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AT A GLANCE

2024 Issue 5 at a Glance:

Esteemed colleagues,

In its fifth issue of 2024, the Turkish Journal of Ophthalmology brings you six original studies, one review, and three case reports.

A clinical study by Korkmaz et al. titled "Evaluation of Medically Reversible Limbal Stem Cell Deficiency" aimed to evaluate the clinical characteristics and treatment strategies of patients with limbal stem cell deficiency (LSCD) that regressed as a result of medical treatment. Among 29 eyes of 21 patients examined, the pre-treatment LSCD stage was determined to be stage 1A in 5 eyes (17.2%), stage 1B in 12 eyes (41.4%), stage 1C in 4 eyes (13.8%), stage 2A in 4 eyes (13.8%), and stage 2B in 4 eyes (13.8%). With etiology-targeted medical treatment, LSCD completely resolved in 6 eyes (20.7%) and in the remaining eyes decreased in severity to below stage 2B, which is the threshold for surgery. The authors emphasized that although limbal stem cell transplantation is generally accepted as the main treatment approach for LSCD, in the early stages it can be treated with the right medical treatment, without the need for surgical intervention (See pages 251-256).

In their study titled "Effects of Glaucoma Treatment on Ocular Surface and Tear Functions: Comparison of Trabeculectomy and Antiglaucoma Drops", Mermer et al. investigated tear function and ocular surface disease (OSD) findings in glaucoma patients treated with antiglaucoma medication in one eye and trabeculectomy surgery in the other eye. The patient group included 38 eyes of 19 patients who underwent mitomycin C-augmented trabeculectomy at least 6 months earlier and were followed up without medication in the operated eye while continuing to use antiglaucoma drugs in the fellow eye. The control group comprised 20 eyes of 20 healthy individuals. While no difference in the incidence of OSD was observed between the eyes that underwent trabeculectomy and those receiving antiglaucoma medications, both eyes of the glaucoma patients differed significantly from controls in terms of tear break-up time, corneal and conjunctival fluorescein staining, Schirmer II test, and Nelson stages ($p<0.05$) (See pages 257-262).

A retrospective study by Akmaz and Talay titled "Does Laser Iridotomy Cause Secondary Epiretinal Membrane?" aimed to determine the frequency of epiretinal membrane (ERM) in the long term after neodymium yttrium-doped aluminum garnet laser iridotomy (LI). The study examined 94 eyes with at least 4 years of follow-up and a control group of 66 eyes followed up for suspected glaucoma. ERM developed in 36 (38.2%) of the 94 eyes in the LI group versus 13 (19.6%) of the 66 eyes in the control group. The authors emphasized that the LI procedure is a predisposing factor for the development of ERM (See pages 263-267).

Özdemir Zeydanlı et al. retrospectively evaluated the effectiveness of human amniotic membrane (hAM) transplantation in the surgical treatment of complicated retinal detachments (RD) due to various etiologies in their study titled "Human Amniotic Membrane: A Seal for Complex Retinal Detachments". Surgical indications included RD associated with high myopic macular hole (MH) (n=5), RD associated with traumatic large macular tears (n=4), combined tractional RD and MH associated with cicatricial retinopathy of prematurity (n=2), combined RD associated with severe retinitis (n=1), and RD associated with morning glory syndrome (n=1). The authors emphasized that the use of the described technique, especially in pediatric cases, was a distinguishing feature of the study. During an average follow-up period of 15 months (range, 6-30 months), 75% of MHs closed with a single surgery, while 25% required a second surgery due to hAM contraction/dislocation. In 92% of the cases, silicone could be removed during follow-up and the retina remained attached (See pages 268-274).

In their study titled "Multilayered Inverted Internal Limiting Membrane Flap Technique in Optic Disc Pit Maculopathy", Özdemir et al. applied the multilayer inverted internal limiting membrane (ML-ILM) flap technique previously used in MH surgery in eyes with optic disc pit maculopathy (ODPM) and evaluated the anatomical and visual outcomes. Anatomical and functional gains were observed in all eyes during follow-up, and the authors stated that the ML-ILM flap technique may be a preferable surgical option to achieve both high anatomical and functional success and flap stabilization (See pages 275-281).

In their study titled "Turkish Retinoblastoma Research: A Bibliometric Analysis (1966-2024)", Aykut and Sarıgül Sezenöz aimed to conduct the first bibliometric analysis of retinoblastoma studies conducted in Türkiye and determine the leading institutions, authors, international collaborative studies, and areas open to development. Results obtained by searching international databases (Web of Science [WoS] and Scopus), a national database (TR Index), and gray literature sources (theses and Scientific and Technological Research Council of Türkiye projects) were cleaned and analyzed using bibliometric tools. A search from 1966 to 2024 yielded a total of 122 publications on the subject in WoS and Scopus, with articles being the most common document type (n=78, 63.9%). More than two-thirds of the publications were contributed by Istanbul University (48 publications, 23.8%),

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AT A GLANCE

Hacettepe University (34 publications, 16.8%), Ankara University (33 publications, 16.3%), and Istanbul University-Cerrahpaşa (22 publications, 10.9%) (See pages 282-290).

The review in this issue was penned by Yan et al. and is titled "Caffeine and Vision: Effects on the Eye". The article presents a comprehensive analysis of the ocular effects of caffeine, a psychoactive substance widely consumed in almost every social stratum in recent years, and is notable for its rich and current bibliography on the subject (See pages 291-300).

In the case reports section, Dudu Deniz Açar presents the first case under the title "Partial Lateral Rectus Avulsion Due to Cat Scratch" along with detailed visuals, emphasizing that traumatic isolated rectus muscle rupture without associated globe damage is extremely rare (See pages 301-303).

In an article titled "Pulsatile Proptosis and Sphenoid Wing Dysplasia with no Evidence of Neurofibromatosis Type 1: A Case Report and Review of the Literature", Delibay Akgün et al. share detailed data from a 17-year-old male patient and present a comprehensive review of the related literature (See pages 304-308).

In a case report titled "Conjunctival Collagen Cross-Linking for the Treatment of Leaking Avascular Cystic Bleb", Koçer and Turpçuoğlu comprehensively analyze the treatment process of a 70-year-old male patient who underwent trabeculectomy surgery 7 years earlier and was found to have a leaking avascular cystic bleb (See pages 309-312).

We hope that the articles selected for this issue will provide you interesting and enjoyable reading.

Respectfully on behalf of the Editorial Board,
Hakan Özdemir, MD

Original Article

Evaluation of Medically Reversible Limbal Stem Cell Deficiency

İlayda Korkmaz, Nihat Furkan Eratılgan, Melis Palamar, Sait Eğrilmez, Ayşe Yağcı, Özlem Barut Selver

Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye

Abstract

Objectives: To evaluate the clinical characteristics and treatment strategies of limbal stem cell deficiency (LSCD) patients managed with medical therapy.

Materials and Methods: The study included 29 eyes of 21 patients with LSCD who were managed medically at Ege University Faculty of Medicine, Department of Ophthalmology between May 2013 and May 2023. LSCD stages before and after medical treatment were recorded according to the LSCD staging system published by the International LSCD Working Group. The medical records of patients showing improvement in LSCD stage with medical treatment without surgical intervention were evaluated.

Results: The mean age was 35.5±23.8 years (range, 5-71 years) with a male-to-female ratio of 6:15. The primary etiology of LSCD was ocular rosacea in 12 patients (57.1%), marginal keratitis in the setting of blepharitis in 8 patients (38.1%), and topical medication toxicity in 1 patient (4.8%). The mean baseline best corrected visual acuity (BCVA) was 0.25±0.26 logarithm of the minimum angle of resolution (logMAR) (range, 0-1 logMAR). Pre-treatment LSCD stage was stage 1A in 5 eyes (17.2%), stage 1B in 12 eyes (41.4%), stage 1C in 4 eyes (13.8%), stage 2A in 4 eyes (13.8%), and stage 2B in 4 eyes (13.8%). Complete regression of LSCD was achieved in 6 eyes (20.7%) with medical treatment addressing the primary etiology. In the remaining eyes, after medical treatment, the severity of LSCD decreased below the surgical threshold, which is considered stage 2B. The mean final BCVA was 0.07±0.1 logMAR (range, 0-0.4 logMAR).

Conclusion: This study highlights that LSCD can be completely or partially reversible with appropriate management, especially in cases with underlying limbal niche dysfunction, where inflammation plays a significant role. Although limbal stem cell transplantation is considered the main treatment approach for LSCD, localized and early-stage LSCD can be effectively managed medically without the need for surgical intervention.

Keywords: Limbal stem cell deficiency, marginal keratitis, ocular rosacea

Introduction

The limbus is a specialized region that hosts pluripotent limbal stem cells and forms a physical barrier between the avascular cornea and vascular conjunctiva. A healthy limbus is essential to the regeneration of the corneal epithelium and preservation of corneal transparency.[1,2] Limbal stem cell deficiency (LSCD) is characterized by limbal stem cell damage and impaired limbal barrier function. It may occur due to genetic (e.g., aniridia), acquired (e.g., chemical burns, vernal and atopic keratoconjunctivitis, contact lens use), or immunological (e.g., drug toxicity, ocular surface infection, ocular rosacea) causes.[3]

Limbal stem cell transplantation, the process of transplanting healthy limbal stem cells to the damaged limbal region, is considered the main treatment approach to LSCD. However, localized (i.e., early-stage) LSCD can be treated without surgical intervention.[4] This is especially true in cases where limbal niche function is impaired due to chronic ocular surface inflammation. Therefore, according to the current consensus regarding LSCD, it has become clear that cases associated with limbal niche dysfunction are partially or completely reversible with elimination of the causative factor and correct medical treatment.[3,5,6]

The aim of this study was to perform LSCD staging using the classification system defined by the International LSCD Working Group and evaluate the clinical characteristics and treatment strategies of patients in whom LSCD stage regressed with medical treatment.

Cite this article as: Korkmaz İ, Eratılgan NF, Palamar M, Eğrilmez S, Yağcı A, Barut Selver Ö. Evaluation of Medically Reversible Limbal Stem Cell Deficiency. Turk J Ophthalmol. 2024;54:251-256

This study was presented as a poster at the 57th Turkish Ophthalmological Association National Congress.

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Materials and Methods

Approval for this retrospective, cross-sectional study was obtained from the Ege University Faculty of Medicine Medical Research Ethics Committee (decision number: 24-4T/25, date: 04.04.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The study included 29 eyes of 21 LSCD patients managed medically in the Cornea Unit of Ege University Faculty of Medicine, Department of Ophthalmology between May 2013 and May 2023. The demographic and clinical characteristics of patients with improved LSCD stage after medical treatment without surgical intervention were evaluated from their medical records. Age, sex, laterality (unilateral/bilateral) and primary etiology of LSCD, medical treatment approach, and best corrected visual acuity (BCVA) before and after treatment were recorded.

Two different researchers evaluated the patients' anterior segment photographs and recorded the LSCD stages. LSCD stage before and after medical treatment was determined according to the global consensus on LSCD staging published by the International LSCD Working Group in 2019.[5] According to this staging system, LSCD was divided into 3 main groups based on the degree of corneal epithelial damage: stage 1, normal corneal epithelium in the central 5 mm area; stage 2, epithelial damage in the central 5 mm area; and stage 3, damage to the entire corneal epithelium. Stages 1 and 2 were also subdivided based on the extent of limbal involvement (A, B, and C for stage 1; A and B for stage 2) (Table 1).[5]

Patients who had a history of ocular trauma, underwent surgical treatment for LSCD, or had incomplete medical records were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics 25.0 package program (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.). The significance level was determined as $p<0.05$ for all analyses. Descriptive statistics of the data were given as mean, standard deviation, median, range, frequency, and percentage values.

Table 1. Global consensus on limbal stem cell deficiency staging published by the International LSCD Working Group in 2019[5]

Main stages		Subgroups	
Stage 1	Normal corneal epithelium in the central 5-mm zone	**A**	<50% limbal involvement
		B	≥50% to 100% limbal involvement
		C	100% limbal involvement
Stage 2	Corneal damage in the central 5-mm zone	**A**	<50% limbal involvement
		B	≥50% to 100% limbal involvement
Stage 3	Damage to the entire corneal surface		

LSCD: Limbal stem cell deficiency

Results

The mean age was 35.5±23.8 years (range, 5-71 years) and the male-to-female ratio was 6:15. LSCD was unilateral in 13 patients (62%) and bilateral in 8 patients (38%). The primary etiology of LSCD was ocular rosacea in 18 eyes of 12 patients (57.1%), blepharitis-related marginal keratitis in 10 eyes of 8 patients (38.1%), and drug toxicity in 1 eye of 1 patient (4.8%). The mean BCVA before treatment was 0.25±0.26 logarithm of the minimum angle of resolution (logMAR) (range, 0-1 logMAR). Pre-treatment LSCD stage was stage 1A in 5 eyes (17.2%), stage 1B in 12 eyes (41.4%), stage 1C in 4 eyes (13.8%), stage 2A in 4 eyes (13.8%) eyes, and stage 2B in 4 eyes (13.8%).

The mean BCVA after treatment was 0.07±0.1 logMAR (range, 0-0.4 logMAR). With etiology-targeted local and systemic medical treatment, LSCD resolved completely in 6 eyes (20.7%). The distribution of post-treatment LSCD stages in the other eyes was as follows: stage 1A in 16 eyes (55.2%), stage 1B in 4 eyes (13.8%), stage 1C in 1 eye (3.4%), and stage 2A in 2 eyes (6.9%) (Table 2).

Table 2. Demographic data and clinical findings of the patients

Demographic and clinical data	Results
Mean age (years), mean ± SD (range)	35.5±23.8 (5-71)
Sex (patients), n (%)	
Female	15 (71.4%)
Male	6 (28.6%)
Laterality (patients), n (%)	
Unilateral	13 (62%)
Bilateral	8 (38%)
Primary etiology (patients), n (%)	
Ocular rosacea	12
Blepharitis-related marginal keratitis	8
Medication toxicity	1
Medical treatment modality (eyes), n (%)	
Conservative treatment (topical steroid, antibiotic, lubrication)	9 (31%)
Topical cyclosporine	6 (20.7%)
Systemic treatment	14 (48.3%)
Pre-treatment LSCD stage (eyes), n (%)	
Stage 1A	5 (17.2%)
Stage 1B	12 (41.4%)
Stage 1C	4 (13.8%)
Stage 2A	4 (13.8%)
Stage 2B	4 (13.8%)
Post-treatment LSCD stage (eyes), n (%)	
Complete resolution	6 (20.7%)
Stage 1A	16 (55.2%)
Stage 1B	4 (13.8%)
Stage 1C	1 (3.4%)
Stage 2A	2 (6.9%)

SD: Standard deviation, LSCD: Limbal stem cell deficiency

Combined treatment with conservative measures (e.g., eyelash base cleaning, warm compress), lubrication support with preservative-free artificial tears (Eyestil single dose, Sifi, Italy), topical antibiotic (moxifloxacin 0.5%, Moxai, Abdi İbrahim, Türkiye), and topical corticosteroid (loteprednol etabonate 0.5%, Dolte, Abdi İbrahim Pharmaceuticals, Türkiye) resulted in improved LSCD stage in 9 eyes (31%; 7 with marginal keratitis, 2 with ocular rosacea). In another 6 eyes (20.7%) with ocular rosacea, improved LSCD stage was achieved by adding topical cyclosporine (cyclosporine A 0.05%, Depores, Deva, Türkiye) to this treatment. Systemic therapy was required for 13 (44.9%) eyes that did not respond to medical treatment (3 with marginal keratitis, 10 with ocular rosacea). Of these, 8 regressed with oral doxycycline (Tetradox, Teva Pharmaceuticals, Türkiye) and 5 regressed with oral azithromycin (Azitro, Deva Pharmaceuticals, Türkiye) (Figure 1). In 1 patient who developed LSCD due to topical antiglaucoma medication toxicity (0.5% betaxolol; Betoptic-S; Novartis; Alcon), the LSCD stage decreased from 2A to 1C after discontinuation of the preserved topical agents and treatment with topical corticosteroid, autologous serum, and oral doxycycline.

The mean follow-up period of the patients was 5.3±3 months (range, 1-13 months).

Discussion

The presence of healthy and functional limbal stem cells is critical for regeneration of the corneal epithelium and lifelong maintenance of ocular surface homeostasis. Limbal stem cells are found in the limbus region, and damage to this area from various etiologies results in LSCD, characterized by corneal vascularization, recurrent epithelial erosions, and corneal opacification. LSCD occurs as a result of limbal stem cell loss or dysfunction. The underlying mechanism varies according to the primary etiology.[7,8] Direct physical damage to the limbal region, as in chemical burns, Steven-Johnson syndrome, microbial keratitis, and contact lens use, may cause limbal stem cell aplasia. Alternatively, LSCD may develop due to impaired limbal stem cell function resulting from an abnormal microenvironment or insufficient stromal support, as in aniridia, peripheral inflammatory diseases, chronic limbitis, and neurotrophic keratopathy.[3]

The treatment approach in LSCD also varies according to the primary etiology and associated pathogenesis. Although there are different medical and surgical treatment approaches, until recently there was no clear consensus on the definitive surgical indication.[9,10,11] The International LSCD Working Group recently defined an LSCD staging system, and a global consensus on the diagnosis and treatment algorithm of LSCD was formed based on this system.[5,6] According to this consensus, a more conservative approach including medical therapy is recommended as initial treatment for asymptomatic and early-stage (stage 1 and 2A) LSCD cases. The primary goal of treatment is to provide ocular surface optimization, tear film stabilization, inflammation control, and sustained epithelial regeneration.[6] With the global consensus on the LSCD treatment algorithm, the importance of adopting a stepwise treatment approach has been emphasized.[6] There are a few studies in the literature showing that especially in early-stage LSCD secondary to inflammatory etiologies, elimination of the triggering factor and treatment with ocular surface lubrication, topical anti-inflammatory therapy, and systemic tetracycline leads to LSCD regression. However, data are scarce regarding the effectiveness of medical treatment in LSCD and what treatment algorithm to follow in such cases.[12,13,14] The present study showed that, in light of the recently published consensus on LSCD staging, LSCD can regress with appropriate medical treatment, especially in the early stages.

Another problem is that LSCD diagnosis and stage are determined using different criteria. LSCD staging is mostly based on clinical findings, which introduces the potential for subjectivity and bias when assessing treatment response.[14,15,16] In contrast, pre-treatment and post-treatment LSCD stages in our study were determined according to the global consensus on LSCD classification. This classification, defined by the

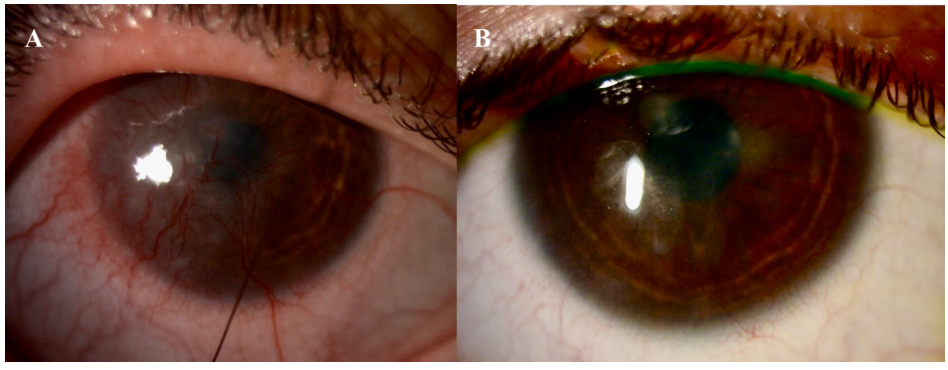

Figure 1. A 14-year-old girl diagnosed with ocular rosacea presented with redness and blurred vision. (A) On initial examination at the time of admission, 270 degrees of limbal insufficiency and central corneal opacity were observed. LSCD stage was recorded as 2B. The patient was treated with topical artificial tears (Eyestil single dose, Sifi, Italy), topical antibiotic (moxifloxacin 0.5%, Moxai, Abdi İbrahim, Türkiye), topical corticosteroid (loteprednol etabonate 0.5%, Dolte, Abdi İbrahim İlaç, Türkiye), topical cyclosporine A (0.05%, Depores, Deva, Türkiye), and oral doxycycline (Tetradox, Teva İlaç, Türkiye). (B) LSCD stage decreased to 1B after 6 months of treatment
LSCD: Limbal stem cell deficiency

International LSCD Working Group in 2019, aims to prevent the use of different parameters and subjective evaluations in determining LSCD severity.[5,6] Therefore, using this current and well-defined system for LSCD staging can provide a more objective interpretation when evaluating treatment response.

With appropriate patient selection and the right treatment algorithm, ocular surface healing can be achieved in LSCD patients without surgical intervention. The first step in medical treatment is to eliminate possible triggering factors such as contact lenses and preserved topical medications. Providing ocular surface lubrication to protect and support residual limbal stem cells is very important. Another step of treatment is controlling ocular surface inflammation with anti-inflammatory agents (e.g., topical corticosteroid, topical cyclosporine, oral tetracycline, systemic immunomodulators). When planning medical treatment, a stepwise treatment approach should be preferred, taking into account factors such as the primary etiology of LSCD, the condition of the ocular surface, and degree of LSCD.[6,17,18] In this study, medical treatment taking all of these parameters into account brought about regression in LSCD stage. The fact that most patients in the study (86.2%) had stage 2A or lower LSCD, in line with global consensus recommendations, may be a factor that increased the success of treatment. However, the 4 eyes (13.4%) with stage 2B LSCD also had an improved LSCD stage with medical treatment.

In advanced LSCD unresponsive to medical treatment, surgical treatment is unavoidable to ensure corneal homeostasis and healthy corneal epithelial regeneration. Limbal stem cell transplantation, the process of transplanting healthy limbal stem cells to the area of damage, is considered the main treatment approach for advanced LSCD.[2,3] According to the treatment algorithm established by the International LSCD Working Group in 2020 based on the LSCD staging system, limbal stem cell transplantation is recommended for stage 2B or higher LSCD.[6] However, our observation that LSCD stage regressed with medical treatment in 4 eyes with advanced (stage 2B) LSCD highlights the importance of medical treatment in advanced-stage patients as well. Therefore, in eyes with advanced-stage LSCD that indicates surgery, progression can be prevented with medical treatment until surgery. In these patients, medical treatment should be regarded as preparation for surgery, keeping in mind that it may contribute to ocular surface stability until limbal stem cell transplantation is planned.

In addition to the stage of LSCD, it is also important to recognize the etiologies of LSCD that can regress with medical treatment. Limbal niche dysfunction is the main pathogenetic factor in LSCD of inflammatory etiologies.[19] Pajoohesh-Ganji et al.[20] reported that limbal niche dysfunction due to trauma and inflammation caused goblet cell migration to the cornea. Tear film stabilization and inflammation control restore the limbal microenvironment, thereby helping to restore limbal niche function. Kim et al.[14] reported that LSCD could be managed with medical treatment alone in 22 eyes that developed LSCD due to contact lens wear, benzalkonium chloride toxicity, and idiopathic causes. Our study showed that LSCD stage regressed with medical treatment and conservative measures in patients who developed LSCD due to ocular rosacea, blepharitis-related marginal keratitis, and drug toxicity, which are inflammatory causes of LSCD.

Rosacea is a chronic skin disease, and approximately 58-72% of patients have ocular involvement. Ocular rosacea manifests with increased inflammation in the eyelids and ocular surface. The most common ocular effects are dry eye, conjunctivitis, and meibomian gland dysfunction. However, corneal involvement occurs in approximately 30% of patients with ocular rosacea. Increased ocular surface inflammation in untreated ocular rosacea cases causes loss of limbal niche and limbal stem cells. This can result in corneal neovascularization, recurrent epithelial defect, and corneal opacity.[21,22] In addition to conservative measures, artificial tear therapy, systemic and topical anti-inflammatory agents, and topical antibiotherapy are recommended when necessary. Kim et al.[14] showed that LSCD regressed with conservative measures plus a combination of topical corticosteroid, topical cyclosporine, and oral doxycycline in 3 eyes with ocular rosacea and soft contact lens use. In our study, 12 patients diagnosed with ocular rosacea developed LSCD without a history of contact lens use, and all of them exhibited regression of LSCD stage with medical treatment.

