persisted despite erlotinib cessation. The authors prescribed eye lubricants and ciprofloxacin ointment, but they did not specify the active ingredient of the artificial tears and whether it was preservative-free. They also did not note the severity of ectropion.[1] On the other hand, Methvin and Gausas[2] used only a combination antibiotic/steroid ointment as first-line treatment for a patient

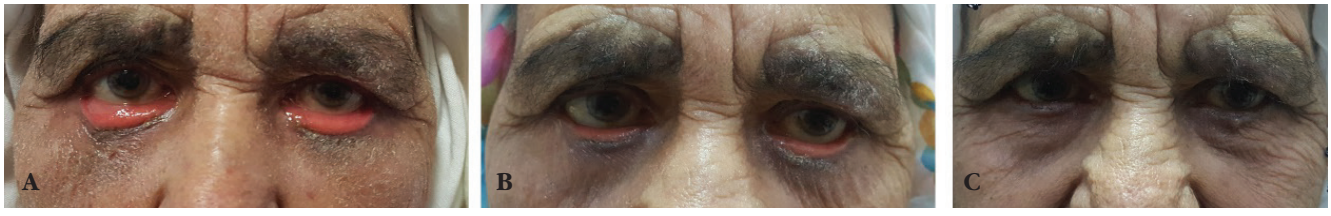

Figure 1. (A) Clinical images of the patient demonstrating severe cicatricial ectropion involving the entire lower eyelid and diffuse dry, scaling skin and desquamation on the patient's face. (B) On day 4 of treatment, the patient's findings were significantly improved. (C) After 1 week, the cicatricial ectropion was dramatically improved and the patient's ocular complaints were completely resolved

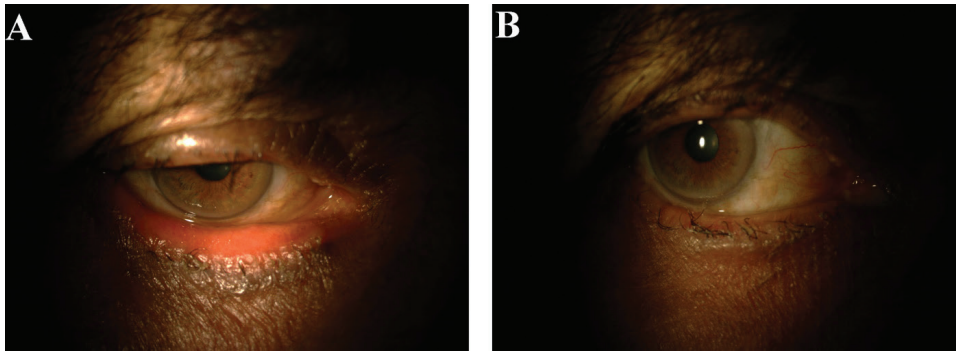

Figure 2. (A) Slit-lamp biomicroscopic photograph of the patient demonstrating lower eyelid ectropion and madarosis. (B) After 1 week, there was dramatic regression of the cicatricial ectropion and the patient's eyelashes had started to grow back

who developed ectropion in week 6 of erlotinib (150 mg/day) therapy. Later they reduced erlotinib from daily to every-other-day dosing but observed no improvement in the ectropion. Finally, they discontinued erlotinib and reported improvement in side effects 6 weeks later. Frankfort and Garibaldi[3] observed medial ectropion 1 week after starting erlotinib (150 mg/day) that did not improve after reducing the erlotinib dose by half (75 mg/day). The authors initiated bacitracin ointment and topical fluorometholone for ophthalmic treatment. When this treatment showed no effect, they added artificial tears with more frequent application of the bacitracin ointment. Later, 3 weeks after cessation of erlotinib, the findings started to improve. Salman et al.[4] observed erlotinib-related mild ectropion in week 2 of treatment. They opted not to discontinue systemic erlotinib but initiated ophthalmic treatment, and reported that the ectropion was completely resolved at 6-month follow-up.

However, the authors did not specify which medications were used as ophthalmic treatment.

In contrast to these reports, our patient had severe cicatricial ectropion involving the entire lower eyelid and diffuse punctate corneal epitheliopathy. Additionally, she had been receiving erlotinib (150 mg/day) treatment for 3 years and the cumulative dose was much higher than in the patients reported in previous studies.[1,2,3,4] Therefore, in terms of potential corneal perforation risk, we preferred to temporarily discontinue erlotinib treatment with the approval of the oncology department. Because ocular toxicity results from an inflammatory reaction, we also chose to use a potent topical steroid eye ointment at frequent intervals. We also aimed to minimize ocular surface and tear toxicity by administering preservative-free artificial tears at frequent intervals. We did not prefer an antibiotic eye ointment because there were no signs of infection and their preservative ingredients may increase ocular toxicity. We think that the dramatic improvement of severe cicatricial ectropion within one week in our patient may be due to our choice of ophthalmic treatments and good communication between the oncology and ophthalmology departments, which enabled the immediate discontinuation of erlotinib.

Our approach may reduce the need for surgical interventions to repair both the eyelid and cornea, and therefore may be preferred in cases with potential risk of corneal perforation. In addition, we think that risk assessment and mutual decision-making as a result of good communication between oncologists and ophthalmologists may decrease both systemic and ocular complications. Further studies with larger patient series are warranted to support this speculation. Although ocular complications with erlotinib are usually encountered early in treatment, it should be kept in mind that erlotinib-related ocular complications may also arise with long-term use.

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