Contact lens wear itself is an important cause of LSCD due to chronic trauma to the ocular surface. Eliminating this factor alone often leads to dramatic improvement.[23] Martin[13] showed that whorl-like epitheliopathy in contact lens users responded to medical treatment. Because cases of contact lens-associated LSCD were usually followed up and treated on an outpatient basis in our clinic and resolved with modification of contact lens use without the need for aggressive medical treatment, these patients were not included in this study.

Increased bacterial flora at the lid margin and associated chronic inflammation play a major role in the pathogenesis of blepharitis-related marginal keratitis. In untreated cases, increased ocular surface inflammation leads to limbal niche dysfunction and secondary LSCD. Although the pathogenesis of secondary LSCD is common to both diseases, less aggressive treatment is generally sufficient for clinical regression in marginal keratitis compared to ocular rosacea.[3] In the present study, the majority of eyes diagnosed with marginal keratitis (70%) recovered without the need for systemic treatment, whereas most eyes with ocular rosacea (88.9%) required topical cyclosporine and systemic doxycycline therapy.

Drug toxicity is a relatively uncommon cause of LSCD. Iatrogenic causes account for approximately 5.5-7.3% of LSCD cases, and approximately 30% of them are due to drug toxicity. Drug toxicity-associated LSCD is especially associated with long-term use of topical agents containing preservatives.[12,24,25,26]

In this study, there was a history of long-term use of 3 anti-glaucomatous medications in the patient who developed LSCD due to drug toxicity. Discontinuing the preserved agents and providing supportive treatment resulted in regression of LSCD findings.

Study Limitations

The main limitations of this study include its retrospective design and the relatively small number of patients. There is a need for prospective studies that include more participants and compare different patient groups.

Conclusion

While chemical injuries or severe autoimmune reactions cause severe LSCD, certain pathological conditions such as ocular rosacea, blepharitis-related marginal keratitis, and medication toxicity give rise to a clinical picture of LSCD with limbal niche dysfunction. Consistent with the literature, the present study demonstrated that inflammation has a fundamental role and that LSCD is fully or partially reversible with correct management in cases with limbal niche dysfunction. With etiology-targeted local and systemic medical treatment, LSCD completely resolved in 6 eyes (20.7%) and in all other eyes regressed in severity to below stage 2B, which is the threshold for surgical treatment. Therefore, in the early stages and with the right indications, LSCD can be treated medically, without surgical intervention. Although limbal stem cell transplantation is the main treatment approach in eyes with advanced LSCD, medical treatment administered before surgery may contribute to ocular surface stabilization.

Ethics

Ethics Committee Approval: Ege University Faculty of Medicine Medical Research Ethics Committee (decision number: 24-4T/25, date: 04.04.2024).

Informed Consent: Retrospective study.

Authorship Contributions

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

Conflict of Interest: Sait Eğrilmez, MD, is an Associate Editor of the Turkish Journal of Ophthalmology. He was not involved in the peer review of this article and had no access to information regarding its peer review. The other authors have no disclosures.

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Original Article

Effects of Glaucoma Treatment on Ocular Surface and Tear Functions: Comparison of Trabeculectomy and Antiglaucoma Drops

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Abstract

Objectives: To investigate tear function and ocular surface disease (OSD) findings in patients with glaucoma who received antiglaucoma medication in one eye and trabeculectomy surgery in the other eye.

Materials and Methods: The patient group included 38 eyes of 19 patients who had undergone trabeculectomy surgery with mitomycin C (MMC) treatment in one eye at least 6 months prior. These eyes were followed up without medication while the fellow eye continued receiving antiglaucomatous medication. The control group comprised 20 eyes of 20 healthy individuals. Demographic data, follow-up period after trabeculectomy, antiglaucoma medications, number of drops per day, and duration of medication were recorded. Tear break-up time (BUT), corneal and conjunctival fluorescein staining, Schirmer II test, and conjunctival impression cytology were performed.

Results: A statistically significant difference was observed in BUT, corneal and conjunctival fluorescein staining, Schirmer II test, and Nelson staging levels in both eyes of patients with glaucoma compared to the control group (p=0.05). Although not statistically significant, BUT, Schirmer II test, punctate staining, and Nelson staging results showed improvement with increasing postoperative time.

Conclusion: In our patient group, antiglaucoma medications and trabeculectomy surgery with MMC induced OSD to a similar degree. No superiority was observed between trabeculectomy with MMC and antiglaucoma drops in terms of OSD incidence.

Keywords: Antiglaucoma drugs, conjunctival impression cytology, glaucoma, ocular surface disease, trabeculectomy

Introduction

The goal of glaucoma treatment is to maintain intraocular pressure within the target range, thereby protecting the optic nerve. Antiglaucoma drugs are usually the first line of treatment. However, prolonged topical antiglaucomatous therapy is associated with an increase in ocular surface disease (OSD). The most important factor in this is the preservatives rather than the active substance.[1]

Trabeculectomy remains the gold standard in glaucoma surgery. The main factor determining the success of trabeculectomy is wound healing. Unlike other surgeries, partial wound healing after surgery is desired. The premature or excessive formation of scar tissue at the interface of the conjunctiva, Tenon's capsule, and episclera at the bleb site results in surgical failure. Antifibrotic agents such as 5-fluorouracil and mitomycin C (MMC) have enhanced the success rates of filtering glaucoma surgery.[2] OSD can occur after trabeculectomy and antimetabolite use.[3]

In this study, glaucoma patients received topical antiglaucoma medication in one eye and MMC-augmented trabeculectomy with no further medical treatment in the fellow eye. The incidence and severity of OSD after treatment were compared between the patients' fellow eyes and with a healthy control group. Hence, we aimed to compare antiglaucoma drugs and MMC-augmented trabeculectomy in terms of OSD occurrence.

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Materials and Methods

Ethical approval was obtained from the Mersin University Faculty of Medicine Clinical Research Ethics Committee (protocol no: 06/251, date: 17.03.2021). The study was conducted according to the principles of the Declaration of Helsinki. Informed consent forms were obtained from all patients and control participants.

Patients who underwent unilateral trabeculectomy with MMC (0.2 mg/mL, 2 minutes) for glaucoma between January 2012 and January 2021 at the Mersin University Medical Faculty Hospital, Department of Ophthalmology were screened. The patient group comprised 38 eyes from 19 patients who underwent trabeculectomy with MMC and subsequent follow-up without medication in one eye while the fellow eye remained unoperated and was treated with various topical antiglaucoma medications.

The control group included the right eyes of 20 healthy volunteers. These individuals sought care at Mersin University Faculty of Medicine Hospital, Department of Ophthalmology between March and May 2021. The control group had no history of OSD or ocular surgery.

The age range was 7 to 80 years in both groups. Exclusions from the study comprised patients who had undergone trabeculectomy less than six months ago, continued to use topical antiglaucoma medication in the operated eye after trabeculectomy, had a history of ocular trauma or surgery other than trabeculectomy, used artificial tears, used contact lenses, were pregnant or lactating, or had a history of uveitis.

All eyes included in the study underwent the tear break-up time (BUT) test, Schirmer II test, corneal and conjunctival fluorescein staining, and conjunctival impression cytology. At least 15 min were allowed between tests. Age and sex of the participant were recorded.

In the patient group, the following details were also recorded: antiglaucoma medications used, number of drops per day, duration of use, and time elapsed since MMC-augmented trabeculectomy (months). All test results were compared between patient subgroups defined according to the time since trabeculectomy (8-47 months vs. ≥48 months).

Tear Break-up Time Test

A standard fluorescein strip was applied to the lower fornix without topical anesthetic. The patient was asked to blink several times to spread the dye well, and the tear film layer was observed under wide illumination using a cobalt blue filter on a slit lamp. The time from the patient's last blink to the first dry area was determined in seconds. This measurement was repeated thrice, and the mean value was recorded as the BUT value. Tear BUT was graded as follows: <5 s (severe), 5-9 s (mild), and ≥10 s (normal).

Schirmer II Test

A 35-mm-long, 5-mm-wide standard filter paper was moistened with topical anesthetic and placed in the outer third of the lower eyelid for the test. Care was taken to prevent the filter paper from touching the cornea. Patients were told to blink if necessary and to keep their eyes open. The wetted portion of filter paper from the lid edge was measured in millimeters after 5 min. The grading used for the test was as follows: <5-mm (severe), 5-10-mm (mild), and ≥11-mm (normal).

Corneal and Conjunctival Fluorescein Staining Test

The corneal staining tests were graded using a slit lamp microscope at x16 magnification, under uniform illumination, and by the same observer. Care was taken to slightly elevate the upper eyelid to evaluate the entire corneal surface. The grading denoted the degree of staining, not the number of stained spots. The Oxford grading scheme was employed to standardize the degree of dye uptake.[4]

Conjunctival Impression Cytology

Samples were obtained from the superotemporal bulbar conjunctiva using one drop of 0.5% proparacaine hydrochloride topical anesthesia (all patients had trabeculectomy surgery in the upper nasal quadrant). Cellulose acetate filter paper with 0.22-µm pore diameter (Millipore) was cut into 5 mm x 5 mm x 5 mm triangles. The filter paper was held with toothless pliers, and the matte surface was pressed against the conjunctiva for 4-5 s. After lifting the edge of the filter paper with pliers, the cell samples were placed face-up in a fixation solution containing glacial acetic acid, 37% formaldehyde, and 70% ethyl alcohol at a volume ratio of 1:1:20. Cellulose acetate filter papers soaked and containing conjunctival epithelial cells were stored in a refrigerator at +4 °C. The samples were fixed to a microscope slide with a metal clip and stained with periodic acid Schiff/hematoxylin/eosin. Cellular changes were staged between 0 and 3 according to the Nelson staging system (Figure 1).[5,6]

Statistical Analysis

Descriptive statistics are presented as mean (± standard deviation) for continuous variables, whereas categorical variables are presented as frequencies and percentages. Independent t-test

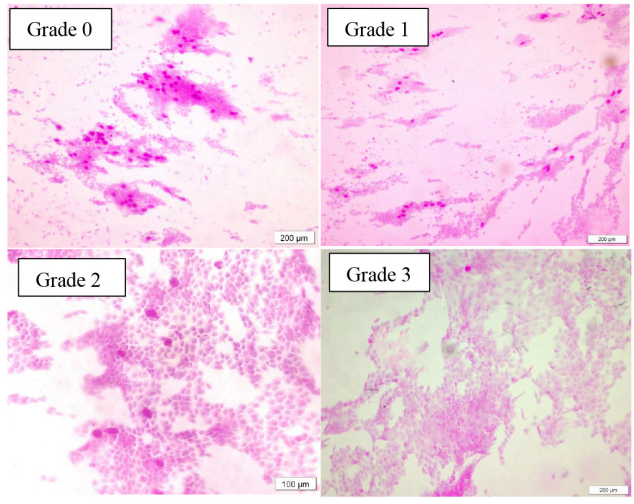

Figure 1. Examples of our conjunctival impression cytology images according to Nelson grading system

was used to determine the difference between the two groups, and one-way analysis of variance was used for more than two groups. The chi-square test was used to analyze categorical variables. The significance level (p value) was set at 0.05 for all variables. All statistical analyses were performed using the Statistica 13 package program.

Results

The study involved 19 glaucoma patients, consisting of 13 males (68.4%) and 6 females (31.6%). Additionally, there were 20 control participants, including 14 males (70%) and 6 females (30%). The mean age of the glaucoma patients was 53.11 (±21.17) years, whereas that of the control group was 56.20 (±19.94) years. There was no statistically significant difference between the patient and control groups in terms of age or sex distribution (p>0.05).

The mean duration of topical antiglaucoma medication was 6.62 (±3.06) years, and the mean number of drops per day was 2.42 (±0.83) drops. The mean follow-up time after trabeculectomy was 38.63±26.29 months.

In the drug group, Schirmer II values were below 5 mm in 1 patient, 5-10-mm in 7 patients, and over 10-mm in 11 patients. In the MMC-augmented trabeculectomy group, Schirmer II values were below 5-mm in 2 patients, 5-10-mm in 5 patients, and over 10-mm in 12 patients. All individuals in the control group had Schirmer II values greater than 10 mm. In the drug group, tear BUT was less than 5 seconds in 4 patients, 5-10 seconds in 4 patients, and longer than 10 seconds in 11 patients. In the MMC-augmented trabeculectomy group, tear BUT was less than 5 seconds in 1 patient, 5-10 seconds in 7 patients, and longer than 10 seconds in 11 patients. BUT was longer than 10 seconds in all individuals in the control group. There were no statistically significant differences between the surgically and medically treated fellow eyes in either test (p>0.05). However, both eyes of the patients had significantly lower results in the BUT and Schirmer II tests when compared with the control group (p<0.05) (Figures 2 and 3).

There was no fluorescein staining in 8 patients in the drug group, while there was mild staining in 4, moderate staining in 5, and severe staining in 2 patients. There was no fluorescein staining in 8 patients in the MMC-augmented trabeculectomy group, while there was mild staining in 3, moderate staining in 7, and severe staining in 1 patient. There was no fluorescein staining in any of the control group individuals. Corneal and conjunctival fluorescein staining did not differ significantly between the surgically and medically treated eyes of patients with glaucoma (p>0.05) but was more severe in patients than controls (p<0.05) (Figure 4).

In conjunctival impression cytology, the distribution of patients staged as grade 0, 1, 2, and 3 was 5, 5, 5, and 4 in the drug group and 2, 7, 3, and 7 in the MMC-augmented trabeculectomy group, respectively (p>0.05). A statistically significant difference was observed between both eyes of the patients and the control group in terms of Nelson staging (p>0.05) (Figure 5).

When patients with postoperative periods of 8-47 months and ≥48 months were compared, there was no statistically significant difference in BUT, Schirmer II, corneal and conjunctival fluorescein staining, or conjunctival impression cytology results (p>0.05, independent t-test). Nevertheless, with an increase in the postoperative period, all test results were observed to improve, although not statistically significantly (Table 1).

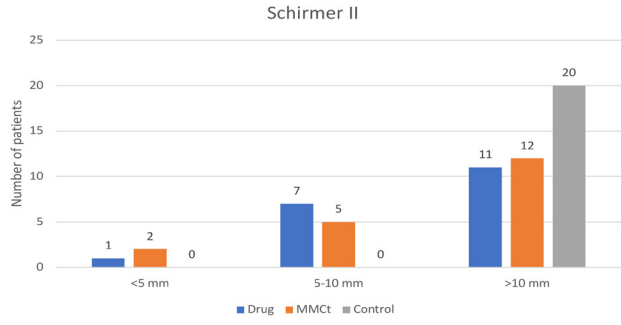

Figure 3. Distribution of Schirmer II results in the drug, MMCt, and control groups
MMCt: Mitomycin C augmented trabeculectomy

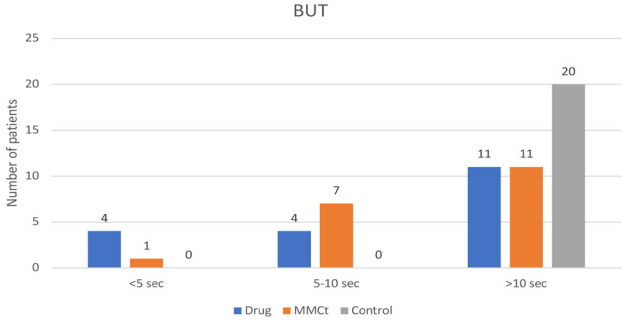

Figure 2. Distribution of tear break-up time results in the drug, MMCt, and control groups
BUT: Tear break-up time, MMCt: Mitomycin C augmented trabeculectomy

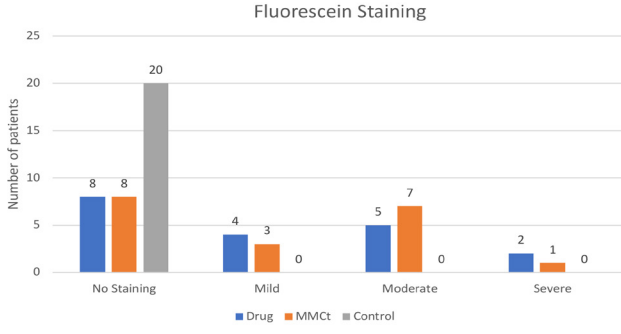

Figure 4. Distribution of fluorescein staining test results (Oxford scheme) in the drug, MMCt, and control groups
MMCt: Mitomycin C augmented trabeculectomy

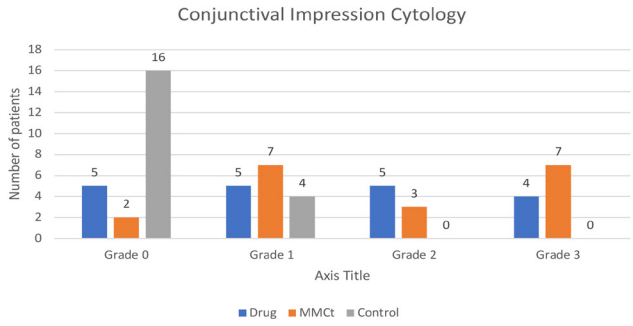

Figure 5. Distribution of conjunctival impression cytology results (Nelson grading system) in the drug, MMCt, and control groups
MMCt: Mitomycin C augmented trabeculectomy

Table 1. Comparison of tear break-up time, Schirmer II, fluorescein staining and conjunctival impression cytology results of 8-47 months and ≥48 months subgroups according to the time since trabeculectomy surgery (independent t-test)

		8-47 months (n=10)	≥48 months (n=9)	p value
BUT	<5 sec	10%	0%	0.553
	5-10 sec	40%	33.3%	
	>10 sec	50%	66.7%	
Schirmer II	<5 mm	20%	0%	0.340
	5-10 mm	20%	33.3%	
	>10 mm	60%	66.7%	
Fluorescein staining	No staining	40%	44.4%	0.699
	Mild	10%	22.2%	
	Moderate	40%	33.3%	
	Severe	10%	0%	
Conjunctival impression cytology	Grade 0	10%	11.1%	0.903
	Grade 1	40%	33.3%	
	Grade 2	10%	22.2%	
	Grade 3	40%	33.3%	

BUT: Tear break-up time

Discussion

In our daily practice, dry eye syndrome is diagnosed based on the results of Schirmer's test, BUT, ocular surface staining with fluorescein, and the presence of ocular irritation symptoms.[7] In glaucoma patients, tear dysfunction is mainly attributed to the chronic administration of preservative-containing glaucoma medications. While moderate dry eye is known to develop with age, the rate of age-related dry eye disease is 15% in patients of comparable age without glaucoma.[8] Given the impact of patient age on the tear film, our study exclusively included patients and controls with similar age and sex distributions.

In a recent study, Yıldırım et al.[9] reported that 45% of ophthalmologists noticed OSD was evident in least 25% of their patients. Antiglaucoma therapy-induced OSD is largely due to preservatives rather than the active molecule.[10,11,12] Benzalkonium chloride (BAK) is the most commonly used preservative. BAK disrupts tear film stability and causes goblet cell loss, conjunctival squamous metaplasia, apoptosis, corneal epithelial barrier disruption, and corneal nerve damage.[13,14,15,16,17,18,19]

Trabeculectomy is a widely used surgical intervention to manage intraocular pressure in patients with glaucoma unresponsive to medical therapy. Previously, MMC was only used as an adjunctive treatment for failed trabeculectomy or complicated cases. Currently, MMC is used for primary trabeculectomy in both adults and children. In our study, all patients with glaucoma underwent trabeculectomy with MMC. Kim[20] indicated potential long-term damage to the bleb's conjunctival epithelium after trabeculectomy with MMC. In subsequent years, through immunofluorescent staining on impression cytology samples taken from the bleb area, Amar et al.[21] demonstrated that blebs without antimetabolites exhibited only scattered inflammatory cells, whereas blebs with MMC showed a higher presence of dendritiform inflammatory cells. Baiocchi et al.[22] found that the inflammatory reaction after trabeculectomy using MMC was more pronounced than that after the surgical procedure associated with the Xen 45 Gel Stent. MMC increases the success rate of trabeculectomy but may have toxic effects on the conjunctiva. Various studies have indicated that trabeculectomy efficiently reduces intraocular pressure and improves control of 24-hour mean pressure but can extensively alter the ocular surface anatomy, inducing a persistent clinical or subclinical inflammatory process.[23,24]

Comparison of tear function tests between the patient and control groups demonstrated significantly lower BUT and Schirmer II values in both eyes of the patients. Schirmer II test results were similar in the trabeculectomy group and topical medication group (p=0.701). Despite the shorter tear BUT in medically treated eyes, there was no statistically significant difference compared to the trabeculectomy group (p=0.270). These results suggest that both antiglaucoma drugs and trabeculectomy with MMC may affect the mucin and aqueous layers of the tear film and result in OSD at a similar rate. The presence of a bleb may also disrupt the uniform distribution of tears on the cornea, leading to worsening of tear function test results. However, there were no data on tear function and degree of ocular surface discomfort in patients before trabeculectomy.

When corneal and conjunctival fluorescein staining results were compared between the patient and control groups, significantly higher Oxford grading scores were observed in both eyes of the patients. Similar results were reported in other studies in which BAK-preserved topical medications were mostly used for treatment. Superficial punctate keratitis has been reported in 50% of patients treated with three drugs per day.[25,26,27,28] This result shows that chronic ocular surface cell damage can occur in

both treatment groups.

Impression cytology is a well-established method to diagnose OSDs. After long-term use of antiglaucoma drugs, ocular surface and tear secretion changes have been noted. There is a relationship between the course of topical antiglaucoma treatment and conjunctival changes like thickened conjunctival epithelium, abnormal keratinization, and loss of conjunctival goblet cells.[29] The most common changes after the use of 0.02% MMC are loss of goblet cells, abnormal nucleus/cytoplasm ratio, less cell-to-cell adhesion, and reduced cellularity.[30] Our comparison of the conjunctival impression cytology samples based on the Nelson staging system revealed a deterioration in the morphological structure of the conjunctival epithelial cells and a significant decrease in goblet cell density in the eyes of glaucoma patients compared to controls. Contrary to our expectation, Nelson staging results were more severe in the trabeculectomy group. However, there was no statistically significant difference in comparison to the topical medication group (p=0.401). This result may be attributed to the fact that patients undergoing trabeculectomy receive multidrug therapy for several years preoperatively, along with the negative effects of MMC and the filtration bleb on the conjunctival epithelium and goblet cells.[10,11,12,22] We also observed an improvement in the conjunctival impression cytology results with an increasing time after trabeculectomy, although the improvement was not statistically significant.

In eyes undergoing trabeculectomy surgery, these outcomes may be attributed to several factors: the chronic impact of BAK on the ocular surface due to long-term topical antiglaucoma treatment received preoperatively; extensive alteration of the ocular surface anatomy by the postoperative bleb; and/or the effect of MMC on the conjunctival epithelium and goblet cells. The number of individuals included in the patient group may also have affected our results. Results may differ in larger patient groups. Studies that follow patients from the initial diagnosis will be useful in detecting ocular surface changes during the treatment process.

In a recent prospective study, Pathak Ray et al.[31] concluded that the ocular surface was affected even in asymptomatic patients in the drug group but near normalcy is possible following trabeculectomy when blebs are diffuse. The authors compared 36 eyes in the trabeculectomy group, 33 eyes in the drug group, and 35 normal eyes. As their study included a larger sample than ours, it could be a valuable study on this subject. In our opinion, our study is important because it is the only study in the literature comparing antiglaucoma drug therapy and trabeculectomy in the same individuals.

Study Limitations

There are limiting factors in this study. The frequency of OSD increases over time in patients with glaucoma. Before trabeculectomy, all patients were receiving maximum topical antiglaucoma therapy. However, no information was available about how long they used this treatment. There was no data regarding the BAK or other preservative content of the drugs used in the patient eyes. However, as one eye of each patient was included in the medication group and the fellow eye was included in the trabeculectomy group, similar medications were used in both groups.

Conclusion

Topical antiglaucoma medications and trabeculectomy surgery with MMC caused similar severity of OSD in our glaucoma patient group. When selecting a medication, it is essential to consider the long-term nature of the treatment. Whenever possible, initiation of the treatment should involve a single drug, and preservative-free alternatives should be considered. After trabeculectomy surgery with MMC, OSD findings tended to improve with a longer follow-up, although the improvement was not statistically significant. Therefore, in terms of OSD in patients with glaucoma, there is no superiority between drug therapy and trabeculectomy with MMC in the early period. However, trabeculectomy with MMC may become more advantageous in later years with the elimination of drug use.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Mersin University Faculty of Medicine Clinical Research Ethics Committee (protocol no: 06/251, date: 17.03.2021).

Informed Consent: Obtained.

Authorship Contributions

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

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Original Article

Does Laser Iridotomy Cause Secondary Epiretinal Membrane?

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Abstract

Objectives: This study aimed to determine the frequency of epiretinal membrane (ERM) in the long term after neodymium-doped yttrium aluminum garnet laser iridotomy (LI) using spectral domain optical coherence tomography (SD-OCT).

Materials and Methods: This retrospective study included 94 eyes that underwent LI for primary angle-closure glaucoma, were followed for at least 4 years, and had no ERM before the procedure. The control group consisted of 66 eyes that were followed for suspected glaucoma did not have a previous ERM. We compared the ERM frequencies of the groups at the last visit. Additionally, ERM frequencies were compared between those who had cataract surgery in the post-LI period and those who did not.

Results: After a follow-up period of at least 4 years, ERM developed in 36 of 94 eyes (38.2%) in the LI group. Of these, 32 were stage 1 ERM (34.0%) and 4 were stage 2 ERM (4.2%). In the control group, ERM developed in 13 of 66 eyes (19.6%), 12 of which were stage 1 ERM (18.1%) and 1 was stage 2 ERM (1.5%) (p=0.012). ERM developed in 14 of 32 eyes (43.7%) who underwent phacoemulsification surgery after LI and in 22 of 62 eyes (35.4%) that underwent only LI without subsequent cataract surgery (p=0.435). ERM developed significantly more frequently in the 62 phakic eyes that underwent only LI than in the eyes in the control group (p=0.045)

Conclusion: LI appears to be a predisposing factor for the development of ERM, regardless of subsequent cataract surgery.

Keywords: Epiretinal membrane, laser iridotomy, spectral domain optical coherence tomography

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Introduction

Epiretinal membrane (ERM) is an avascular fibrocellular proliferation at the vitreomacular interface.[1,2] It mostly occurs idiopathically at older ages. However, it can also develop secondary to retinal vascular diseases, inflammatory diseases, trauma, repeated intravitreal injections, previous cataract and glaucoma surgery, and rhegmatogenous retinal detachment surgery.[3,4,5,6,7,8] Although ERMs are usually identified by fundus examination, optical coherence tomography (OCT) is more sensitive than slit-lamp examination.[9]

Primary angle-closure glaucoma (PACG) is one of the major causes of blindness worldwide. Although more than one mechanism may be effective in angle closure, the main pathology in most cases is pupillary block. Therefore, the first treatment option is neodymium-doped yttrium aluminum garnet (Nd:YAG) laser peripheral iridotomy (LI).[10] A temporary low-grade iritis may develop after the procedure. Additionally, iris pigments are scattered into both the anterior chamber and the posterior chamber.[11] While anterior segment complications such as corneal endothelial damage, iris bleeding, temporary intraocular pressure (IOP) elevation, and lens damage can often be observed after LI, posterior segment complications are encountered less frequently.[12,13,14]

It has been shown that the frequency of ERM increases after trabeculectomy and Ex-Press glaucoma filtration device implantation surgeries due to increased inflammation and IOP fluctuations.[8,15]

This study investigated the effect of LI on the frequency of ERM in the long term with spectral domain (SD)-OCT.

Materials and Methods

Ethical Approval

This retrospective study was approved by the Institutional Ethics Board of the University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital (reference number: 2023/152; date: 06/09/2023) and was performed in accordance with the principles of the Declaration of Helsinki.

Since the study was retrospective, informed consent was not required.

Participants

The records of patients diagnosed with PACG, primary angle-closure (PAC), or as a primary angle-closure suspect (PACS) and treated with LI in the glaucoma unit of our clinic between January 2017 and June 2019 were retrospectively examined. LI was applied to 312 eyes. Reliable pre-procedural OCT records could not be found for 71 of these eyes, and 88 eyes did not have a follow-up period of at least 4 years. Exclusion criteria were as follows: 1) history of ocular surgery (including cataract) before LI; 2) ocular surgery other than uncomplicated phacoemulsification surgery during the follow-up period after LI; 3) any vitreomacular interface disease (such as posterior vitreous detachment, vitreomacular adhesion, vitreomacular traction, macular hole, pseudohole, or ERM) at the first visit; 4) age-related macular degeneration or any retinal vascular disease; 5) retinal argon laser treatment for any reason; 6) exfoliation material in the anterior segment; 7) anti-vascular endothelial growth factor treatment; 8) media opacity impeding reliable OCT imaging (defined as signal strength >6); 9) axial length (AL) <21 mm or >26 mm; and 10) spherical refraction greater than ±5 diopters (D) or cylindrical refraction greater than ±3 D. Additionally, eyes with acute angle-closure glaucoma treated with LI were excluded from the study. Another 59 eyes were not included in the study due to the exclusion criteria. Thus, 94 eyes of 52 patients were included in the study.

The control group consisted of 66 eyes of 36 age-matched patients who were referred to the glaucoma unit due to suspicion of glaucoma, were examined annually due to risk factors, underwent imaging with the same SD-OCT device, had at least 4 years of follow-up, and met the selection criteria.

After at least 4 years of follow-up, the frequency of ERM was compared between eyes treated with LI and the eyes of controls. In addition, the frequency of ERM was compared between eyes that did and did not undergo cataract surgery after LI.

All subjects underwent a complete ophthalmologic examination. Visual acuity, IOP measurements, gonioscopy, optic nerve status, visual field examinations, number of medications, and the presence or absence of exfoliation were recorded. The best corrected visual acuity of all patients was measured according to the Snellen chart and converted to logarithm of the minimal angle of resolution (logMAR) values for statistical evaluations. AL was measured by optical biometry (IOLMaster 500, Carl Zeiss Meditec, Dublin, CA, USA). The trabecular meshwork was evaluated by gonioscopy using a goniolens with undilated pupil in a dark room. Images were taken using a Cirrus HD-OCT (Model 5000 Carl Zeiss Meditec, Inc., Dublin, CA, USA) at all visits. As previously described, eyes with iridotrabecular contact where at least 180 degrees of pigmented trabecular meshwork could not be seen on gonioscopic examination, IOP <21 mmHg, and no peripheral anterior synechiae were classified as PACS. Eyes with an iridotrabecular contact of at least 180 degrees and an IOP >21 mmHg or peripheral anterior synechiae detected on gonioscopic examination were defined as PAC. In addition to these findings, eyes that showed characteristic optic disc damage or loss of the retinal nerve fiber layer by other examination methods were defined as PACG.[16]

Laser Procedures

In all patients, 2% pilocarpine (Pilosed, Bilim ilaç, İstanbul, Türkiye) was instilled 3 times at 5-minute intervals before the procedure. A Q-switched Nd-YAG laser device was used for the procedure (Tango, Ellex, Adelaide, Australia). LI was applied by an experienced glaucoma specialist (N.T.) in the areas where the iris was thin in the upper quadrants (between 10 and 2 o'clock) using an Abraham iridotomy contact lens (Ocular Instruments Inc.). The power started at 2 mJ and went up to 6 mJ. The number of shots varied with iris thickness. The total energy used and the number of shots were recorded. Observation of the passage of aqueous humor from the posterior chamber to the anterior chamber and the spread of iris pigments from the iridotomy area indicated sufficient LI patency. One hour later, the patients were examined again. The patency of the LI was evaluated both directly and by retroillumination during slit-lamp examination. In 4 eyes evaluated as having insufficient LI patency, the procedure was repeated and the number of shots and energy used were added to the values of the first procedure. Topical loteprednol etabonate 0.5% (Lotemax, Bausch+Lomb, NY, USA) was prescribed to all patients 4 times a day for 1 week.

Optical Coherence Tomography Imaging

All OCT scans were performed with SD-OCT (Cirrus HD-OCT 5000, Carl Zeiss Meditech, Dublin, CA, USA) which has an A-scan velocity of 27,000 scans/second with a 5-µm axial and 15-µm lateral resolution and a scanning depth of 2 mm. The instrument uses light of 840 nm wavelength. The Macular Cube protocol acquires 128 B-scans, each composed of 512 A-scans. Central macular thickness (CMT) was calculated using the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. CMT was defined as the mean thickness of the macula on the central 1 mm of the ETDRS grid. All measurements were performed by the same technician. All OCT images were evaluated by two experienced researchers (O.A., N.T.). There was consensus on all images.

ERM staging was performed using the classification described by Govetto et al.[17] According to this staging, in stage 1 ERM, the foveal contour is preserved and the retinal layers can be well distinguished (Figure 1). In stage 2 ERM, retinal layers can be distinguished but the foveal depression has disappeared. Additionally, tension in the outer nuclear layer is evident (Figure 2). In stage 3, in addition to stage 2, an ectopic inner foveal layer (EIFL) is seen passing through the central fovea. In stage 4, retinal thickness has increased significantly. There is a significant deterioration in the macula. The EIFL is also seen at this stage, but the retinal layers cannot be distinguished.

Statistical Analysis

SPSS version 26 program (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis of the study. Descriptive data were expressed as mean and standard deviation. Independent

t-test was used for comparisons of continuous variables between the LI group and the control group. The chi-square test was used for categorical variables. All statistical analyses were 2-sided and a p value lower than 0.05 was considered statistically significant.

Results

The clinical and demographic characteristics of the patients are shown in Table 1.

Nd:YAG LI was applied to a total of 94 eyes, including 30 eyes with a diagnosis of PACS, 33 eyes with a diagnosis of PAC, and 31 eyes with a diagnosis of PACG. A mean of 15.01±5.03 mJ of energy was used in a mean of 5.2±2.3 shots. The mean IOP was 16.7±3.2 mmHg before LI and 16.1±1.9 mmHg at the last follow-up (p=0.015). A mean of 1.59±1.3 topical antiglaucoma drugs were used before LI, while 1.18±1.2 were used at last follow-up (p<0.001). Uncomplicated phacoemulsification surgery was performed in 32 of the eyes in the LI group an average of 13.9±9.1 months after the procedure.

After a follow-up period of at least 4 years, ERM developed in 36 of 94 eyes (38.2%) in the LI group. Of these, 32 were stage 1 ERM (34.0%) and 4 were stage 2 ERM (4.2%). In the control group, ERM developed in 13 of 66 eyes (19.6%). Twelve of these were stage 1 ERM (18.1%) and 1 was stage 2 ERM (1.5%) (p=0.012) (Table 2). There was no development of stage 3 or 4 ERM in either group.

ERM developed in 14 of 32 eyes (43.7%) that underwent phacoemulsification surgery after LI. Twelve of these were stage 1 ERM (37.5%) and 2 were stage 2 ERM (6.2%). ERM developed in 22 of 62 eyes that underwent LI only (35.4%). Twenty of these were stage 1 ERM (32.2%) and 2 were stage 2 ERM (3.2%) (p=0.435) (Table 2).

ERM developed significantly more frequently in the 62 phakic eyes in the LI group than in the control group (p=0.045). At the end of the follow-up period, ERM developed in 10 of 30 eyes with PACS, 23 of 33 eyes with PAC, and 16 of 31 eyes with PACG (p=0.171). The mean IOP of patients in the LI group was 16.7 mmHg before the procedure and 17.3 mmHg at 1 hour after the procedure (p=0.053).

In the control group, visual acuity decreased from 0.06±0.09 logMAR to 0.09±0.13 logMAR during follow-up (p<0.001). In the LI group, it increased from 0.39±0.17 logMAR to 0.1±0.11 logMAR in those who had cataract surgery (p<0.001) and decreased from 0.1±0.12 logMAR to 0.14±0.15 logMAR in phakic eyes (p<0.001).

The CMT values of the LI and control groups were similar both at baseline and the last visit (Table 1).

Discussion

In this study, we tried to determine the long-term effect of Nd:YAG LI on the frequency of ERM. We observed that ERM developed significantly more in the eyes of the LI group than in controls. We found that phacoemulsification surgery performed after LI had no additional effect on the development of ERM.

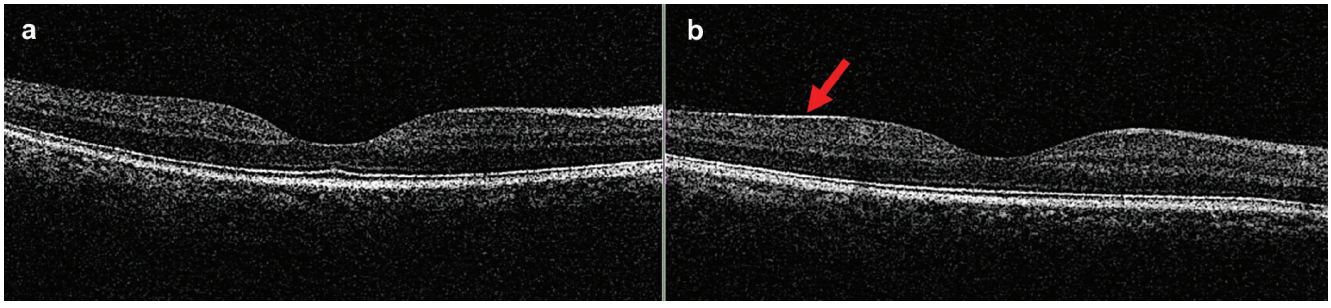

Figure 1. Two spectral-domain optical coherence tomography images of the same patient taken before Nd:YAG laser iridotomy (a) and after 56 months of follow-up (b). The red arrow shows the stage 1 ERM
Nd:YAG: Neodymium-doped yttrium aluminum garnet, ERM: Epiretinal membrane

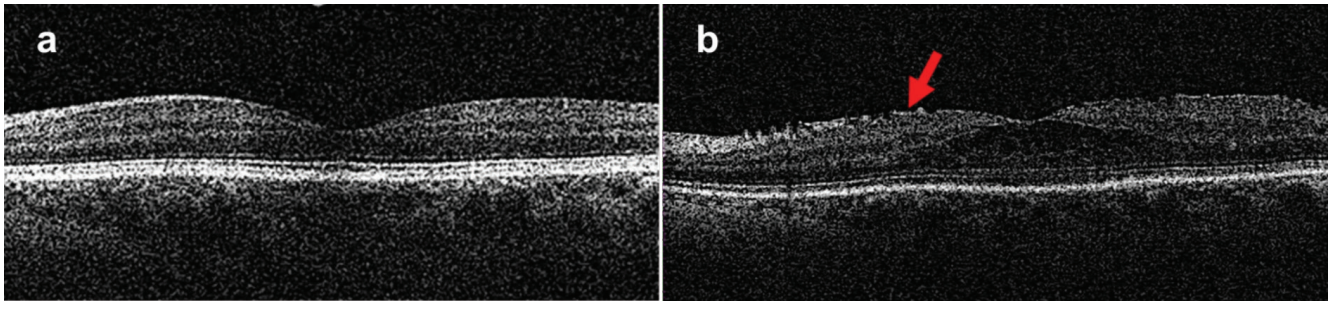

Figure 2. Two spectral-domain optical coherence tomography images of the same patient taken before Nd:YAG laser iridotomy (a) and after 61 months of follow-up (b). The red arrow indicates stage 2 ERM
Nd:YAG: Neodymium-doped yttrium aluminum garnet, ERM: Epiretinal membrane

Table 1. The clinical and demographic characteristics of the patients

	LI group (n=94)	Control group (n=66)	p value
Age (years)	64.03±8.2 (48-80)	66.2±5.9 (51-80)	0.063
Sex (F/M)	33/19	17/19	0.131
BCVA (logMAR) at baseline	0.2±0.2	0.06±0.09	**<0.001**
BCVA (logMAR) at last visit	0.13±0.14	0.09±0.13	0.097
IOP (mmHg)	16.7±3.2	16.1±2.6	0.244
AL (mm)	23.35±0.9	23.31±0.9	0.781
CMT (µm) at baseline	246.6±19	248.1±19	0.636
CMT (µm) at last visit	262.4±21	260.9±21	0.658
Follow-up time (months)	59.1±5.8	55.05±4.1	**<0.001**

Significant p values (<0.05) are indicated in bold. LI: Laser iridotomy, F: Female, M: Male, BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimal angle of resolution, IOP: Intraocular pressure, AL: Axial length, CMT: Central macular thickness

Table 2. The frequency of ERM between the phakic and pseudophakic eyes in the LI group and between the LI and control groups

	LI group				Control group	p value*
	Phakic LI	Pseudophakic LI	p value	Total		
ERM, n/total (%)	22/62 (35.4)	14/32 (43.7)	0.435	36/94 (38.2)	13/66 (19.6)	**0.012**

*LI vs. control group. Significant p values (<0.05) are indicated in bold. ERM: Epiretinal membrane, LI: Laser iridotomy

Vieira et al.[8] attempted to determine the frequency of ERM after trabeculectomy in eyes diagnosed with primary open-angle glaucoma. For this purpose, they retrospectively examined 50 eyes of 40 patients with an average follow-up of 27.5 months. They observed that ERM developed in 28 of 50 eyes (56%), 19 (38%) of which were cellophane macular reflex (CMR) and 9 (18%) were premacular fibrosis (PMF). They reported that 16 of these patients had preoperative OCT, 3 of them (18.8%) developed ERM, and 4 of them (25%) had progression from CMR to PMF. They observed that intraoperative antimetabolite use or phacoemulsification surgery combined with trabeculectomy had no additional effect on the development of ERM. In our study of 94 eyes that underwent LI, ERM developed in 36 eyes (38.2%) within an approximately 5-year follow-up period. The lower prevalence of ERM development despite the longer follow-up in our study may be attributed to several factors. First, it can be considered that trabeculectomy is a more traumatic surgery for ocular tissues than LI. The resulting increased inflammation may cause more secondary ERM development. Another factor may be greater IOP fluctuations after trabeculectomy. No large IOP fluctuations are seen after LI except in acute angle-closure glaucoma. Patients with acute angle-closure glaucoma were not included in our study.

Loiudice et al.[15] reported that over a 6-month follow-up with SD-OCT, ERM developed in 18 of 54 eyes (34%) in which they implanted an Ex-Press glaucoma filtration device due to primary open-angle glaucoma. They observed that ERM developed in 9 (17%) of these patients' fellow eyes treated with only topical antiglaucoma drugs as the control group. They also reported that the combined phacoemulsification surgery had no effect on the development of ERM. The authors concluded that although the pathophysiology of ERM development after this surgery is not fully known, the lower incidence of ERM might be explained by the presence of less inflammation and less IOP fluctuations compared to trabeculectomy. The rate of ERM was higher in our study, but we think this is due to our long follow-up period, not to inflammation or IOP fluctuation. In addition, in the study by Loiudice et al.[15], there was a significant increase in visual acuity in eyes that underwent combined surgery, whereas there was no significant change in those that received only the Ex-Press glaucoma filtration device implant. In our study, there was a significant increase in visual acuity in patients in the LI group who underwent cataract surgery. However, there was a decrease in visual acuity in both the phakic patients who underwent LI and the patients in the control group. We think that this may be due to refractive changes or nuclear thickening that may occur over the long follow-up period.

Acharya et al.[18] and Sar et al.[19] reported cases of macular hole developing after Nd:YAG LI. In both cases, the authors thought that the shock waves generated during Nd:YAG LI may be responsible for the development of macular hole. According to this theory, during the procedure, the shock waves that occur during photodisruption and plasma formation in the anterior chamber first reach the vitreous. There they cause contraction of the vitreous fibers, resulting in traction at the vitreomacular interface that may cause a macular hole.

Similar to the authors above, we think that inflammation occurring after LI and the changes at the vitreomacular interface caused by shock waves associated with the procedure may be responsible for the development of ERM.

Cataract surgery is known to be one of the causes of secondary ERM.[9,20] In this study, we compared the ERM frequencies in eyes treated with LI alone and eyes in which cataract surgery was performed after LI. Similar to the studies of both Vieira et al.[8] and Loiudice et al.[15], we observed that cataract surgery did not have an additional effect on the frequency of ERM.

Study Limitations

The first limitation of our study was that it was retrospective and included data from a limited number of patients. Another limitation was that glaucoma stage was not evaluated. In addition, determining the frequency of ERM progression from early stages to advanced stages during an average 5-year follow-up after LI would also be very valuable. Despite these limitations, to our knowledge this study was the first study to evaluate the frequency of ERM after LI.

Conclusion

Although studies with more eyes are needed, Nd:YAG LI appears to be a predisposing factor for the development of ERM, regardless of subsequent cataract surgery.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Institutional Ethics Board of the University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital (reference number: 2023/152; date: 06/09/2023) and was performed in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

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

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

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Original Article

Human Amniotic Membrane: A Seal for Complex Retinal Detachments

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Abstract

Objectives: To evaluate the efficacy of human amniotic membrane (hAM) transplantation for complex retinal detachments (RD).

Materials and Methods: A retrospective analysis of consecutive patients who underwent vitreoretinal surgery with hAM transplantation for complex RD was conducted. The indications included high myopic macular hole (MH)-associated RD (n=5), traumatic large macular tears (n=4), combined RD with MH due to cicatricial retinopathy of prematurity (n=2) and severe retinitis (n=1), and morning glory syndrome (n=1). Surgical procedures, anatomical and functional results, and complications were noted.

Results: Thirteen eyes of 13 patients with a median age of 7 years (range, 0-65 years) were included. The follow-up was 15 months (range, 6-30 months). All eyes achieved MH sealing. Sealing occurred after a single surgery in 75% of eyes, while 25% required a second surgery due to hAM contraction/dislocation. The retina was attached and silicone oil could be removed in 92% of eyes during follow-up. The mean logarithm of the minimum angle of resolution visual acuity increased from 2.08±0.49 to 1.78±0.70 (p=0.07). Optical coherence tomography showed good integration of the hAM grafts with the retina, albeit without discernible retinal layer differentiation in any case.

Conclusion: Amniotic membrane grafting appears to be promising for anatomical sealing of MHs and posterior retinal tears in complex RDs such as those associated with degenerative myopia, severe trauma, tractional membranes, and retinal shortening, where conventional surgical techniques are likely to fail. Further research is needed to clarify the regenerative potential and functional capacity of hAM grafts in severe retinal pathologies.

Keywords: Human amniotic membrane, retinal detachment, macular hole, high myopia

Introduction

Human amniotic membrane (hAM) has been successfully used for decades for the treatment of ocular surface pathologies.[1] With its excellent anti-inflammatory, anti-fibrotic, and anti-angiogenic properties and low immunogenicity, hAM acts as an optimal biological support for damaged tissues and promotes re-cellularization.[2,3]

As in the anterior segment, *in vitro* studies have shown that hAM can provide a viable support matrix for retinal pigment epithelium (RPE) restoration.[4,5] Evidence suggests that human RPE cells can proliferate on a layer of hAM, forming a tightly organized monolayer of epithelial cells and secreting growth factors to maintain retinal homeostasis.[4,5]

Recently, research teams led by Rizzo et al.[6] reported successful *in vivo* applications of hAM for different retinal pathologies such as refractory macular hole (MH),[7,8] retinal detachment (RD) associated with MH,[9] posterior retinal breaks,[10,11] and age-related macular neovascularization.[12] Besides high rates of MH closure and retinal reattachment with hAM transplantation in these cases, the results were also very encouraging in terms of retinal regeneration. Amniotic membrane plugs exhibit promising integration into the retina, resulting in partial restoration of the outer retinal layers without any immunologic reactions.[6,9,10,12]

Current knowledge indicates that the use of hAM in vitreoretinal surgery is a novel and innovative technique that certainly has great potential but needs further investigation and understanding. In this report, we present our experience regarding the feasibility and efficacy of hAM transplantation in complex vitreoretinal pathologies in adult and pediatric eyes.

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Materials and Methods

A retrospective chart review was performed for consecutive patients undergoing vitreoretinal surgery with hAM transplantation for complex RDs associated with various pathologies from January 2019 to December 2022. The study received approval from the Gazi University Ethics Committee (protocol no: E.711694, date: 27.07.2023) and followed the principles of the Declaration of Helsinki.

Preparation of Amniotic Membranes

The hAM grafts were prepared under sterile conditions from a human placenta obtained shortly after elective caesarean delivery. Serological screening of donors was performed to exclude the risk of transmissible infections such as human immunodeficiency virus, hepatitis virus types B and C, and syphilis. The placenta was first washed free of blood clots with sterile saline solution. Then the amniotic membrane was separated from the rest of the chorion and rinsed with sterile saline solution containing 100 U/mL of benzyl penicillin, 200 µg/mL of ciprofloxacin, and 2.5 µg/mL of amphotericin B.[13,14] After incubating the amniotic membrane in this saline-antibiotic solution for 24 hours, it was flattened on a sterile ophthalmic drape, then cut into pieces (often 3x4 cm) and stored in plates containing a 1:1 mixture of glycerin and Dulbecco's modified Eagle medium at -80 °C for later use.

Surgical Procedures

All surgical procedures were performed by the same experienced vitreoretinal surgeon (Ş.Ö.). The patients underwent a standard 3-port, 23-gauge (G) pars plana/plicata or limbal vitrectomy with or without lens surgery. A complete vitrectomy with adequate vitreous base shaving was performed along with membrane/internal limiting membrane (ILM) peeling, retinotomy, or retinectomies as necessary.

The dimensions of the hAM graft were adjusted with vitreoretinal scissors before insertion into the vitreous cavity. Depending on the size of the graft, it was introduced to the vitreous cavity either through a 23-G valved trocar or directly through the sclerotomy following transient removal of one of the trocars. Once in the vitreous cavity, the hAM graft was gently manipulated under fluid or perfluorocarbon liquid and transplanted through the MH or retinal break into the subretinal space, with the graft edges positioned under the edges of the defective area as much as possible, and with the chorion side facing the RPE. The orientation of the graft was determined mainly by identifying the adhesiveness of the tissue using a retinal forceps, as described by Caporossi et al.[9]

In three cases, the hAM grafts were placed over the retina. The first one was a case of cicatricial retinopathy of prematurity (ROP) in which a large hAM graft was placed over the MH to address PVR/RD. The second was a case of morning glory syndrome where the hAM graft was inserted into the colobomatous disc under perfluorocarbon liquid to fill the anomalous disc pit. In the last case, the hAM graft placed during primary surgery had contracted and two new grafts were placed in a sandwich-type fashion, with one in the subretinal space and the other in an epimacular position.

After positioning the grafts appropriately, fluid-air exchange was performed, followed by silicone oil injection. All patients were instructed to maintain face-down position for 5 days.

Data Collection

The following data were obtained for each case: demographics, clinical features, indication for hAM use, surgical procedure(s) performed, complications, pre- and postoperative best corrected visual acuity (BCVA), anatomic outcomes, and length of follow-up.

Due to the difficulty of obtaining raster scans and the frequent lack of visibility of MH alignment on the RPE using optical coherence tomography (OCT) in detached retinas, MH size was determined intraoperatively by estimating its approximate average diameter in optic disc diameters (DD) after assuring retinal reattachment. Postoperative hAM graft appearance and microstructural regeneration of the retinal layers were assessed using spectral domain-OCT whenever possible. Axial length was measured using optical biometry (IOL Master 500; Carl Zeiss Meditec, Germany) or contact ultrasound biometry (A-scan).

BCVA was assessed with age-appropriate Snellen-equivalent methods and converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analyses. In infants or younger patients for whom acuity testing was not possible, response to light stimuli and ability to fix and follow a penlight or an object were assessed.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics v22.0 (IBM Corp, Armonk, NY, USA) and statistical significance was set at a 2-tailed p value <0.05. Categorical data were reported as the number of cases and percentages, while normally distributed continuous data (tested with Shapiro-Wilk test) were reported as means with standard deviations and non-normal data as medians and ranges. Due to the non-normal distribution of some variables and a relatively small sample size, comparisons of continuous data were carried out with the non-parametric Mann-Whitney U and Wilcoxon signed rank tests.

Results

Thirteen eyes of 13 patients (9 male, 4 female) were included. The median age at presentation was 7 years, ranging from 3 months to 65 years. Nine (69.2%) were pediatric cases aged 14 years or younger. The mean length of follow-up was 15±9.3 months (range, 6-30 months).

The indications for hAM graft transplantation were as follows: five eyes (38.5%) suffered from a high myopic MH-associated RD (mean axial length: 29.8±5.3 mm; mean spherical equivalent: -15.5±7.4 diopters). Four eyes (23.5%) had trauma-related RD with large macular tears with or without peripheral tears and proliferative vitreoretinopathy (PVR), including one case of shaken baby syndrome. Three eyes (17.6%), two with cicatricial ROP and one with cytomegalovirus retinitis, had combined tractional and rhegmatogenous RD associated with MH with or

without posterior retinal tears. One eye (5.9%) had total bullous RD associated with morning glory syndrome without MH or retinal break. At the time of hAM transplantation, the majority of cases (84.6%) were phakic (2 adults and 9 pediatric cases). Of these, both adults underwent combined phacoemulsification and vitrectomy surgery, whereas all except two pediatric patients underwent lens-sparing vitrectomy. One had cytomegalovirus retinitis and the other had trauma-related severe PVR/RD. Detailed characteristics of all cases are given in Table 1 and two cases are illustrated in Figures 1 and 2.

Table 1. Preoperative clinical characteristics, postoperative outcomes, and complications of the study population

No/sex	Age	Pathology	Previous intervention	Preop BCVA	Surgery and tamponade	Complications	Clinical remarks	Final BCVA
1/F	65 y	High myopic MH, RD	-	20/400	PPV, hAM (sub-MH), SO	-	SO removal (18 mo), MH sealed, R attached	20/100
2/M	2 y	High myopic MH, RD, PVR grade C1	-	LP	SB-PPV, hAM (sub-MH), SO	-	SO removal (15 mo), MH sealed, R attached	F/F
3/M	4 y	High myopic MH, RD, PVR grade C1	-	CF 1m	PPV, subretinal band removal, hAM (sub-MH and under retinotomy site), SO	hAM (sub-MH) contraction, RD	Re-PPV with double-layer hAM (4 mo), SO removal (3 mo), MH sealed, R attached	CF 1m
4/F	2.5 y	High myopic MH, RD	-	LP	SB, PPV, hAM (sub-MH), SO	-	SO removal (3 mo), MH sealed, R attached	F/F
5/F	8 mo	High myopic MH, RD	-	LP	SB, PPV, hAM (sub-MH), SO	hAM contraction, subretinal SO, RD	Re-PPV with sub-MH hAM, MH sealed, SO removal (4 mo)	F/F
6/M	7 y	Trauma, MH, post tear, peripheral tear, RD, PVR grade C2	SB, PPV (x2), ILMP, SO	HM	PPV, hAM (sub-MH and under post tear)- SO	-	hAM stable, MH sealed, R attached under SO; SO could not be removed due to persistent PVR	HM
7/M	40 y	Trauma, MH, RD, PVR grade C2	PPV, Retinectomy, SO	CF 1m	PPV, ILMP, Retinotomy, hAM (sub-MH), SO	-	SO removal (3 mo), MH sealed, R attached	20/250
8/F	52 y	Trauma, high myopia, MH, Post tears (x3), RD	-	LP	PPV, ILMP, hAM (sub-MH and under post tears), SO	-	SO removal (24 mo), MH sealed, R attached	HM
9/F	3 mo	Trauma (shaken baby), persistent MH, RD	PPV, ILMP, SO	NA	PPV, hAM (sub-MH), SO	-	SO removal (3 mo), MH sealed, R attached	F/F
10/M	26 y	Cicatricial ROP, MH, RD, PVR grade C1	SB, PPV, SO	20/400	PPV, ILMP, hAM (large epi-MH), SO	-	SO removal (3 mo), MH sealed, R attached	20/400
11/M	14 y	Cicatricial ROP, MH, RD, PVR grade C3	SB, PPV, ILMP, SO	CF 1m	PPV, Retinectomy, hAM (sub-MH), SO	hAM dislocation, PVR-RD	Re-PPV with sub-MH hAM, MH sealed (27 mo), re-PPV with 360° retinotomy for PVR-RD (24 mo), SO removal (18 mo), R attached	20/400
12/M	13 y	CMV retinitis, MH, post tears, RD	SB, PPV, air for TRD	HM	PPV, hAM (sub-MH and under post tears), SO	-	hAM remained stable and MH sealed, re-PPV, SO for recurrent retinitis with hemorrhage, TRD (1 mo), SO removal (3 mo), R partially attached	HM
13/M	5 y	Morning glory anomaly, total RD	-	LP	PPV, Internal drainage, hAM (in colobomatous disc pit), SO	hAM mobilization during SO removal	SO could not be removed due to hAM mobilization and immediate RD; hAM remained stable, R attached under SO (6 mo)	LP

BCVA: Best corrected visual acuity, CF: Counting fingers, CMV: Cytomegalovirus, F: Female, M: Male, F/F: Fix/follow, hAM: Human amniotic membrane, HM: Hand motions, ILMP: Internal limiting membrane peeling, LP: Light perception, M: Male, MH: Macular hole, mo: Months, NA: Non-applicable, No: Patient number, Post: Posterior, PPV: Pars plana vitrectomy, Preop: Preoperative, PVR: Proliferative vitreoretinopathy, R: Retina, RD: Retinal detachment, ROP: Retinopathy of prematurity, SB: Scleral buckling, SO: Silicone oil, TRD: Tractional retinal detachment, y: Years

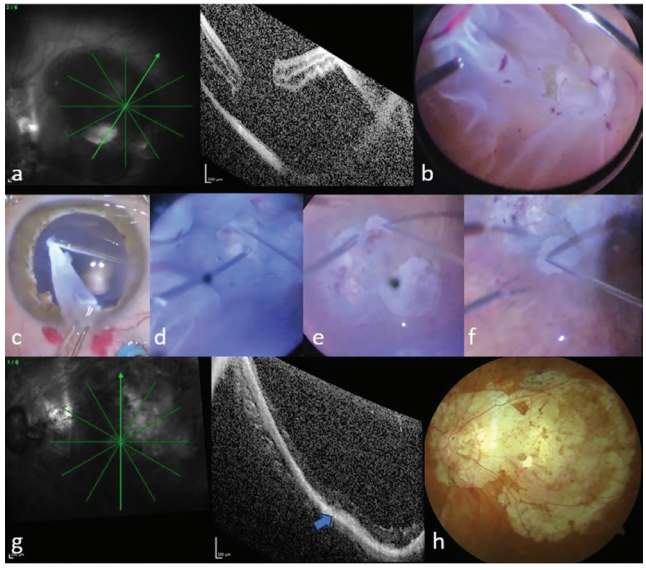

Figure 1. Case 8. A 52-year-old female patient with degenerative myopia (axial length: 35 mm) presented after an episode of psychosis and self-mutilation with macular hole-related posterior pole retinal detachment (a) which progressed to total rhegmatogenous retinal detachment with multiple posterior breaks in a few days in the left eye (b). The patient had previously experienced a similar trauma resulting in the loss of her right eye. Following phacoemulsification, a large piece of amniotic membrane was introduced through the anterior chamber (c) and placed under the large macular break (d). Two smaller pieces were then placed under the remaining posterior breaks (e, f). The surgery ended with the application of endolaser to a temporal peripheral retinal break and 360° periphery and silicone oil tamponade. Two years after silicone oil removal, the retina remained attached, and the patient achieved ambulatory vision. The optical coherence tomography image shows the amniotic membrane graft (arrow) overlaid by thin retina (g). The entire retina displayed extensive atrophy with no observable distinction between layers. The amniotic membrane grafts were not discernible in the fundus view, which exhibited significant posterior staphyloma and chorioretinal atrophy (h)

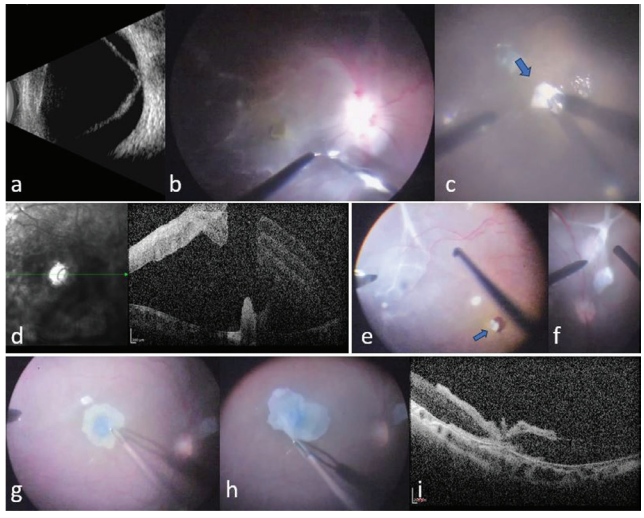

Figure 2. Case 3. A 4-year-old male patient diagnosed with Knobloch syndrome presented with retinal detachment (RD) associated with a high myopic macular hole (MH). During surgery, two amniotic membrane grafts were utilized, with one placed under the MH and the other one under the inferonasal retinotomy area created for the removal of subretinal bands. At postoperative 2 weeks, the graft contracted, resulting in reopening of the MH and subsequent RD. The graft was observed to have remained in place, still adhered to the RPE (d, e). The graft placed under the retinotomy area remained stable and was effectively closing that area (f). For the second surgery, two oversized amnion grafts were placed in a sandwich-like manner, with one positioned in the subretinal area (g) and another placed directly on top of the retina (h). The procedure was followed by tamponade with silicone oil. The retina remained attached during a 3-month follow-up period after silicone oil removal (i)

The estimated MH size ranged from 0.5 to 3 DD, with a mean of 1.5±0.9 DD. Overall, MH sealing was achieved in all cases with hAM transplantation, after a single surgery in 9 eyes (75%) and a second surgery in 3 eyes (25%). Three eyes required repeat surgery due to immediate graft dislocation (n=1) or graft contraction in the early postoperative period (n=2) (Figure 2). The mean MH size in these eyes was not significantly different from the remaining eyes (p=0.37). The contracted grafts were observed to have remained in place, still adhered to the RPE. However, their rapid shrinkage created a space for fluid leakage that resulted in MH reopening and RD recurrence. A second intervention including removal of the contracted graft via the MH and transplantation of larger grafts (submacularly in case 5 and in a sandwich-type fashion in case 3) provided successful re-sealing of the MH. Of 12 eyes, the retina was attached and silicone oil could be removed from 11 eyes (91.7%) by the final follow-up. The hAM grafts, including ones over the retina, remained securely in place following silicone oil removal. Silicone oil could not be removed in one eye despite a well-adherent hAM graft and stable sealing of the MH due to persistent PVR/RD (case 6). The hAM grafts placed under posterior tears and at the retinotomy site in four eyes remained stable, with no PVR development in these areas, providing successful sealing of these defects without the need for laser retinopexy.

In one patient with morning glory syndrome (case 13), the subretinal fluid had totally resorbed after primary vitrectomy with hAM transplantation and the retina remained attached under silicone oil for 4 months. However, the graft immediately became mobile during silicone oil removal surgery and RD recurred intraoperatively. As a result, the subretinal fluid was once again drained with a 39-G cannula, the retina was attached, and a multi-layered hAM graft was placed and stabilized in the colobomatous disc pit and tamponaded with silicone oil. The patient has been followed up for 6 months since the surgery without any recurrence of RD or silicone-oil related complications.

Overall, vision improved in 8 eyes (61.5%) and remained unchanged in 5 eyes (38.5%) after surgery. The mean preoperative BCVA for the 9 eyes (69%) with measurable vision was 2.08±0.49 logMAR (Snellen equivalent 20/2400) and improved slightly to 1.78±0.70 logMAR (Snellen equivalent 20/1200) at the final visit. However, the difference did not reach statistical significance (p=0.07).

OCT images were available for evaluation in 8 patients (61.5%), all of whom demonstrated good integration of the hAM grafts with the retina. Retinal layer differentiation was not discernible in any case. In four eyes (cases 1, 6, 7, 8), a thin to medium-thickness layer of new tissue grew over the hAM graft without stratification of the retinal layers. The remaining four

eyes (cases 3, 10, 11, 12) had hAM grafts completely filling the defective area like a plug, and there was no apparent growth of new retinal tissue.

None of the eyes showed signs of infection, inflammation, or rejection during the follow-up period.

Discussion

Posterior tears and MHs that are large and persistent or are associated with high myopia, posterior staphyloma, or RD pose significant challenges for vitreoretinal surgeons. Cases involving severe retinal shortening or tractions, such as PVR or cicatricial ROP, are particularly difficult to manage with conventional techniques, necessitating the use of novel sealing materials. In the pursuit of an effective sealing material, vitreoretinal surgeons have explored various options, including fragments of the ILM or lens capsule,[15,16,17] and autologous neurosensory retina transplantation.[18,19,20] However, each of these approaches has its own set of advantages and disadvantages, and none of them has emerged as the clear gold standard. More recently, hAM has emerged as a popular option for sealing in the vitreoretinal surgeon's toolkit.

The technique of using hAM was first introduced by Rizzo et al.[6] in 2019 for the treatment of complex MHs, and later the same team pioneered its application in different clinical scenarios.[7,8,9,10,11,12,21] In their initial study, the authors reported a 100% closure rate with improvement in visual acuity and time-dependent regeneration of the retinal layers over the hAM graft in 14 eyes with persistent MH or RD.[6] Encouraged by these results, we began to apply hAM transplantation for even more complex vitreoretinal cases where there was no reasonable alternative to closing retinal defects and where anatomic failure was highly likely. Accordingly, the main pathology of concern in this study was complicated RDs associated with high myopic MHs, traumatic MHs and posterior tears, tractional membranes, and severe PVR. Notably, half of the study group had previously undergone surgeries with adequate ILM peeling, rendering ILM flap techniques unsuitable. Of those undergoing primary repair, one was a severe trauma case with multiple large macular tears in which ILM peeling alone would not be sufficient to close the defects and reattach the retina. The remaining cases had high myopia, and creating ILM flaps was challenging due to very poor staining and high risk of iatrogenic retinal tears, although attempts were made to peel off as much of the ILM as possible. Also, given that more than half were pediatric cases and lens-sparing surgery was preferred, the use of lens capsule materials was not possible. Autologous retinal transplant could have been an alternative option, particularly in cases where a peripheral retinotomy was performed. However, besides being more technically challenging and carrying a higher risk of recurrent PVR/RD, it was often difficult to obtain adequate viable tissue in our cases due to extensive fibrosis in the peripheral retina or previous retinectomies.

Despite the inherent complexity of the study cases, the use of hAM grafts yielded encouraging anatomic outcomes. The final MH closure rate was 100%, achieved after one or two surgeries. Also, hAM grafts successfully sealed retinal breaks/retinotomy sites without the need for additional laser retinopexy, and no PVR development was observed in those areas.

While overall success was consistent with previous studies reporting complex MH closure rates ranging from 76.5% to 100% after hAM transplantation,[6,7,9,22,23,24,25] repeated surgeries were needed in our patient cohort due to graft-related complications. Previous studies by Caporossi et al.[7] and Huang et al.[23] reported cases of graft dislocation/contraction resulting in recurrence of MHs. Caporossi et al.[7] suggested that the likely cause of the failure was incorrect graft orientation with the epithelial layer facing the RPE, whereas Huang et al.[23] noted larger hole size as the possible cause. Although we did not observe a significant difference in the MH sizes between stable and unstable grafts, it is likely that the grafts in these eyes were not adequately large and unexpectedly rapid shrinkage led to MH reopening in two of them. Regarding the case with graft dislocation, in addition to suboptimal graft sizing, incorrect graft orientation and poor postoperative positioning may have been potential contributors. Determining graft orientation is particularly challenging with hAM grafts. There are several tips that can be used, such as observing the chorion layer, which tends to stick to the forceps, or identifying the villi present on the chorion layer using high magnification. However, these tips are not always helpful in the vitreous cavity. When the orientation of the graft is incorrect, it may lead to weak adhesion, increasing the risk of dislocations and possibly rapid contractions, which can negatively impact surgical success. Other than these three cases, hAM instability was also noted in the case of morning glory syndrome as soon as silicone oil support was removed during surgery, requiring reposition of the graft and re-injection of silicone oil. Caporossi et al.[26] reported the only other similar case in the literature, where two surgeries with gas and silicone oil tamponade failed and a third surgery was performed with a larger amniotic graft and silicone oil. Although the authors reported successful retinal reattachment under silicone oil, they only provided 3-month follow-up data and did not remove the oil. These cases suggest that hAM graft alone may not offer a permanent solution to fluid leakage caused by such large optic nerve defects in the short-term. However, long-term follow-up is required to evaluate its efficacy in providing adequate stabilization to allow silicone oil removal.

In contrast to several studies that have reported substantial improvements in visual acuity following successful closure of macular defects through hAM grafting,[6,9,10,22,23,24,25] the functional outcomes of our study were not in line with the favorable anatomic outcomes. Specifically, the increase in visual acuity was only modest and did not reach statistical significance. This outcome may be attributed to the fact that the majority of our study participants had limited retinal functional reserve, such as cases of infantile high myopia, ROP, severe retinitis, and traumatic cases with a history of multiple failed surgeries. Moreover, accurate measurement of visual acuity was often challenging in pediatric cases with low vision, and amblyopia

was also a limiting factor that may have contributed to the overall poor functional outcomes. Nevertheless, given the intricate nature of the underlying pathologies, achieving anatomic success was the primary goal in these cases.

The potential of hAM for promoting retinal regeneration, although exciting, remains controversial. While early studies by Rizzo et al.[6] and Caporossi et al.[8] showed promising results, with tissue ingrowth and differentiation of retinal layers over the hAM graft, recent studies have failed to replicate these findings. Ventre et al.[27], Huang et al.[23], and Yadav et al.[28] reported that the external layers remained disorganized after follow-up periods ranging from 1 to 13 months. In our study with follow-up periods ranging from 6 to 30 months, we observed either a thin new tissue growth over the hAM without recognizable layers, or no growth at all. Concerns have also been raised about the permanent placement of an exogenous tissue in the subretinal space, as it appears not to dissolve over time according to previous studies.[23,25] To address this issue, Garcin et al.[22] proposed epiretinal placement of hAM grafts with the chorion facing the vitreous to avoid injuring the RPE and neuroretina during manipulations and improve photoreceptor layer recovery. However, despite successful MH closure, they also reported mostly persistent external limiting membrane and ellipsoid zone defects at 1 year. Discrepancies between studies may be due to heterogeneous baseline characteristics, with certain cases having more limited regeneration potential than others. Different types and sizes of hAM used and possible damage to viable cells during manipulations may also have contributed to the differing results.

Study Limitations

Our study was limited by a small sample size, retrospective design, and heterogeneity of underlying pathologies. Additionally, the suboptimal visual acuity measurements and OCT documentation inherent to pediatric patients may have affected the interpretation of results in terms of retinal regeneration and functional recovery.

Conclusion

This study presents the largest series of hAM graft use in unique pediatric challenges, such as complex RD associated with cicatricial ROP, infantile high myopia, shaken baby syndrome, and morning glory syndrome. While more research is needed to elucidate the regenerative effects of hAM grafts on the retina, they appear to be a safe, viable, and relatively simple option to achieve anatomic sealing of complex defects in both adult and pediatric cases.

Ethics

Ethics Committee Approval: The study received approval from the Gazi University Ethics Committee (protocol no: E.711694, date: 27.07.2023).

Informed Consent: Retrospective study.

Authorship Contributions

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

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Original Article

Multilayered Inverted Internal Limiting Membrane Flap Technique in Optic Disc Pit Maculopathy

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Abstract

Objectives: To evaluate the anatomical and visual outcomes of the multilayered inverted internal limiting membrane (ML-ILM) flap technique in the treatment of optic disc pit maculopathy (ODPM).

Materials and Methods: In this retrospective interventional case series, medical records and macular spectral-domain optical coherence tomography images of patients who underwent combined pars plana vitrectomy with ML-ILM flap surgery for ODPM were analyzed. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) at postoperative 6 months were compared with baseline findings. Intraoperative and postoperative complications, fluid resolution time, and recurrence during follow-up were recorded.

Results: Five eyes of 5 patients with ODPM were included in the study. According to the preoperative macular fluid characteristics, 2 patients had only intraretinal fluid, while 3 patients had intraretinal and subretinal fluid. The preoperative median BCVA was 1.0 logarithm of the minimum angle of resolution (logMAR) (range, 1.0-1.3 logMAR), and the CMT was 560 µm (range, 452-667 µm). At the 6-month postoperative follow-up, the median BCVA was 0.40 logMAR (range, 0.1-0.7 logMAR), and CMT was 315 µm (range, 265-326 µm) (p=0.042 and p=0.043, respectively). During the 6-month follow-up period, no recurrence or full-thickness macular hole formation was observed.

Conclusion: The ML-ILM flap technique is a preferable surgical option to achieve both high anatomical and functional success and flap stabilization.

Keywords: Multilayered inverted internal limiting membrane flap, optic disc pit maculopathy, pars plana vitrectomy

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Introduction

Optic disc pit (ODP) is one of the cavitary anomalies of the optic nerve head and is typically congenital and unilateral.[1] It has been suggested that ODP may develop as a result of herniation of dysplastic primitive retinal tissue within a pocket into the subarachnoid space through a defect in the lamina cribrosa.[2,3] ODP is a rare pathology, with an estimated incidence of 2/10,000, and occurs equally in men and women.[4,5,6] It arises most commonly in the inferotemporal aspect of the optic nerve head.[5] Although ODP is often asymptomatic, 25-75% of patients may develop vision-threatening maculopathy, a condition which is referred to as ODP maculopathy (ODPM) and is characterized by cystoid macular changes and/or serous macular detachment.[7,8] Various techniques have been used in the treatment of ODPM, including peripapillary barrier laser photocoagulation, pars plana vitrectomy (PPV) and posterior vitreous detachment (PVD) induction, gas endotamponade with or without laser, and internal limiting membrane (ILM) peeling, but the results have been controversial.[9,10,11,12] The inverted ILM flap technique was first reported in the treatment of ODPM by Mohammed and Pai[13] and was subsequently adopted by many vitreoretinal surgeons.[14,15,16,17]

In the inverted ILM flap technique, which is frequently used in macular hole surgery, flap separation or rupture may occur due to intraoperative fluid-air exchange or failure to maintain postoperative patient positioning. To prevent these undesirable situations that may result in surgical failure, the multilayered inverted (ML) ILM flap technique was recently introduced and is reported to be effective in the treatment of macular hole.[18,19,20] ODPM patients undergoing ILM flap surgery also face postoperative risks comparable to those associated with the single-layered inverted ILM flap technique. However, to our knowledge there is no previous study evaluating the ML-ILM flap technique in the treatment of ODPM.

This study aimed to evaluate the visual and anatomical outcomes of PPV combined with the ML-ILM flap technique in the management of ODPM.

Materials and Methods

Patient Selection

The medical records of patients who were diagnosed with ODPM confirmed by spectral domain-optical coherence tomography (SD-OCT) in a tertiary ophthalmology clinic between January 2016 and October 2023 and underwent PPV with inverted ILM flap surgery were retrospectively examined. The patients' demographic data, detailed preoperative and postoperative ophthalmological examination findings, and previous macular SD-OCT images were recorded. Patients who underwent ML-ILM flap surgery performed by the same experienced vitreoretinal surgeon were included in the study; those whose surgeries involved techniques other than the ML-ILM flap technique (detailed below) were excluded. Patients with a postoperative follow-up of less than six months and patients with additional ocular or systemic disease that may cause visual impairment were also excluded. The study was conducted in accordance with the principles of the Declaration of Helsinki. Bezmialem Vakıf University Local Ethics Committee approval was obtained for the study (ethics committee decision number: 2024/212-09, date: 15.05.2024) and the written consent of the patients or their legal guardians was on file.

Preoperative Assessment

The best-corrected visual acuities (BCVA), intraocular pressures (IOP), and anterior and posterior segment examination findings on record were noted for all patients. Detailed imaging of the macula was performed with SD-OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). Central macular thickness (CMT) was recorded from cross-sectional 25 A-scan SD-OCT images of the macula. The presence of subretinal and/or intraretinal fluid and ellipsoid zone (EZ) integrity were evaluated qualitatively from cross-sectional SD-OCT images.

Surgical Procedure

All surgeries were performed by a single experienced vitreoretinal surgeon (H.Ö.) under general anesthesia, starting with 23-gauge (G) PPV via a standard three-port transconjunctival scleral entry. After central vitrectomy, intravitreal triamcinolone acetonide (KENACORT-A intramuscular/intraarticular retard 40 mg ampule; Deva Holding Inc., İstanbul, Türkiye) was used to induce PVD. The ILM was stained using a dual dye (OCUBLU ILM/ERM Blue, Miray Medical, Bursa, Türkiye). Using 23G Eckhart ILM forceps, at least 3 inverted ILM flaps were created from the area between the fovea and optic disc toward the optic disc head (Figure 1). The ML-ILM flaps were inverted and placed so as to cover the ODP but were not used to plug the pit. The ILM was peeled in an area of two disc diameters around the temporal fovea (Figure 2A). Parts of the inverted ILM flaps that extended beyond the optic disc were trimmed using a vitrector (Figures 2B and 2C). Fluid-air exchange was then performed, taking care not to separate the ILM mound from the optic disc head. During fluid-air exchange, the globe was gently tilted nasally. This allowed the fluid on the retinal surface to be aspirated from nasal to the optic disc using a 23G silicone-tipped backflush needle and the ILM flaps were stabilized over the ODP with air (Figure 3). ILM flap formation and stabilization were done without the use of perfluorocarbon fluid. The surgery concluded with intraocular air tamponade and subconjunctival ceftazidime (ZIDIM 1 g intramuscular/intravenous vial, Tüm Ekip Pharmaceuticals Inc., İstanbul, Türkiye) and dexamethazone (DEKSAMETAZON-PF 8 mg/2 mL solution, Polifarma Medical, Tekirdağ, Türkiye) injection. After extubation, the patients were placed in a lateral lying position according to which eye was operated (left side for the right eye, right side for the left eye) to support the spread of the flaps over the optic disc. Patients were instructed to

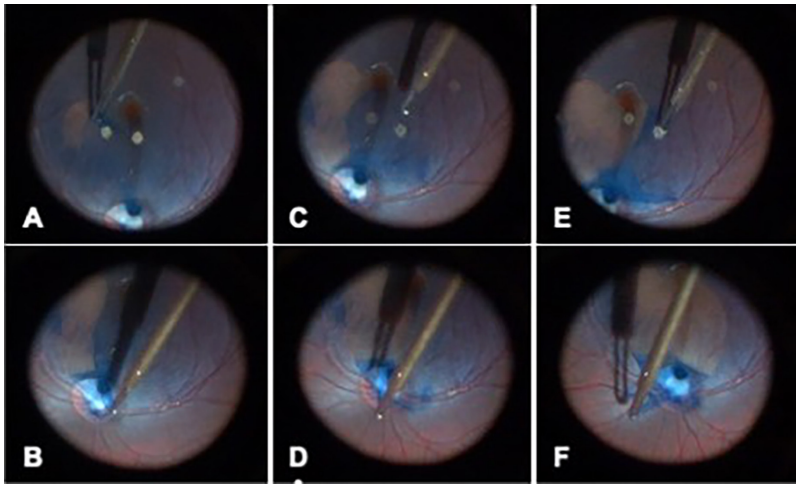

Figure 1. Intraoperative images of a patient with optic disc pity maculopathy showing staining of the internal limiting membrane (ILM) with trypan blue (0.06%) followed by the creation of the inverted multilayered ILM (ML-ILM) flap. Three inverted ML-ILM flaps were made from the macular area between the fovea and optic to the optic pit. Creation of the first flap is shown in images A and B, the second flap in images C and D, and the third flap in images E and F

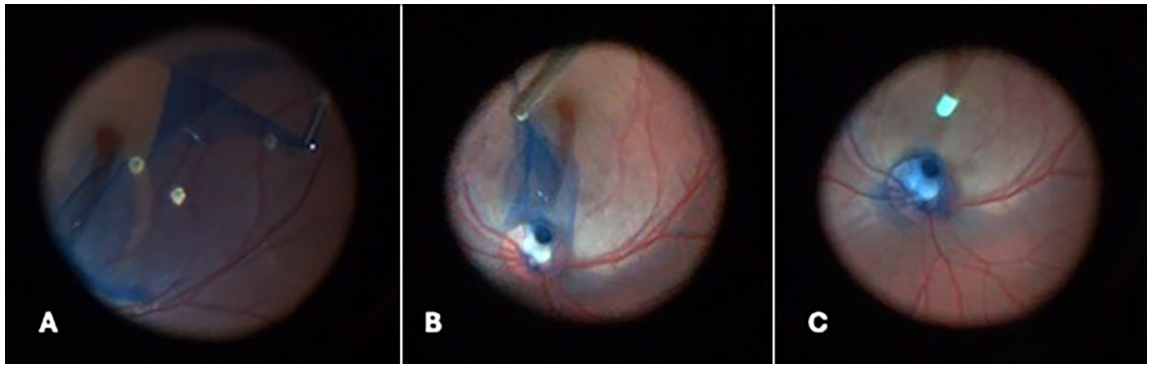

Figure 2. (A) After creating three internal limiting membrane (ILM) flaps, the remaining ILM was peeled between the vascular arcades in the posterior pole without creating a flap. (B) Excess ILM flap extending beyond the optic disc was trimmed using a vitrector. (C) The ILM flaps were stacked over the optic disc using a 23-gauge silicone-tipped backflush needle

maintain this positioning for 2 days postoperatively. All patients were prescribed topical 0.5% moxifloxacin (MOXAI 0.5% eye drops, Abdi İbrahim Medical Inc., İstanbul, Türkiye) and 0.1% dexamethasone (ONADRON SIMPLE 0.1% eye/ear drops, İ.E. Ulagay Medical Inc., İstanbul, Türkiye) 5 times a day for 2 weeks postoperatively. Any intraoperative and early postoperative (within the first 2 weeks) complications were noted.

Postoperative Evaluation

Findings from ophthalmological examinations conducted at postoperative 1 day, 2 weeks, and 1, 3, and 6 months were obtained from patient records. Macular SD-OCT imaging performed at all follow-up visits starting from postoperative 2 weeks was evaluated. BCVA and IOP values, anterior and posterior segment examination findings, CMT, residual macular fluid pattern, EZ integrity, and presence of recurrence at postoperative 1-, 3-, and 6-month follow-ups were recorded (Figure 4).

Statistical Analysis

Statistical analysis was performed using SSPS version 20.0 statistical software (IBM Corp, Armonk, NY, USA). Categorical variables were presented as numbers (percentages) and continuous variables were presented as median (range). Statistical analysis of BCVA was performed by converting Snellen values to logarithm of the minimum angle of resolution (logMAR). For continuous variables, Wilcoxon signed-rank test was used to compare initial findings to those at postoperative 6 months. $P<0.05$ was accepted as statistical significance.

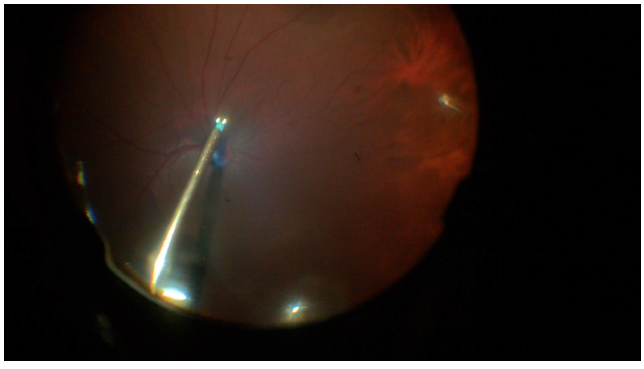

Figure 3. Image of the intraoperative fluid-air exchange phase. The globe was gently tilted nasally and the fluid on the retinal surface was passively aspirated from nasal to the optic disc using a 23-gauge silicone-tipped backflush needle. Thus, the internal limiting membrane flaps were stabilized over the optic disc pit with air

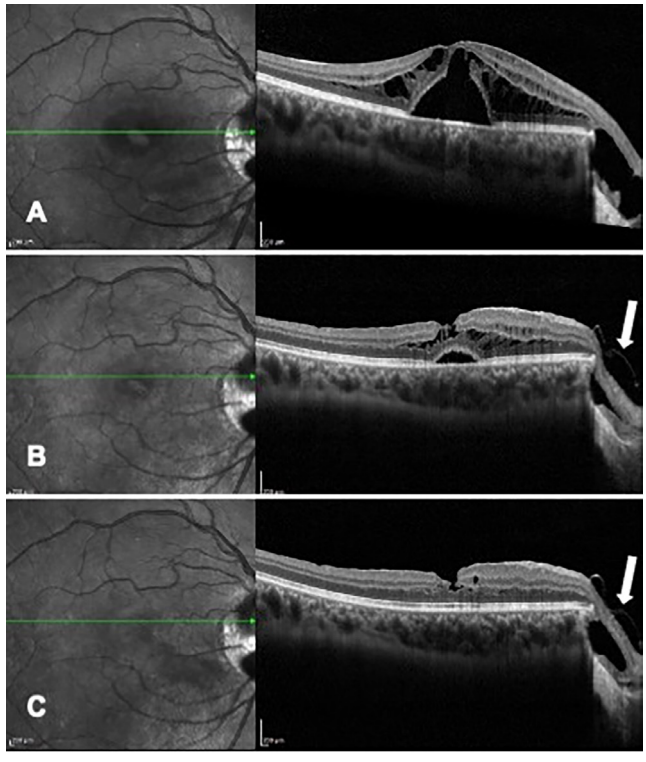

Figure 4. Preoperative and postoperative fovea-centered cross-sectional optical coherence tomography (OCT) images of a patient with optic disc pity maculopathy in the right eye (patient 1, 17-year-old female). (A) Preoperative OCT images. The OCT cross-section shows the coexistence of retinochisis and serous macular detachment (bilaminar fluid pattern). (B) OCT image at postoperative 3 months shows minor intraretinal cystoid spaces with minimal serous macular detachment. In the cross-section, the inverted internal limiting membrane flap (arrow) can be seen over the optic disc. (C) OCT image at postoperative 6 months shows the intraretinal and subretinal fluid have been resorbed and the flap (arrow) remains in situ over the optic disc

Results

Five eyes of 5 patients diagnosed with ODPM who underwent surgery using the ML-ILM flap technique were included in the study. The median age was 29 years (range, 17-34 years), and 3 patients (60%) were female. ODP was located temporal to the optic disc in all cases. Preoperative median BCVA was 1.0 logMAR (range, 1.0-1.3 logMAR) and CMT was 560 µm (range, 452-667 µm). According to the macular fluid characteristics on preoperative SD-OCT imaging, 2 patients had intraretinal fluid only, while 3 patients had both intraretinal and subretinal fluid. At postoperative 6 months, the median BCVA was 0.4 logMAR (range, 0.1-0.7 logMAR) and CMT was 315 µm (range, 265-326 µm) (p=0.042 and p=0.043, respectively). The comparison of the patients' preoperative and postoperative 6-month clinical characteristics is summarized in Table 1. EZ disruption was observed in 3 patients (60%) preoperatively and persisted at postoperative 6 months in 2 patients (40%). No intraretinal or subretinal residual fluid was observed in any patient at 6 months and no recurrence was detected during follow-up. None of the patients had intraoperative or postoperative complications such as cataract or full-thickness macular hole. The demographic and clinical characteristics of all patients are presented in Table 2.

Discussion

Although uncomplicated ODP remains asymptomatic, maculopathy may develop over time and asymptomatic patients should be followed closely for ODPM. Complicated ODP can cause severe visual impairment, warranting an aggressive treatment approach.[5,9,10,11] The main aim of treatment in ODPM is to stop fluid passage to the macular area, which causes visual impairment. Various treatment modalities have been trialed for this purpose.[10,11] However, there is currently no gold standard treatment defined for ODPM. One of the first described treatment modalities was laser photocoagulation of the temporal edge of the ODP, but this approach has been abandoned in recent years because it can cause papillomacular bundle damage, resulting in permanent vision loss.[10] PPV is often preferred in the current management of ODPM.[9,10] The main reason for choosing PPV in ODPM is PVD induction, because traction from the vitreous and posterior hyaloid on the peripapillary and macular area allows fluid ingress through the ODP and can promote separation of the retinal layers, thereby facilitating the passage of fluid into the retina.[21,22,23] Studies in the literature have shown that PPV and posterior hyaloid separation are effective for resolving maculopathy.[23,24] PPV can be performed alone or combined with various techniques such as juxtapapillary laser photocoagulation, radial optic neurotomy, and ILM peeling or flaps.[25,26,27,28] However, a meta-analysis by Zheng et al.[25] failed to demonstrate significant superiority of any of these methods over the others.

It has been noted that ILM peeling may be an important surgical maneuver to ensure the successful resolution of ODPM through eliminating tangential traction on the retina.[29] Marticorena et al.[30] reported a case in which treatment with a second intervention performed after ILM peeling was successful after initial failure with PVD and laser. In a retrospective analysis of patients who underwent PPV and gas tamponade with or without ILM peeling, Skaat et al.[31] reported that serous macular detachment persisted in patients without ILM peeling. In contrast, a recently published multicenter study indicated that ILM peeling did not provide any additional benefit.[32] More recent studies have investigated the idea of covering the ODP with an ILM flap, as used in the treatment of macular holes.[16,33,34] As an autologous physiological tissue, ILM placed over the optic pit can form a permanent barrier that acts as a physiological dam against fluid ingress to the macula through the pit opening, and may induce gliosis and cell proliferation in the ODP cavity.[14,34] Supporting this hypothesis, recent studies have concluded that the inverted ILM flap brings about functional and anatomical restoration and is an effective and safe treatment option for ODPM.[14,15,16,17]

The inverse ILM flap technique is already known to provide successful outcomes in macular hole surgery.[35] However, various flap-related problems can occur in macular hole surgery, such as incorrect ILM flap orientation, flap loss to the cutter probe, and postoperative flap dehiscence. The ML-ILM flap technique was recently introduced as a surgical modification to reduce these risks and has yielded higher rates of anatomical closure compared to standard ILM peeling and PPV.[18,19] In the present case series, we have shown for the first time that the ML-ILM flap technique, which was 100% successful at the end of the 6-month follow-up period, can be used as an effective treatment option in the treatment of ODPM. Unlike the single-layered inverted ILM flap technique previously preferred in the treatment of ODPM, this method is believed to be advantageous

Table 1. Demographic characteristics of the patients and their clinical status at baseline and six months after surgery with the multilayered inverted internal limiting membrane flap technique

	Preoperative median (range)	Postoperative 6 months median (range)	p
Age, years	29 (17-34)		-
Gender, female/male (%)	3 (60%)/2 (40%)		-
BCVA, logMAR	1.0 (1.0-1.3)	0.4 (0.1-0.7)	**0.042***
CMT, µm	560 (452-667)	315 (265-326)	**0.043***
Impaired EZ integrity, n (%)	3 (60%)	2 (40%)	1.000**

*Wilcoxon signed-rank test, **McNemar test, BCVA: Best-corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, CMT: Central macular thickness, EZ: Ellipsoid zone

Table 2. Demographic and clinical characteristics of the patients

Patient information		Preoperative				Postoperative 1 month				Postoperative 3 months				Postoperative 6 months			
Patient	Age, sex	BCVA	MCT	Retinal fluid	EZ defect	BCVA	MCT	Retinal fluid	EZ defect	BCVA	MCT	Retinal fluid	EZ defect	BCVA	MCT	Retinal fluid	EZ defect
1	17, F	20/400 (1.3)	560	IRF+SRF	+	20/200 (1.0)	385	IRF	+	20/40 (0.3)	335	IRF	-	20/40 (0.3)	326	-	-
2	22, F	20/200 (1.0)	524	IRF	-	20/200 (1.0)	455	IRF	-	20/50 (0.4)	380	IRF	-	20/25 (0.1)	315	-	-
3	34, M	20/200 (1.0)	645	IRF+SRF	+	20/100 (0.7)	486	IRF + SRF	+	20/100 (0.7)	285	IRF	+	20/100 (0.7)	265	-	+
4	30, F	20/400 (1.3)	667	IRF+SRF	+	20/200 (1.0)	385	SRS	+	20/100 (0.7)	345	-	+	20/100 (0.7)	325	-	+
5	29, M	20/200 (1.0)	452	IRF	-	20/200 (1.0)	286	–	-	20/50 (0.4)	288	-	-	20/50 (0.4)	286	-	-

F: Female, M: Male, BCVA: Best-corrected visual acuity (Snellen fraction with corresponding logMAR values in parentheses), CMT: Central macular thickness, EZ: Ellipsoid zone, IRF: Intraretinal fluid, SRF: Subretinal Fluid, -: Absent, +: Present, logMAR: Logarithm of the minimum angle of resolution

in terms of flap stabilization. Previous studies have reported that intraoperative perfluorocarbon fluid, viscoelastic material, and silicone or gas tamponades may be selected for flap stabilization.[36,37] However, the presence of an anatomical orifice in ODP may allow intraocular tamponades to pass into the subretinal, intraretinal, or even intracranial spaces and cause various complications.[38,39,40] As multiple ILM flaps are stacked in the ML-ILM technique, flap stabilization was achieved under air tamponade alone, without the need for gas or silicone tamponade. In addition, perfluorocarbon fluid was specifically avoided when creating flaps to prevent the risk of toxic retinopathy that may occur as a result of perfluorocarbon fluid ingress to the intraretinal space via the cavitary opening.

There are also studies indicating that creating ILM flaps in eyes with ODPM can cause macular hole formation.[41,42] Some vitreoretinal surgeons have recommended fovea-sparing ILM peeling to prevent this complication.[15,43] However, in eyes where the ILM is retained, it has been reported that a full-thickness macular hole may occur if performing PPV with gas tamponade and laser photocoagulation.[44] Ultimately, there are limited data regarding whether ILM peeling causes full-thickness macular hole in eyes with ODPM, and some have suggested that macular hole formation may be associated with posterior hyaloid detachment.[16,45] Furthermore, it is known that ODPM itself can also lead to the formation of a full-thickness macular hole.[9] Although the development of iatrogenic full-thickness macular hole associated with ILM peeling was not observed in any of the cases in the present series, patients should be followed closely for this complication in the postoperative period.

A limited number of studies have shown that successful outcomes can be obtained by plugging various biological structures other than ILM into the pit opening for a similar purpose.[17,46,47,48] However, as the potential for occlusive vasculitis and progressive peripapillary retinal nerve fiber layer thinning has been reported, especially with scleral plugs, ILM flaps can be considered advantageous considering these complications.[49,50] In this case series, the multiple ILM flaps created were not placed in the pit opening as a plug, but were only placed over the optic pit and stabilized. The fact that the ILM flap technique utilizes the patient's own tissue eliminates the described risks associated with external tissue.

Although there is no clear consensus on the fluid source that causes maculopathy in ODPM, suggested sources are cerebrospinal fluid, vitreous fluid, or leakage from dural vessels in the pit base.[9,11] OCT imaging greatly facilitates the recognition of the intraretinal and/or subretinal fluid accumulation causing ODPM. Moreover, OCT imaging is useful in the preoperative and postoperative evaluation of EZ integrity, which is closely related to visual prognosis, as well as in postoperative follow-up for recurrence and investigating for the presence of residual fluid. ODPM may manifest with retinochisis in the outer retinal layers due to the ingress of intraretinal fluid, or macular neurosensory detachment due to the ingress of subretinal fluid. The coexistence of both subretinal and intraretinal fluid in ODPM was named the bilaminar pattern and reported at a rate of 83.3% by Karacorlu et al.[51] In our case series, the bilaminar fluid pattern was observed in 60% of the patients. In addition, there are studies reporting that as with other macular pathologies, EZ disruption may be associated with poor visual prognosis in ODPM. In our case series, we noted that patients with postoperative EZ defect (patients 3 and 4) had an increase of less than 3 lines in Snellen

BCVA. In one case (patient 1), the preoperative EZ defect resolved postoperatively and BCVA increased by more than 3 lines. The authors of a previous case report also documented a dramatic visual gain (increase from counting fingers to 6/6) in a young patient with an outer retinal hole after ILM peeling with SF6 gas tamponade.

Study Limitations

One of the main limitations of this study is the small case number and lack of a control group that would allow comparison with another method. However, as mentioned previously, ODPM is a rare macular pathology. Nevertheless, achieving surgical success in all five patients using the ML-ILM flap may serve as a guide for future studies. In addition, evaluating the patients' 6-month outcomes can be considered another limitation. Although it was reported in an earlier case presentation that resolution could continue for up to 22 months, achieving complete resolution by the end of a 6-month period in all patients also suggests that this technique may be effective in the short term.

Conclusion

To our knowledge, this study is the first to investigate the effectiveness of the ML-ILM flap technique in the treatment of ODPM, and the results demonstrate that this method seems to be a preferable option in the management of ODPM to ensure both high anatomical and functional success and flap stabilization. Larger ODPM case series in which the ML-ILM flap technique is applied and prospective studies comparing it with other surgical techniques are needed.

Ethics

Ethics Committee Approval: Bezmialem Vakıf University Local Ethics Committee approval was obtained for the study (ethics committee decision number: 2024/212-09, date: 15.05.2024).

Informed Consent: Written consent of the participants or their legal guardians is on file.

Authorship Contributions

Surgical and Medical Practices: H.Ö., Concept: H.Ö., Design: H.Ö., F.K., Data Collection or Processing: G.E.A., B.P.A., Analysis or Interpretation: H.Ö., F.K., Literature Search: G.E.A., B.P.A., Writing: H.Ö., F.K.

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

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Original Article

Turkish Retinoblastoma Research: A Bibliometric Analysis (1966-2024)

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Abstract

Objectives: To conduct the first bibliometric analysis of retinoblastoma research in Türkiye and identify leading institutions, authors, collaboration patterns, and potential growth areas.

Materials and Methods: We conducted a search on international databases (Web of Science [WoS] and Scopus), a national database (TR Dizin), and gray literature sources (thesis/Scientific and Technological Research Council of Türkiye project reports). Data were cleaned and analyzed using bibliometric tools, including Open Refine and VOSviewer. Bibliometric indicators such as number of publications, journals, h-index, collaboration patterns, and co-occurrence of keywords were examined.

Results: A search of WoS and Scopus entries published between 1966 and 2024 yielded 122 relevant publications, with articles (n=78, 63.9%) being the most common document type. More than two-thirds of the publications were from 4 institutions: İstanbul University (n=48, 23.8%), Hacettepe University (n=34, 16.8%), Ankara University (n=33, 16.3%), and İstanbul University-Cerrahpaşa (n=22, 10.9%). The total number of citations was 1,148, with an average of 10.16 per publication and an h-index of 16. Excluding 8 internationally collaborated articles, the citations and h-index decreased to 661 and 14, respectively. *Pediatric Blood & Cancer* was the most preferred journal, with 22 publications (19.5%). The national database search yielded 18 publications with 0 citations. Of 29 relevant theses, only 4 (13.8%) were published. The estimated publication growth predicted an increase in publication numbers per year until 2030.

Conclusion: This study represents the first bibliometric analysis of retinoblastoma research conducted in Türkiye. Our findings underscore the concentration of research in a few institutions, the importance of international collaborations, and the potential for growth in particular areas. Addressing these areas strategically can empower Turkish researchers to enhance their contributions to the field and improve patient care.

Keywords: Bibliometrics, retinoblastoma, Türkiye

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Introduction

Retinoblastoma, the most common intraocular tumor in children, poses significant challenges in diagnosis and treatment due to its unique characteristics and impact on young patients.[1,2,3] Management of retinoblastoma requires a multidisciplinary approach involving ophthalmologists, pediatric oncologists, and radiologists. Collaborative care coordination is essential to optimize treatment outcomes, minimize side effects, and improve survivors' quality of life.[4] Understanding the landscape of retinoblastoma research is crucial for advancing knowledge and improving patient outcomes.

Bibliometric analysis offers a powerful tool for evaluating the scientific output of various research components within a field (such as papers, authors, keywords, journals, institutions, and nations). It differs from other forms of research in several aspects. In contrast to meta-analysis, which synthesizes empirical data by analyzing the direction, strength, and relationships of effects, bibliometric studies use quantitative techniques to synthesize the bibliometric capital of a field by examining the relationships between different scientific elements at the intellectual, social, and conceptual levels.[5,6] Additionally, due to the possibility of interpretation bias by scholars from different backgrounds, bibliometric research provides objectivity that systematic literature reviews may not provide.[7] However, bibliometric analysis should not be viewed as a replacement for other traditional methods of discussing developments in a field, such as meta-analyses or systematic literature reviews. Rather, they complement the areas where these methods are lacking.[5] Bibliometric analysis could offer a valuable tool for mapping the retinoblastoma research landscape, enabling researchers to identify trends, patterns, and gaps in the existing literature, which can inform future research directions and ultimately contribute to improved patient care.

The current landscape of bibliometric analysis in Turkish ophthalmology literature appears to be limited. We found few articles presenting Turkish ophthalmologists' contributions to international bibliometric studies, and only one study directly targeted the Turkish context.[8,9,10,11] This highlights a potential

gap in the use of bibliometric analysis to understand the dynamics of national ophthalmology research. Such analyses could be invaluable to Turkish institutions and researchers, providing insights into publication trends, leading contributors, focus areas, collaboration patterns, and opportunities for strategic growth.

This study aims to address the gap in bibliometric research within the context of Turkish ophthalmology literature, specifically focusing on retinoblastoma. Recognizing the absence of prior comprehensive bibliometric analyses in this domain, we conducted an extensive search encompassing international, national, and gray literature sources across a broad timeframe.

Materials and Methods

International Database Search Strategy

A comprehensive search was conducted on the Web of Science (WoS) Core Collection and Scopus. These databases were chosen for their extensive coverage of peer-reviewed literature across various disciplines and detailed bibliographic data necessary for bibliometric analysis.

Web of Science Search

The search query was formulated as follows: All fields=(retinoblastoma) AND All fields=(Turkey). No language restrictions or time limits were applied to ensure a comprehensive coverage of relevant literature. The search was conducted on March 22, 2024, and the results were exported in a tab-delimited file, including full records and cited references.

Inclusion and Exclusion Criteria

The search results were filtered to include documents that focused solely on retinoblastoma research, had at least one author affiliated with a Turkish institution, and were classified as articles, reviews, editorials, letters, or conference papers.

We omitted documents not related solely to retinoblastoma research, documents without any Turkish-affiliated authors, and documents with Turkish-affiliated authors if the studies were conducted outside of Türkiye.

Two researchers independently screened the search results for eligibility based on the inclusion and exclusion criteria, and discrepancies were resolved by discussion and consensus.

Scopus Search

We also did a Scopus search with the same criteria that we used for WoS.

Data Cleaning and Clustering

The exported data from WoS was preprocessed using Open Refine (version 3.4.1) to ensure data consistency and accuracy. The following steps were performed:

Harmonizing Keywords: Different writing styles, abbreviations, or name changes over time were identified and harmonized to enable precise keyword analysis.

Author Clustering: Open Refine's clustering algorithms were applied to group together different name variations belonging to the same author. This step helped in correctly attributing publications to individual authors and avoiding author name ambiguity.

Data Analysis

Both WoS and Scopus were used to determine the total number of unique publications. However, the two databases have different indexing systems and rules. Therefore, we chose to use the WoS database, which is the most authoritative database.[12]

Publication years, document types, authors, author affiliations, WoS categories, WoS index, languages, and journal names were recorded using the WoS analyze section. Since most of the data fit into multiple bins within their respective categories, we used the full counting method. As a result, the total percentage of data exceeded 100%.

Although our study mainly focuses on ophthalmology, we also wanted to investigate the research contribution of pediatric oncology clinics to the field of retinoblastoma in Türkiye. To assess this, we specifically searched for articles published solely by pediatric oncology departments without any collaboration with ophthalmology clinics.

As the citation sources of the two databases were different, we used WoS for citation analysis because it contained more articles. To determine the impact of international collaboration, we carried out two analyses, one with and one without international collaboration.

Growth Trends of Publications

Using Microsoft Excel for Microsoft 365, we generated the prediction model $f(x) = ax^3 + bx^2 + cx + d$ to calculate cumulative publications. This allowed us to predict future publication trends and forecast the growth trends of publications in the field. Here, x stands for time (year), and f(x) is the total number of publications per year.[13]

Turkish Database Search

We conducted a search of the TR Index through the website (https://trdizin.gov.tr/) using the keyword "retinoblastoma".

Gray Literature Search

National Theses: To identify theses related to retinoblastoma and explore which ones have been published, we searched the Council of Higher Education Thesis Center website (https://tez.yok.gov.tr/) using the keywords "retinoblastoma'' and "retinoblastom''. The results were then cross-referenced with the TR index and other databases (PubMed, WoS) to determine which theses had been published as articles in peer-reviewed journals.

Scientific and Technological Research Council of Türkiye (TÜBİTAK) Projects: We searched the TÜBİTAK project database using the keyword "retinoblastoma" to find relevant projects (https://app.trdizin.gov.tr/search/projectSearch.xhtml).

Visual Analysis

Using VOSviewer (version 1.6.20), co-authorship networks with and without international collaborations and keyword co-occurrence maps were generated. The author and keywords with most total link strength were recorded.

Results

Web of Science and Scopus Results

A total of 113 publications were retrieved from the WoS collection. Another 9 publications that were not on the WoS list were identified from the Scopus search. Most of the publications were research articles (n=78, 63.93%), followed by meeting abstracts (n=25, 20.49%), reviews (n=11, 9.00%), letters (n=5, 4.10%), editorial materials (n=2, 1.64%), book chapters (n=2, 1.64%), proceeding papers (n=2, 1.64%), and early access papers (n=1, 0.82%).

Our analysis of the three most common publication types (articles, meeting abstracts, and reviews) in retinoblastoma research in Türkiye revealed varying trends across different decades. From 1990 to 1999, articles dominated (92.3%), with only one meeting abstract (7.7%) and no reviews. The 2000-2009 period saw a slight decrease in articles (71.4%) and an increase in meeting abstracts (23.8%) and reviews (4.8%). The 2010-2019 decade showed a further shift, with articles comprising only 45.0%, while meeting abstracts (32.5%) and reviews (22.5%) increased. Finally, from 2020 to 2024, articles resurged (83.3%), accompanied by a decrease in meeting abstracts (16.7%) and no reviews.

There were 43 different affiliations associated with the publications in the dataset. The most prominent affiliations were Istanbul University with 48 publications (23.76%), Hacettepe University with 34 publications (16.83%), Ankara University with 33 publications (16.34%), and İstanbul University-Cerrahpaşa with 22 publications (10.89%). These four affiliations together accounted for more than two-thirds (67.82%) of the total affiliations in the dataset.

The dataset included publications in three different languages: English, Turkish, and French. English was by far the most dominant language, with 115 publications, accounting for 94.26% of the total. Turkish followed with 6 publications, representing 4.92% of the dataset.

The top 5 most represented WoS categories were ophthalmology with 49 publications (43.36%), oncology with 44 publications (38.93%), pediatrics with 39 publications (34.51%), hematology with 26 publications (23%), and radiology, nuclear medicine, and medical imaging with 5 publications (4.44%). There was only one article (0.82%) that was published solely by a pediatric oncology clinic without any contribution from an ophthalmology department.

The most represented database was the Science Citation Index Expanded-SCIE, with 104 publications accounting for 92.04% of the total. This was followed by the Emerging Sources Citation Index-ESCI with 8 publications (7.08%), the Conference Proceedings Citation Index-Science-CPCI-S with 5 publications (4.43%), and both the Book Citation Index-Science-BKCI-S and Social Sciences Citation Index-SSCI with 1 publication each (0.89%).

The top 10 most represented journals were *Pediatric Blood & Cancer* with 22 articles (19.46%), *European Journal of Ophthalmology* with 6 articles (5.31%), *Journal of Pediatric Ophthalmology & Strabismus* with 6 articles (5.31%), *Journal of Clinical Oncology* with 5 articles (4.42%), *Turkish Journal of Ophthalmology* with 5 articles (4.42%), *Pediatric Hematology and Oncology* with 4 articles (3.54%), *Japanese Journal of Ophthalmology* with 3 articles (2.65%), *Ophthalmology* with 3 articles (2.65%), *Turkish Journal of Pediatrics* with 3 articles (2.65%), and *British Journal of Ophthalmology* with 2 articles (1.77%).

These top 10 journals collectively published 59 articles, accounting for more than half (52.21%) of the total publications.

Citation Report

Citation analysis of the 113 documents in WoS revealed a total of 1,148 citations, with an average of 10.16 citations per item. The h-index was 16. The 3 most cited and 5 of the 10 most cited articles came from international collaboration. When the 8 documents involving international collaboration were removed, the total number of citations and h-index decreased to 661 and 14, respectively. Figure 1 shows publications and citations over time excluding international collaborated documents. Table 1 shows the top 20 most cited articles excluding international collaborated documents.

Growth Trends Results

Based on the total number of publications over the previous two decades, publication trends for the next 5 years were estimated. The model predicted accelerated growth in publication numbers (Figure 2).

Turkish Database Results

The total publication number was 18. After removing the publications in the WoS and Scopus to prevent duplication, there were 14 publications between 1995 and 2022. The journal with the most publications was *MN Ophthalmology* with 6 documents, the highest contributing author was Kaan Gündüz (Department of Ophthalmology, Ankara University) with 5 publications, and the most frequent affiliation was Ankara University with 7 documents. The total number of citations was zero.

Thesis Results

A total of 33 theses were evaluated. The department with the highest number of theses was Ankara University, Ophthalmology Department with 9 theses (27.3%). Ophthalmology departments collectively accounted for 20 theses (60.6%). Five theses (15.2%) resulted in publications. Hayyam Kıratlı (Ophthalmology Department, Hacettepe University) was the most productive thesis advisor, supervising 7 theses (21.2%).

TÜBİTAK Project Results

The thesis titled "Polymorphic marker (RELP) analysis in cytogenetics and mutant alleles in retinoblastoma cases", done in 1995 at Hacettepe University Faculty of Medicine, Department of Medical Biology, was the only relevant project funded by TÜBİTAK.

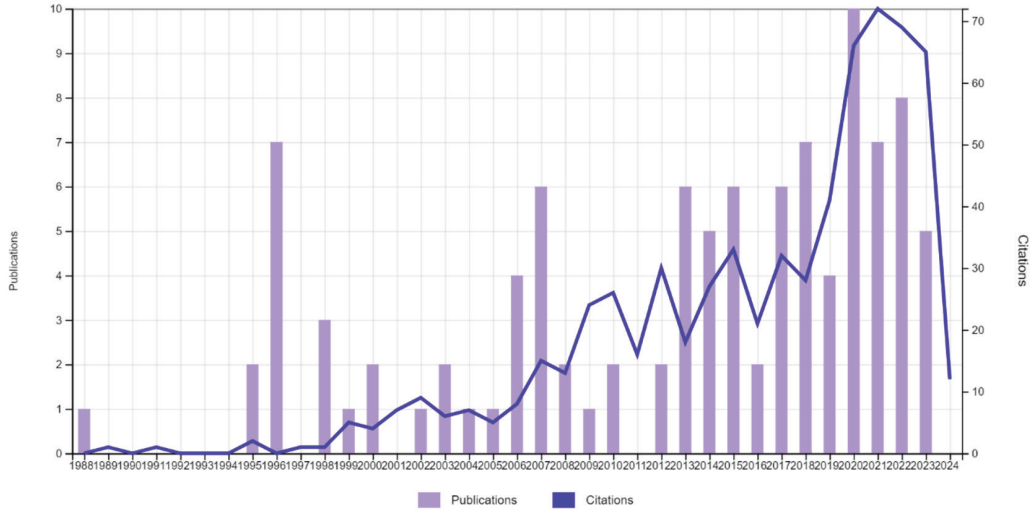

Figure 1. Publications and citations between 1988 and 2024 in WoS. *WoS: Web of Science*

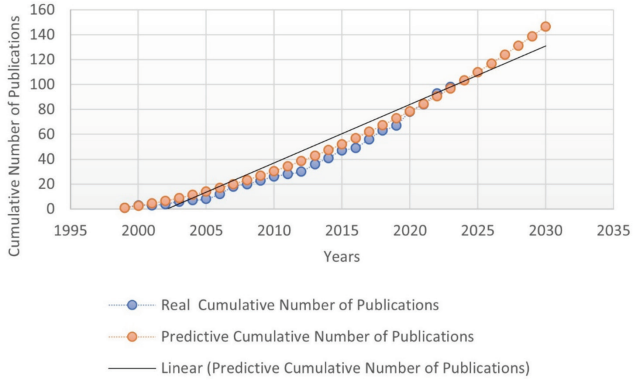

Figure 2. Real and predicted cumulative number of publications in international databases

Author Collaboration Analysis

Figure 3 shows author collaborations with and without international collaborations. Rejin Kebudi (Pediatric Hematology and Oncology Department, İstanbul University) had the highest total link strength.

Keyword Analysis

Figure 4 shows keyword link strength and changes over time. "Chemotherapy" and "management" had the highest link strengths.

Discussion

Bibliometric studies of ocular oncology are remarkably limited, indicating a possible gap in understanding of the research dynamics in this subspecialty.[14,15,16] While broader bibliometric analyses in ophthalmology exist, they may not fully capture ocular oncology research.[17,18]

A recent bibliometric study examining global retinoblastoma research from 2001 to 2021 showed that the United States contributed 643 publications (38.4% of global production), received 16,931 citations (56.2% of total citations), and had the highest h-index of 67. Eleven of the 20 most productive institutions (55%) were located in the United States. Of the remaining 9 institutions, 1 was in Canada, 2 were in Argentina, and 1 was in India.[14] While our study highlights the significant contributions made by Turkish researchers and institutions, no Turkish institution ranked among the top 20 institutions according to that study.[14] Retinoblastoma is a very rare disease with an incidence that does not vary by race.[19] It is expected that due to their large populations, countries like the United States and India would have relatively more patients and consequently conduct more research. However, the presence of 3 centers from countries with smaller populations than ours on this list hints that there may be areas where retinoblastoma research can be improved. As our study shows, most of the patients in Türkiye are currently treated in 4 centers.

However, clinical studies alone are not the only focus of retinoblastoma research. For instance, the pathophysiology of retinoblastoma has been the subject of growing research recently, especially in molecular biology and biochemistry.[20,21] We found that only one of the studies examined in our analysis was classified by WoS in this category. In addition, the retinoblastoma animal model, which is an important part of retinoblastoma translational research, has not been utilized in Turkish studies.[22]

The h-index can be used as a metric that captures the contribution and impact of a country's research on a particular subject.[23] According to the WoS database, the h-index for retinoblastoma research in Türkiye was 16. When compared to the global h-index, Türkiye's impact on retinoblastoma research is relatively modest.[14] Our study showed that the 3 most cited

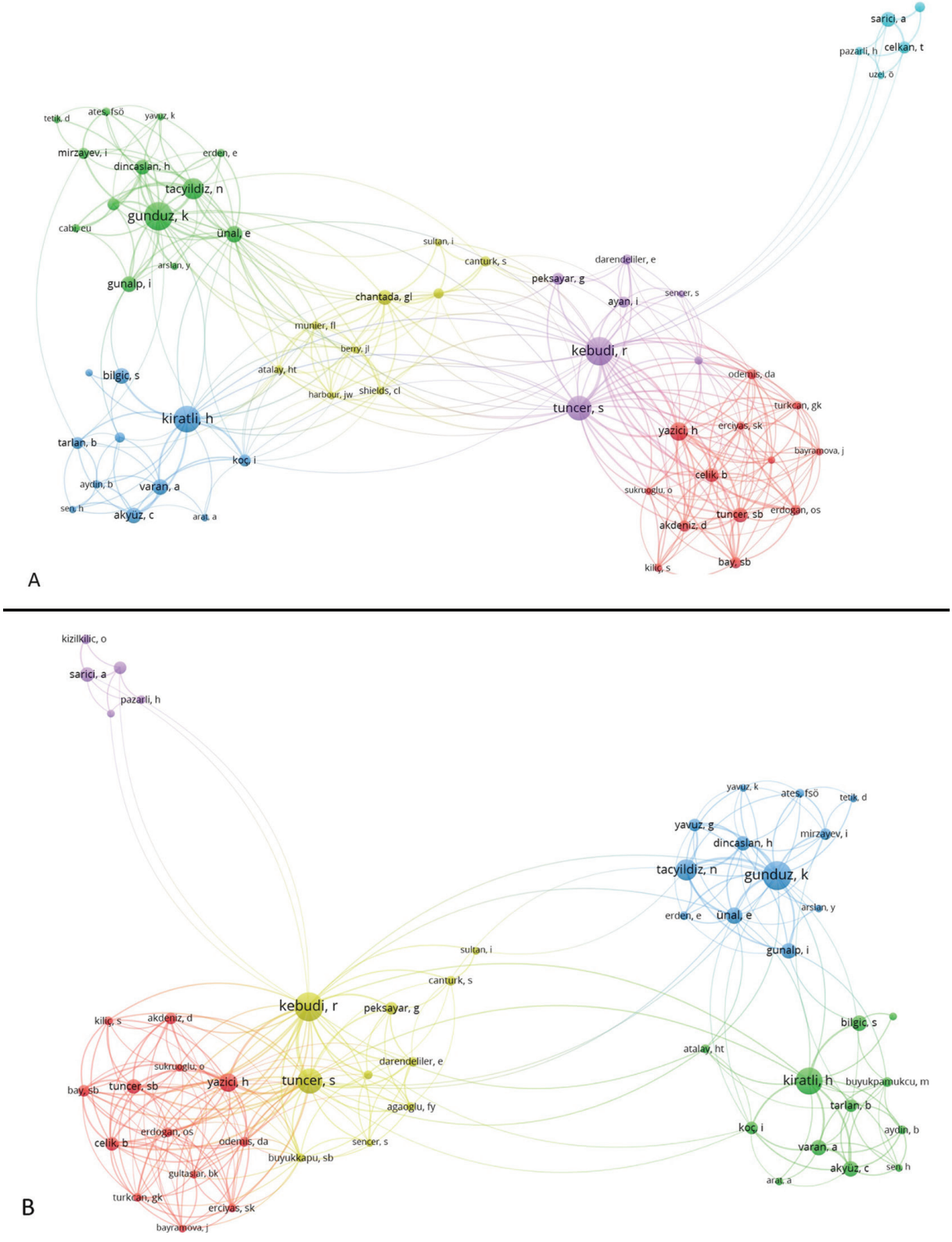

Figure 3. Co-authorship networks in WoS. (A) Including international collaborations. Yellow cluster represents well-known international retinoblastoma researchers. (B) Excluding international collaboration. *WoS: Web of Science*

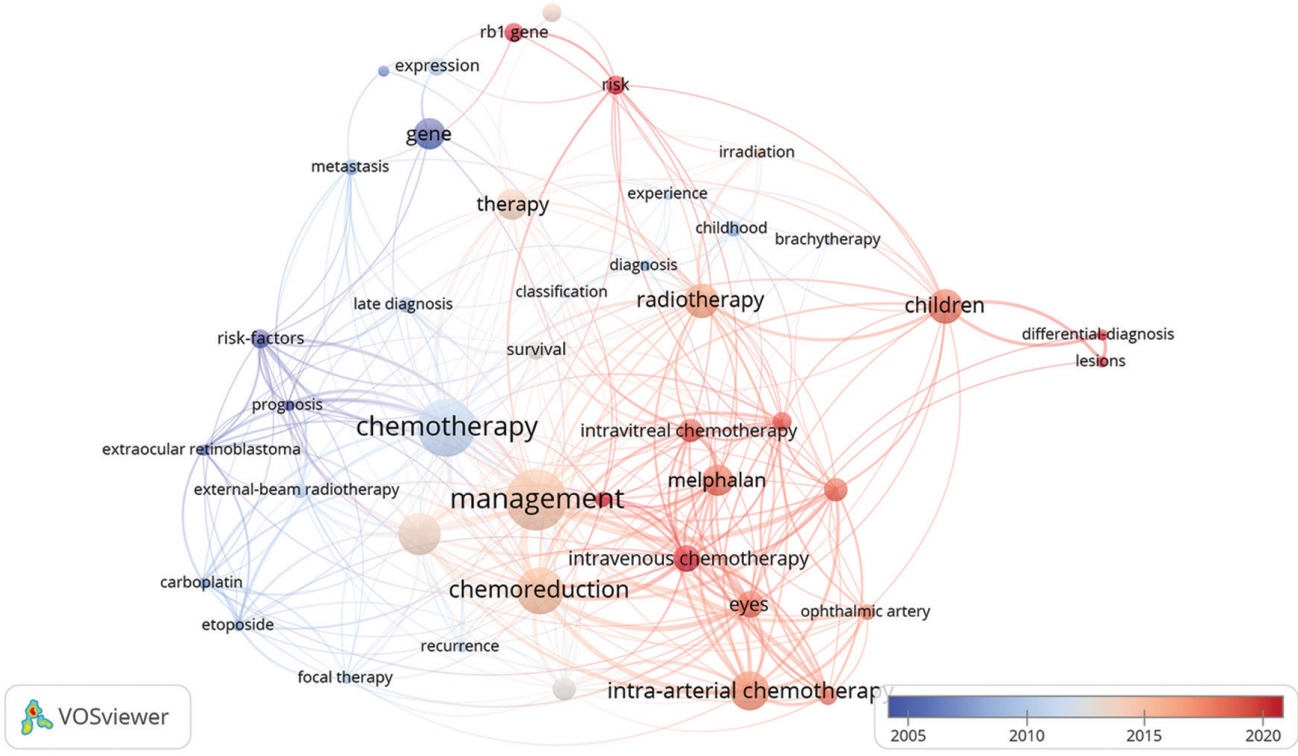

Figure 4. Co-occurrence of keywords and changes over time in WoS. *WoS: Web of Science*

articles from our data set, all of which involved international partnerships, significantly contributed to Türkiye's h-index of 16, because it dropped to 14 when we removed them. Additionally, when we removed 8 internationally collaborated studies, the number of citations dropped by almost half. Therefore, by fostering partnerships with leading international research groups, Türkiye can further improve its h-index. Furthermore, network visualization offered insights into the collaboration patterns between Turkish and international researchers in retinoblastoma. The yellow cluster in Figure 3A, which represents well-known international retinoblastoma researchers, appears interconnected with three universities through the most productive authors in Türkiye.

When examining the top journals publishing retinoblastoma research from Türkiye, we found both similarities and differences compared to global trends.[14] In our dataset, the most represented journal was *Pediatric Blood & Cancer*, accounting for 19.4% of the total publications. This is consistent with the global data, where *Pediatric Blood & Cancer* ranked third, publishing 3.5% of the papers in the field. However, the *British Journal of Ophthalmology*, which published the most retinoblastoma papers globally (5.0%), was not as prominent in the Turkish dataset, ranking tenth with only 1.7% of the publications. In terms of concentration, the top 10 journals in the Turkish dataset collectively published more than half (52.21%) of the total publications, indicating a higher concentration compared to the global data, where the top 20 journals accounted for 38.7% of the papers. This suggests that Turkish researchers tend to target a more focused set of journals for their retinoblastoma research.

Our analysis revealed 18 published documents in the national database between years 1995 and 2022. The reason for this could be that collecting sufficient data requires collaboration and often spans several years. Given the effort invested in these studies, researchers naturally want their work to have the greatest possible impact and visibility. Moreover, publishing in international journals enhances the visibility and credibility of Turkish researchers within the global scientific community. Also surprisingly, the total number of citations for the articles in the national database was zero. This lack of citations raises questions about the visibility and impact of research published in national journals and highlights the need for further investigation into the citation practices of Turkish authors.

Gray literature contains documents with potential for publication, therefore it helps to understand some of the research shortcomings in a particular area.[24] A study done in Türkiye showed that half of the theses (n=154, 50%) were converted to journal articles.[25] However, in our study we found that only 13.8% of retinoblastoma theses resulted in publication. The main reason might be that ophthalmology journals can be more meticulous for retinoblastoma articles,

Table 1. The top 20 most cited articles excluding international collaborated publications

Title	Corresponding author	Journal	Year	Citations	
				Pear year	Total
Metastatic retinoblastoma clinical features, treatment, and prognosis[26]	Gündüz, Kaan	*Ophthalmology*	2006	4.16	79
Causes of chemoreduction failure in retinoblastoma and analysis of associated factors leading to eventual treatment with external beam radiotherapy and enucleation[27]	Gündüz, Kaan	*Ophthalmology*	2018	2.76	58
Chemotherapy in retinoblastoma: current approaches[2]	Yanık, Özge	*Turkish Journal of Ophthalmology*	2015	3.5	35
Superselective intra-arterial chemotherapy in the primary management of advanced intra-ocular retinoblastoma: first 4-year experience from a single institution in Turkey of intra-arterial chemotherapy[28]	Tuncer, Samuray	*Acta Ophthalmologica*	2016	3.67	33
Retinoblastoma in Turkey: survival and clinical characteristics 1981-2004[29]	Özkan, Alp	*Pediatrics International*	2006	1.7	33
Severe pseudo-preseptal cellulitis following sub-Tenon's carboplatin injection for intraocular retinoblastoma[30]	Kıratlı, Hayyam	*Journal of AAPOS*	2007	1.44	26
A 20-year audit of retinoblastoma treatment outcomes[31]	Gündüz, Kaan	*Eye*	2020	4.8	24
Clinical and epidemiological characteristics of retinoblastoma: correlation with prognosis in a Turkish pediatric oncology center[32]	Taçyıldız, Nurdan	*Pediatric Hematology and Oncology*	2007	1.22	22
Management of massive orbital involvement of intraocular retinoblastoma[33]	Kıratlı, Hayyam	*Ophthalmology*	1998	0.74	20
Intravitreal chemotherapy in the management of vitreous disease in retinoblastoma[34]	Kıratlı, Hayyam	*European Journal of Ophthalmology*	2017	2.38	19
Retinoblastoma in Turkey: diagnosis and clinical characteristics[35]	Günalp, İlhan	*Ophthalmic Genetics*	1996	0.66	19
Retinoblastoma in Turkey: results from a tertiary care center in Ankara[36]	Gündüz, Kaan	*Journal of Pediatric Ophthalmology & Strabismus*	2013	1.33	16
Retinoblastoma in Turkey--treatment and prognosis[37]	Gündüz, Kaan	*Japanese Journal of Ophthalmology*	1996	0.55	16
Quantitative analysis of proliferation, apoptosis, and angiogenesis in retinoblastoma and their association with the clinicopathologic parameters[38]	Kıratlı, Hayyam	*Japanese Journal of Ophthalmology*	2003	0.68	15
The treatment of retinoblastoma with four-drug regimen including cisplatin, etoposide, vincristine, and cyclophosphamide[39]	Varan, Ali	*Pediatric Hematology and Oncology*	2012	1.08	14
Clinicopathological parameters and expression of P-glycoprotein and MRP-1 in retinoblastoma[40]	Kıratlı, Hayyam	*Ophthalmic Research*	2007	0.72	13
The final diagnosis: retinoblastoma or pseudoretinoblastoma[41]	Gündüz, Kaan	*Journal of Pediatric Ophthalmology & Strabismus*	2021	3	12
Intravitreal lower-dose (20 µg) melphalan for persistent or recurrent retinoblastoma vitreous seeds[42]	Tuncer, Samuray	*Ophthalmic Surgery Lasers & Imaging Retina*	2015	1.2	12
Intra-arterial chemotherapy for retinoblastoma: a single-center experience[43]	Varan, Ali	*Ophthalmologica*	2015	1.2	12
Blue toe syndrome as a complication of intra-arterial chemotherapy for retinoblastoma[44]	Sarıcı, Ahmet	*JAMA Ophthalmology*	2013	1	12

which appeal to a very small portion of their readers. As a solution to the low publication rate of retinoblastoma theses, young researchers may consider publishing their work in a national database. Publishing in national databases provides an opportunity for young researchers to gain experience in the publication process and can help enrich the Turkish scientific literature on retinoblastoma.

As another kind of gray literature, we found only one research project funded by TÜBİTAK back in 1995. Since adequate financial support is essential for conducting high-quality research, trying to benefit more from the opportunities provided by TÜBİTAK may increase the number of research studies and publications.

The publication growth trend showed that starting from just a few publications in the late 1990s, the cumulative number has consistently grown, indicating a positive trend in retinoblastoma research output in Türkiye. The growth in the real cumulative number of publications appears to have accelerated in recent years, particularly from 2015 onwards. The predictive model also suggests that the curve becomes steeper in the later years, implying that the number of publications added each year is expected to rise in concordance with the global trend.[14]

Keyword visualization analysis revealed a shift in treatment focus over time, with a gradual decrease in the prominence of external beam radiotherapy-related keywords from 2005 and a corresponding increase in chemotherapy, particularly intra-arterial chemotherapy keywords towards 2020. This change reflects the adoption of newer therapies in the Turkish retinoblastoma research landscape. However, genetic and biological research-related keywords appear to be less prominent compared to clinical and treatment-related themes. Compared to the global network, the Turkish network appears to be more treatment-focused, while the global network covers a wider range of topics, suggesting potential areas for growth in Turkish retinoblastoma research.[14]

In our study, we found only one article published by a pediatric oncology clinic without any contribution from the department of ophthalmology. This disparity may be due to several factors, and without further research, it is difficult to determine which of them has the greatest influence. It could be that retinoblastomas are primarily diagnosed and treated by ophthalmologists, resulting in a higher number of ophthalmology publications. Alternatively, there may be a lack of dedicated pediatric oncology clinics specializing in retinoblastoma, resulting in fewer pure pediatric oncology trials. Another possibility is that the multidisciplinary nature of retinoblastoma treatment promotes collaborative research between the two specialties and reduces the number of publications in individual specialties. In addition, our collaboration analysis revealed that a single researcher, Rejin Kebudi (Department of Pediatric Hematology and Oncology, İstanbul University), and the affiliated clinic predominated in the field of pediatric oncology, which may indicate that there are few pediatric oncology clinics that have significant resources for retinoblastoma research in Türkiye. Further studies are needed to investigate these potential factors and their impact on the research landscape of retinoblastoma in Türkiye.

Study Limitations

Our study has some limitations. Firstly, while we aimed to provide a through overview of retinoblastoma research in Türkiye, our analysis focused primarily on quantitative aspects, such as publication counts, citation impact, and collaboration networks. Qualitative aspects, such as the specific research questions, methodological quality, and clinical implications of individual studies were not explored in depth. Secondly, the comparisons made between Turkish and global retinoblastoma research were based on a single bibliometric study, and a more comprehensive comparison would require additional data sources and analyses.

Conclusion

In conclusion, bibliometric studies are powerful tools for assessing a country's research performance in a specific field, providing valuable insights into past achievements and future directions. This study represents the first comprehensive bibliometric analysis of retinoblastoma research conducted by Turkish researchers. Our findings highlight the dominance of a few academic centers, the value of international collaborations, and the potential for further growth in areas like basic science and genetics research. The comparison with global trends reveals areas for growth and the importance of international collaboration in enhancing research impact. Our study lays the groundwork for future bibliometric analyses of the Turkish ophthalmology literature.

Ethics

Ethics Committee Approval: This study was deemed exempt by the Kellog Eye Center Institutional Review Board.

Informed Consent: Not necessary.

Authorship Contributions

Concept: A.A., Design: A.A., Data Collection or Processing: A.A., A.S.S., Analysis or Interpretation: A.A., A.S.S., Literature Search: A.A., A.S.S., Writing: A.A.

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Review

Caffeine and Vision: Effects on the Eye

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Abstract

Caffeine, commonly found in coffee and tea, affects various aspects of eye health as it blocks adenosine receptors, impacting tear production, intraocular pressure, macular perfusion, and choroidal thickness. However, its connection with eye conditions like glaucoma and cataracts remains uncertain due to conflicting research findings. Some studies suggest potential benefits for cataracts, while others warn against frequent caffeine intake in glaucoma and surgical scenarios due to possible increases in intraocular pressure. Conflicting evidence also exists regarding its effects on dry eye, macular degeneration, myopia/hyperopia, diabetic retinopathy, retinopathy of prematurity, and central serous retinopathy. Caffeine does not seem to be a risk factor for dry eye, although studies have shown that caffeine may offer protection against wet age-related macular degeneration, and the metabolite 7-methylxanthine could be a more promising treatment for myopia. Moreover, caffeine can potentially cause tremors and might hinder surgical performance, especially in less experienced surgeons. Recommendations from experts vary, highlighting the need for further research to fully understand how caffeine affects the eye. Individuals genetically predisposed to glaucoma should be cautious due to the possibility of clinically significant elevations in intraocular pressure with caffeine consumption. For delicate procedures like microsurgery, where tremors can be detrimental, caution should be exercised with caffeine. This review underscores the importance of additional studies to provide clearer insights and prudent recommendations regarding caffeine's impact on eye health.

Keywords: Caffeine, ocular health, caffeine and eye diseases, cataract, glaucoma, dry eye, macular degeneration, choroidal thickness, coffee consumption, surgical performance

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Introduction

Caffeine, scientifically known as 1,3,7-trimethylxanthine, is a psychogenic substance present in over 60 plant species, including kola nuts, tea leaves, and coffee beans.[1] It is found in various beverages such as tea, coffee, and soft drinks, as well as chocolate-based goods and metabolic supplements.[1] While adults often consume caffeine from coffee, children and adolescents tend to consume caffeinated soft drinks. A product's caffeine content can vary based on factors such as the type of product (Table 1), the cultivation and processing methods of coffee beans or tea leaves, and the preparation of the beverage.[1]

Global caffeine consumption varies, with many adults in Western countries averaging around 4 mg/kg of body weight per day. For a 70-kg individual, this equates to roughly three cups of coffee or five cups of tea.[1] A daily intake of three to four 8-ounce cups of brewed coffee or five servings of caffeinated soft drinks or tea has been linked to neutral or potentially favorable health benefits.[2] Toxic symptoms such as increased heart rate, anxiety, tremors, and restlessness are possible, but only at much larger doses. Reaching such levels would necessitate drinking approximately 100 cups of coffee.[1] Individual variances in metabolism, situations such as pregnancy and heart disease, and drugs all contribute to variations in caffeine levels and effects.

Pharmacokinetics and Pharmacodynamics of Caffeine

Caffeine is rapidly absorbed into the bloodstream, reaching maximum plasma concentration within 1-1.5 hours after ingestion. It is primarily metabolized by the cytochrome P450 1A2 (CYP1A2) enzyme in the liver, causing demethylation and the formation of paraxanthine, theobromine, and theophylline. These metabolites are subsequently converted into xanthine, uric acid, and uracil derivatives. The half-life of caffeine ranges from 3 to 7 hours, influenced by many factors such as age, sex, medications, pregnancy, cigarette smoking, and liver function. Only 1-5% of caffeine is excreted unchanged in urine over 48

hours due to renal tubule reabsorption (Figure 1).[2] Caffeine primarily functions as an adenosine receptor antagonist and affects various body systems.

There are two main types of adenosine receptors. A1 and A3, coupled through Gi/Go protein, inhibit adenylyl cyclase and decrease cyclic adenosine monophosphate (cAMP) levels, while A2A and A2B, coupled through Gs/Golf protein, activate adenylyl cyclase and increase cAMP levels (Figure 2).[3,4] Adenosine receptors trigger defense mechanisms that control coronary blood flow, myocardial oxygen consumption, immune response, inflammation, and the release of neurotransmitters such as glutamine, acetylcholine, and dopamine.[5]

Caffeine also acts through other mechanisms, including the inhibition of phosphodiesterase, blockage of regulatory sites of gamma-aminobutyric acid type A receptors, and release of intracellular calcium, although these effects are primarily observed at toxic doses.[3]

Role of Caffeine

Caffeine is widely consumed because it enhances central nervous system activity through adenosine receptor antagonism. This stimulation raises levels of monoamines such as dopamine, serotonin, norepinephrine, and acetylcholine, contributing to improvement in subjective energy, mood, and alertness.[6]

Caffeine has also been shown to help with headaches, asthma, and neurodegenerative disorders, including Parkinson's and Alzheimer's disease.[3,7,8] Used as a monotherapy or in combination with analgesics, caffeine can treat tension-type headaches and migraines via vasoconstriction through the inhibition of adenosine receptors.[7] The blockage of adenosine receptors by caffeine has also been shown to improve airway function in asthmatic patients, possibly due to respiratory system stimulation and bronchodilation.[8] Recent studies explored caffeine's potential in the treatment and prevention of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. By inhibiting A2A receptors and increasing expression of nuclear factor erythroid 2-related factor 2, caffeine appears to play a role in regulating antioxidants, mitigating neuroinflammation, and influencing other factors responsible for preventing neuronal cell loss.[3,9]

Table 1. Caffeine concentrations of selected beverages

	Milligrams of caffeine by volume of beverage		
	1 oz. (29.6 mL)	**8 oz. (236.6 mL)**	**12 oz. (354.9 mL)**
Coffee*			
Espresso	51.33	410.64	615.96
Plain, brewed	17.5	140	210
Instant	7.125	56	85.5
Decaffeinated	0.75	6	9
Tea**			
Tea, brewed	7	53	80
Black tea	6.0	47	72
Green tea	5.6	45	68
Soft/energy drinks*			
Monster	10.0	80	120
Rock Star	10.0	80	120
Red Bull	9.5	76	114
Mountain Dew	4.6	37	55
Diet Coke	3.9	31	47
Sunkist	3.5	28	42
Pepsi-Cola	3.1	25	37
Coca-Cola Classic	2.9	23	35

*Caffeine content of drinks. https://www.caffeineinformer.com/the-caffeine-database. Accessed August 1, 2024
**FoodData Central. https://fdc.nal.usda.gov/index.html. Accessed August 1, 2024
oz: United States fluid ounce. Caffeine consumption depends on the type of beverage consumed, with Coca-Cola Classic and espresso containing the least and greatest amount of caffeine per 12 oz, respectively[1]

Physiological Effects of Caffeine on the Eye

Adenosine receptors can be found in various ocular tissues, including the cornea, iris, ciliary body, choroid, and retina.[10,11,12] Caffeine binds competitively to adenosine receptors, dilating the pupils and improving accommodation by targeting muscarinic receptors in the ciliary body and iris sphincter muscle.[8] While there is no literature studying the effects of caffeine on closed-angle glaucoma, pupil dilation is well known to narrow the angle between the iris and cornea. Therefore, further investigation is needed to reach a definitive conclusion.

Caffeine intake affects several ocular parameters, including tear production, intraocular pressure, aqueous humor, and macular perfusion.[13,14,15,16] The impact on dry eye is debated, with some evidence suggesting coffee consumption may improve lacrimal function and protect against dry eyes.[12,13,17] Single nucleotide polymorphisms in the genes encoding adenosine A2 receptors and CYP1A2, the principal enzyme in caffeine metabolism, seem to regulate this effect.[12]

The role of caffeine in intraocular pressure has been a topic of interest since 1997 when Kurata et al.[18] first proposed a positive association. In their study on male Wistar rats, a single dose of caffeine caused a considerable increase in intraocular pressure after 15 minutes and 1 hour, which was attributed to increased aqueous fluid secretion. A later study by Kurata et al.[19] using intravenous caffeine in beagle dogs demonstrated a similar increase in intraocular pressure, suggesting a potential mechanism involving increased aqueous humor secretion. However, a preclinical model conducted by Madeira et al.[20] revealed a potential neuroprotective role of caffeine. In their study, rats with ocular hypertension were given caffeine, which reduced intraocular pressure and decreased retinal neuroinflammation, microglia reactivity, and ganglion cell loss after 3 weeks.

The theorized mechanism of action for increased ocular pressure involves caffeine's antagonism of adenosine receptors, which inhibits aqueous humor outflow by causing smooth muscle relaxation in the filtration system, resulting in closure of the trabecular meshwork. The blockage of adenosine receptors is also associated with caffeine's well-known effect of elevating blood pressure, which is hypothesized to increase the hydrostatic pressure involved with aqueous humor generation.[21] Lastly, hypotheses propose caffeine may elevate intracellular cAMP,

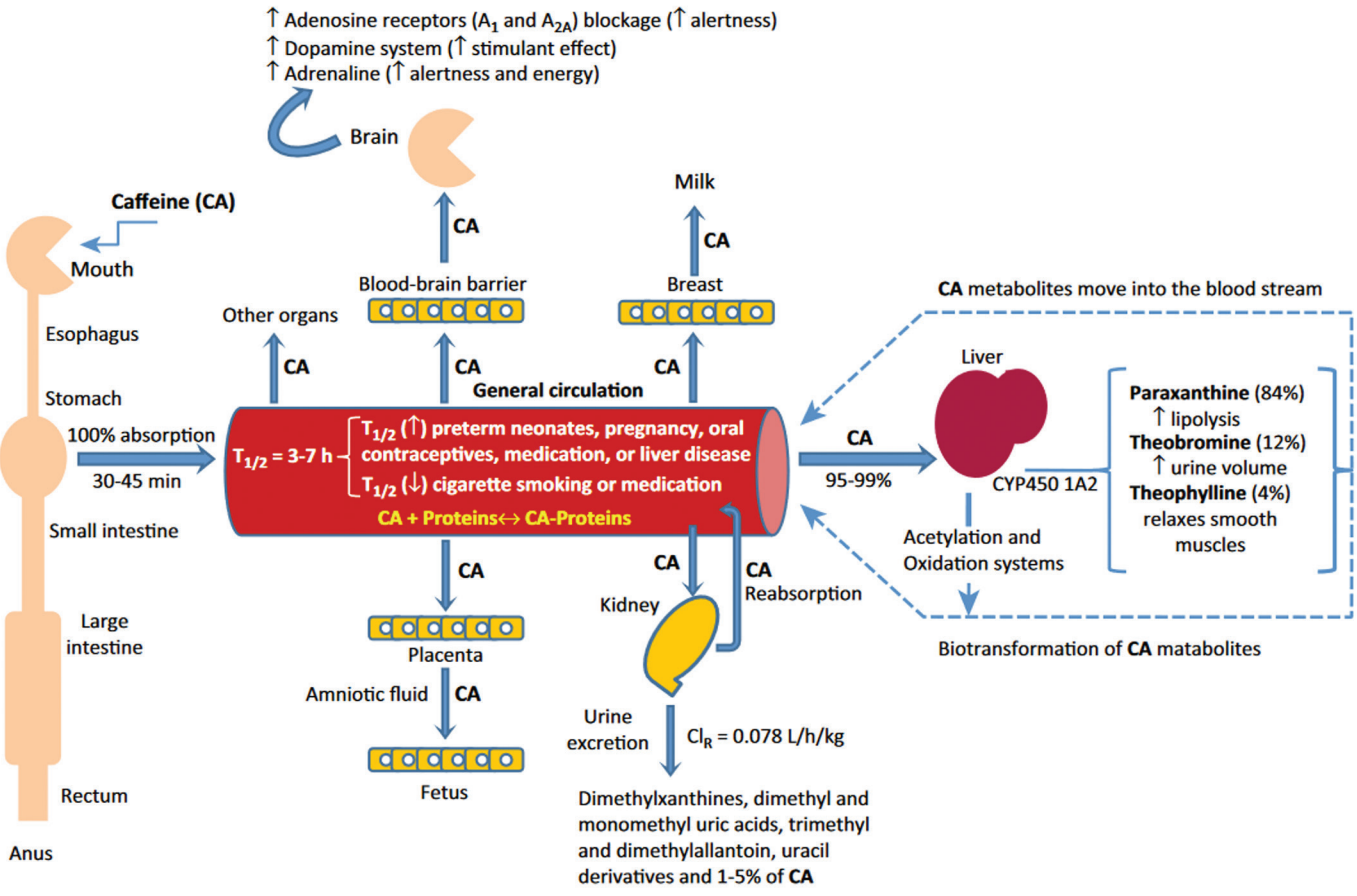

Figure 1. Pharmacokinetics of caffeine. Caffeine consumed orally is rapidly absorbed into the general circulation, metabolized by liver CYP1A2 enzyme, and reabsorbed by renal tubules with only 1-5% excreted unchanged in the urine within 48 hours. Caffeine can enter several organs including the brain, leading to increased adenosine receptor blockage (from Gonzalez de Mejia and Ramirez-Mares[2]; reprinted with permission from Elsevier)

increasing aqueous humor formation.[22] However, current evidence suggests that caffeine blood levels from 2-3 cups of coffee do not suppress phosphodiesterase function.[23]

When evaluating population studies, the clinical significance of caffeine in terms of intraocular pressure remains unclear, especially in non-glaucomatous individuals.[22,24] In those with primary open-angle glaucoma or ocular hypertension, intraocular pressure elevations were statistically significant but clinically insignificant.[14,16,25,26] Higher and more clinically significant pressures were seen in individuals with a genetic predisposition.[27,28] One limitation of these studies is the inclusion of small samples, as habitual coffee use was only weakly associated with lower intraocular pressure in a large study of 121,374 patients.[28]

Caffeine's ability to induce cerebral vasoconstriction and reduce cerebral blood flow is well-documented.[25,29,30,31] However, limited research has been conducted into caffeine's effects on ocular blood flow. In a 1992 study conducted by Lotfi and Grunwald[32], a 13% decrease in macular blood flow was observed 1 hour after the oral administration of 200 mg caffeine. However, their study was limited by the fact that subjective measurement of macular blood flow was conducted only twice during the experiment (pre-administration and 1 hour post-administration).[32] In a more recent investigation, the effects of 100 mg of caffeine were quantitatively tested using a laser speckle technique, and the results showed decreased circulation in the choroid, retina, and ocular nerve head after caffeine administration.[15] A considerable decrease in ocular fundus flow was observed despite the very small amount of caffeine, which is known to have no systemic effect. This suggests that the ocular blood vessels were directly impacted. Subsequent optical coherence tomography (OCT) angiography investigations supported these results, showing a significant reduction in retinal flow area and vessel density following coffee consumption.[33] The most likely source of these effects is an increase in peripheral vascular resistance brought on by the vasodilatory effect of adenosine antagonization.[34] Intriguingly, intravenous injections of adenosine were shown to induce retinal vasodilation and lower intraocular pressure.[34]

Caffeine also affects choroidal thickness, as evidenced by analytical tests including enhanced depth imaging (EDI) OCT.[35,36,37,38] One study noted a significant decrease in choroidal thickness from baseline at 1 and 3 hours after consuming 200 mg

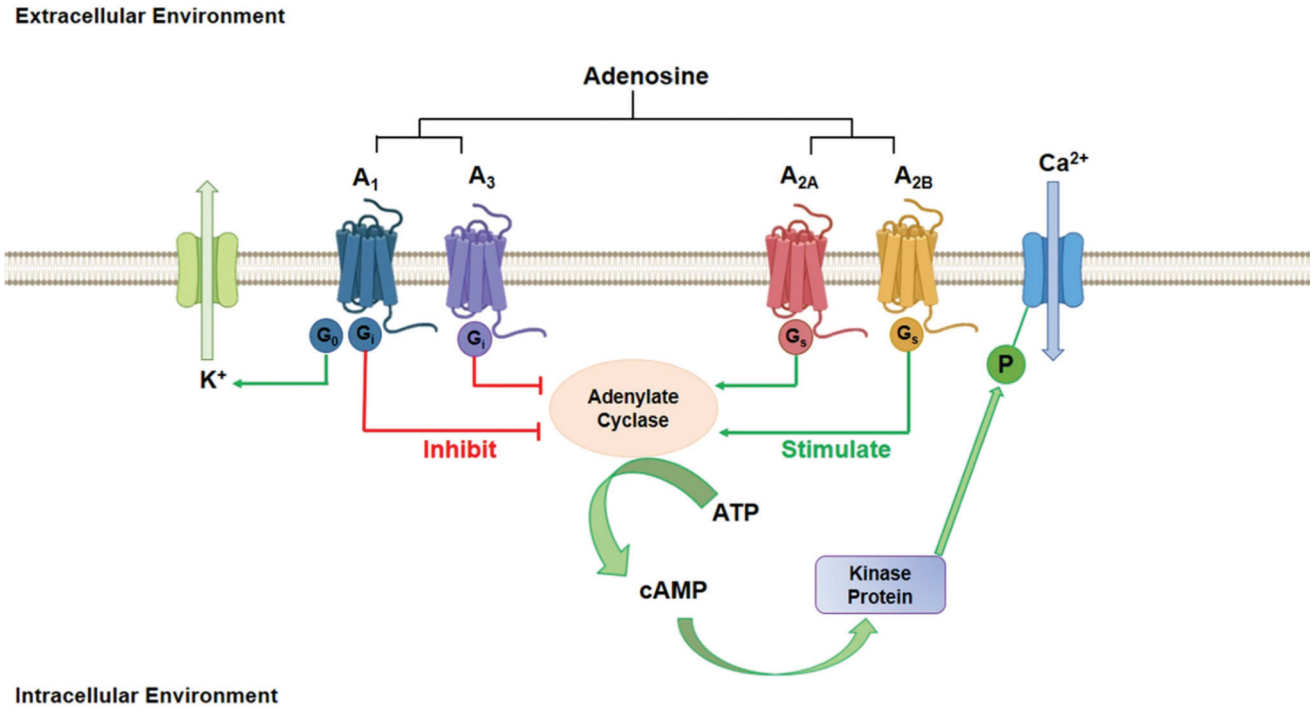

Figure 2. Adenosine receptor signaling pathway. A1 and A3 are couples though Gi/Go protein, inhibiting adenylyl cyclase and decreasing cAMP levels. A2a and A2b are coupled through Gs/Golf protein, stimulating adenylyl cyclase and increasing cAMP levels. (from Mazziotta et al.[4]; reuse permitted under the Creative Commons Attribution 4.0 International License [CC BY 4.0])
cAMP: Cyclic adenosine monophosphate, ATP: Adenosine triphosphate

of caffeine (Figure 3).[35] Another study found that a significant decrease in choroidal thickness persisted for at least 4 hours after consuming 200 mg of caffeine.[38] Notably, a study involving young monkeys found that topical caffeine administration did not prevent normal-age dependent increases in choroidal thickness, suggesting that any potential decrease in thickness may be temporary or overridden by other factors.[39] Age differences and test duration may account for these differences, as the monkey study focused on infants while the human studies involved adult participants. Additionally, the infant monkey study investigated the effects of twice daily administrations over several months, whereas human studies used single administrations.

Finally, caffeine may offer protection against oxidative damage to the crystalline lens due to its antioxidant properties.[37] With advancing age and other conditions, a decrease in these antioxidants such as glutathione and ascorbic acid may cause oxidative stress, protein aggregation, and light scattering, ultimately contributing to cataract formation.[40] Coffee consumption has been associated with reduced cataract formation due to its antioxidant qualities, which are mainly attributed to the adenosine antagonist activity of caffeine. While coffee includes other antioxidants, such as chlorogenic acids, these chemicals are partially destroyed during the roasting process of raw coffee beans.

Effects of Caffeine in Ocular Diseases

Cataract

Cataracts result from oxidative stress damaging the eye lens due to factors like ultraviolet (UV) light exposure, aging, and diabetes.[41,42] Antioxidants like glutathione and ascorbic acid help maintain lens transparency but may be depleted over time, leading to cataract formation.[40]

Varma et al.[42] were among the first researchers to explore the effects of caffeine on cataract development through *in vitro* studies. One such study by Varma and Hedge[43] demonstrated caffeine's ability to mitigate oxidative damage to the lens from free radicals generated by adding iron to the culture medium. In a global investigation including 43 countries, Varma[44] concluded that the lowest rates of cataract blindness were observed in the most developed countries, which also have high caffeine consumption. Notably, the protective effect of caffeine on cataract-associated visual impairment was evident at daily consumption levels of 50 mg and approached near completeness with 100 mg per day.[44] However, it is crucial to note that this study did not account for other factors, such as socioeconomic status and access to healthcare. On the other hand, a sizable study conducted in Beaver Dam, Wisconsin, involving 4,926 people aged 43 to 86, accounted for socio-economic and lifestyle factors and revealed no relationship between coffee consumption and the

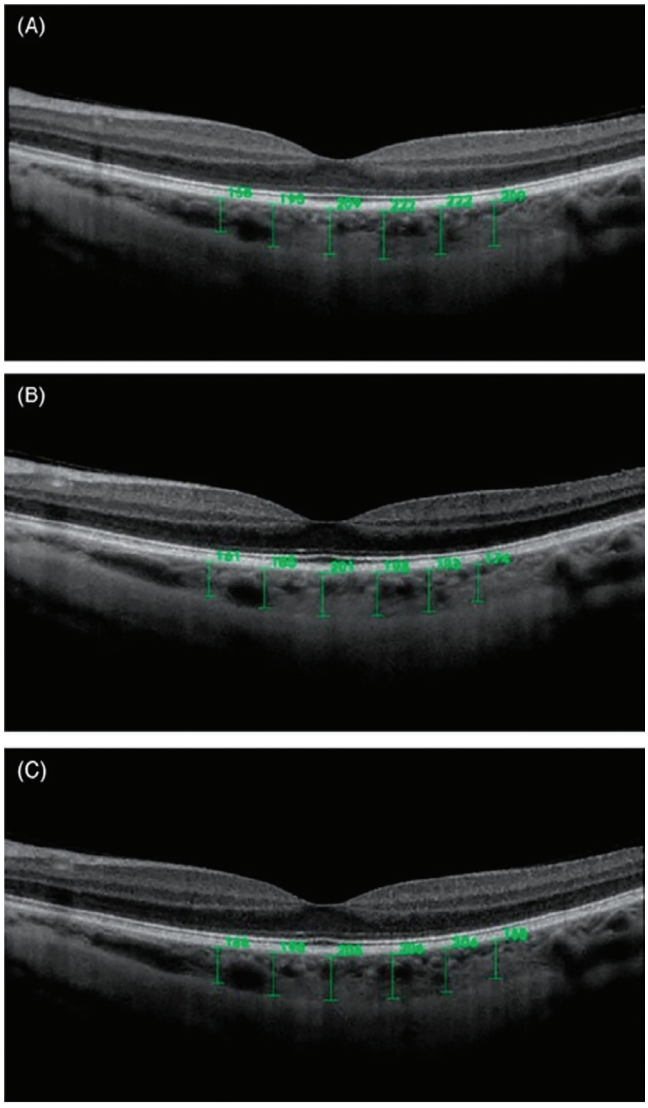

Figure 3. Choroidal thickness measurements obtained before (A), 1 hour after (B), and 3 hours after (C) oral caffeine consumption (200 mg capsule) (from Zengin et al.[35]; reprinted with permission from Taylor & Francis Informa UK Ltd-Journals)

likelihood of developing age-related cataracts such as cortical, posterior subcapsular, or nuclear cataracts.[45]

The association between UV radiation and cataract development has been attributed to the formation of reactive oxygen species in the aqueous humor and lens, leading to the depletion of lens antioxidant reserves.[42,46,47,48] *In vitro* lens culture tests on mouse lenses exposed to UV light at 302 nm caused physiological damage, including inhibition of Na+/K+ adenosine triphosphatase (ATPase) and decreased adenosine triphosphate (ATP) and glutathione levels. Interestingly, caffeine appeared to mitigate these effects.[49] Further studies showed that caffeine prevented glutathione and ATP depletion and maintained Na+/K+ ATPase activity in the presence of kynurenine, which acts as a photosensitizer in the lens.[50] Topical caffeine drops effectively prevented UVB-induced lens opacification, and peroral caffeine administration decreased UV-induced apoptosis in human lens epithelial cells.[51,52]

Individuals with metabolic syndrome or obesity have an increased risk of developing cataracts, but caffeine has been demonstrated to improve metabolic symptoms and promote weight loss in rats.[53] Additionally, caffeine and pyrocatechol, both components of coffee, were associated with a lower incidence of obesity-related cataracts in later research.[54] Mice fed a high-fat diet and treated with coffee had reduced body weight, preserved antioxidant components in their lenses, and avoided elevated cholesterol levels.[53,54]

Furthermore, diabetes can elevate the risk of cataracts by increasing oxidative stress through altered levels of superoxide dismutase, catalase, glutathione peroxidase, malondialdehyde, and advanced oxidation protein product.[55] Studies have shown that in diabetic lenses, caffeine administration led to increased quantities of the antioxidant glutathione and decreased levels of reactive oxygen species. In another investigation, caffeine eye drops significantly inhibited the onset and advancement of cataract formation in young rats with a diet containing 24% galactose.[56]

Glaucoma

Caffeine does not appear to increase intraocular pressure in normal healthy subjects.[24,57,58] However, it may elevate intraocular pressure in those with a history of ocular hypertension, primary open-angle glaucoma, normotensive glaucoma, and glaucoma suspects. The observed effects may not be clinically significant, with transient increases in intraocular pressure after ingesting more than 180 mg of caffeine not likely to impact glaucoma progression.[14,16,25,26,59,60] Although a large prospective study provided evidence against an association between caffeine consumption and intraocular pressure, a 2021 investigation discovered a significant effect in individuals with a strong genetic propensity to elevated intraocular pressure.[27,61] Intraocular pressure has a heritability estimated at 40-70%, with certain genetic variants contributing to its variation. Mutations in genes like *MYOC* (myocilin), *CYP1B1* (cytochrome P450 1B1), *LTBP2* (latent transforming growth factor beta binding protein 2), and *TEK* (TEK receptor tyrosine kinase) can lead to Mendelian primary open-angle glaucoma or primary congenital glaucoma with high intraocular pressure.[62,63,64,65]

In glaucoma, elevated intraocular pressure can compromise the blood supply to vital eye tissues such as the retina, choroid, and optic nerve head.[66] Caffeine's vasoconstrictive properties contribute to decreased ocular blood flow, which may exacerbate glaucoma progression. Studies indicate that coffee consumption is associated with reduced blood flow velocity and microcirculation in these areas, suggesting a potential link between impaired blood flow and glaucoma development.[5,15,32,33]

Notably, topical 1% caffeine eye drops did not appear to change intraocular pressure in patients with primary open-angle glaucoma after 1 week of administration.[31] This suggests that the effects observed with coffee consumption, which contain various physiologically active substances besides caffeine and may vary in

concentration among different brands, may not be attributable solely to caffeine. Thus, topical caffeine eye drops, containing only caffeine, may offer insights into the direct effects of caffeine on ocular physiology.

Dry Eye

Dry eye is a common ocular surface condition characterized by tear production of insufficient quality or quantity to moisturize the eyes. Various therapeutic approaches are available to manage the condition, including dietary modifications with omega-3 supplements, environmental modifications, and the use of over-the-counter artificial tears or anti-inflammatory medications.[67]

Caffeine, traditionally considered a risk factor for dry eyes, has shown mixed effects on tear production and tear film osmolarity. Some studies suggest that both topical application and oral consumption of caffeine can increase tear production and reduce tear film osmolarity.[12,13,17,44,68,69,70] Although two studies suggested caffeine has no significant effect on the risk of developing dry eyes, both employed a cross-sectional design based on self-reported data.[71,72] Because of these limitations, the results of these studies cannot demonstrate causality and may be affected by recall bias.

Macular Degeneration

Age-related macular degeneration (AMD) is characterized by central vision deterioration due to macular damage. Most patients have dry AMD, where the macula thins and accumulates yellow deposits called drusen, leading to retinal degeneration. Wet AMD is a progression of the dry form and involves subretinal neovascularization, which causes edema and hemorrhage.[10] Treatment options include anti-vascular endothelial growth factor (VEGF) injections for wet AMD and antioxidant vitamins and minerals for moderate to severe dry AMD.[73,74]

The choroid, the vascular layer of the eye, plays important functions such as providing nutrition and oxygen to the outer retinal layers, regulating retinal temperature, and eliminating waste.[75] The choroidal vasculature must be physically and functionally normal for the retina to operate properly. People with AMD have been found to have altered choroidal blood flow, which raises the possibility that these changes may influence pathogenesis. For example, early AMD is associated with decreased choroidal thickness.[35,36,37,38,76,77]

The impact of caffeine on AMD is unclear. While one case-control study suggested caffeine consumption may prevent AMD development, another study found no correlation after a 5-year incidence period.[78,79] Recent research indicates that the antagonistic effect of coffee on adenosine receptors may suppress the abnormal choroidal vascular growth associated with wet AMD.[11]

Adenosine receptors, particularly A2A and A3, are expressed in the retina and choroid, with altered expression observed in AMD patients. Upregulation of A2A and A2B receptors in response to hypoxia and inflammation may play a role in AMD progression.[10,20] Significant A3 receptor expression was also observed in the choroid/RPE of human eyes, especially in individuals with dry AMD, and downregulation of this receptor was proposed to have contributed to the death of photoreceptor cells.[80]

Myopia and Hyperopia

Myopia (nearsightedness) and hyperopia (farsightedness) result from differences in corneal curvature and eye length that interfere with the proper focusing of light on the retina. Correction methods include contact lenses, eyeglasses, and laser therapy procedures like laser in situ keratomileusis or photorefractive keratectomy. Topical caffeine has shown promise in preventing myopia progression. Recent studies in monkeys revealed that caffeine application counteracted myopic compensation and impacted choroidal thickness and vitreous chamber elongation.[39] Remarkably, several earlier investigations reported that a single oral dose of caffeine or coffee consumption decreased choroidal thickness in healthy adults.[36,37,38,76] It is improbable that these disparate reactions are exclusively the result of species differences, given the similarities between macaque and human eyes. Additionally, factors such as the age of the population should be considered, as choroidal thickness typically increases during childhood and decreases with age. Results may also be influenced by the duration of exposure. For example, a single application may yield different effects than twice-daily administrations over several months. Further research is needed to investigate if coffee temporarily reduces the thickness of the choroidal wall in adult humans.

In a sample of myopic Danish children, oral administration of the caffeine metabolite 7-methylxanthine (7-MX) was shown to slow the progression of myopia and axial elongation.[81,82] Furthermore, a rat study examining the sub-chronic and chronic toxicity of 7-MX as a possible treatment for myopia demonstrated no mortality or signs of toxicity with 7-MX, compared to 10% mortality in the caffeine-treated group.[83] However, there was no significant correlation between caffeine consumption and the occurrence of myopia in another study involving a cohort of participants 12 to 25 years of age.[82]

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) arises from oxygen-induced damage to the developing retinal vasculature, leading to hyperoxia and vaso-obliteration followed by abnormal new blood vessel formation, primarily driven by the VEGF signaling pathway.[39] Due to advances in neonatology, ROP has become a significant cause of childhood blindness worldwide.[84,85,86] Caffeine therapy has been shown to attenuate the effects of pathological hyperoxia-induced vaso-obliteration and hypoxia-induced angiogenesis, mediated by both A2A receptor-dependent and independent processes.[87] However, contraindicatory findings exist regarding the association between caffeine intake and ROP severity. While a randomized controlled trial suggested early caffeine treatment in premature infants can lower the risk of ROP, a small retrospective study found no correlation.[88,89] Additional randomized controlled trials should be conducted to explore potential biases affecting outcomes.

Diabetic Retinopathy

Diabetic retinopathy is a leading cause of vision loss in type 2 diabetes patients. Available treatments include anti-VEGF

therapy, vitrectomy, and scatter laser surgery. The relationship between coffee consumption and diabetic retinopathy remains unclear. One study suggested a potential protective effect of coffee consumption, as people with type 2 diabetes mellitus who drank more than two cups of coffee daily showed reduced development of diabetic retinopathy. Caffeine was also found to have a protective effect on the blood-retinal barrier in cellular models of diabetic macular edema, potentially reducing apoptosis by 18%.[90]

Conversely, a second study indicated that caffeine negatively impacted the retinal microvasculature, as coffee consumption was positively connected with retinal venular width in those with cardiovascular risks, including diabetes mellitus.[91] Interestingly, caffeine-containing tea and coffee did not correlate, suggesting antioxidants may counteract caffeine's vasoconstrictive effects.

Other findings suggested a dose-dependent protective effect of caffeine, with moderate to high doses associated with a 65% lower risk of diabetic retinopathy in type 2 diabetes patients. However, this association was not observed when caffeine use was analyzed as a continuous variable.[92]

Overall, while caffeine's potential protective effect is promising, more research is needed to clarify its role in diabetic retinopathy development. Studies conducted on diabetic mice did not translate to humans, indicating the need for additional investigation into the mechanisms underlying caffeine's effects.

Central Serous Retinopathy

Central serous retinopathy involves serous detachment of the macula due to subretinal fluid accumulation. It primarily affects young men, and is associated with psychological stress. Other risk factors include corticosteroids, elevated testosterone and aldosterone levels, and hyperopia.[93] Treatment options include intravitreal therapy, systemic medicines such as mineralocorticoid receptor antagonists, photodynamic therapy, argon laser therapy, and surgery (partial sclerectomy).[93] In some cases, the condition may spontaneously resolve. Caffeine abuse has been associated with central serous retinopathy.[94] Caffeine activates the hypothalamic-pituitary-adrenal axis, increasing the secretion of stress hormones such as cortisol. This effect is sex-dependent, with men showing greater cortisol increases in response to psychological stress compared to women.[95] Caffeine may also inhibit adenosine receptors necessary for the absorption of subretinal fluid.[36] However, more studies are needed, as available articles are limited. Additional studies on the impact of caffeine on choroidal thickness could offer valuable perspectives on its possible involvement in central serous retinopathy.

Implications of Coffee in Surgical/Clinical Performance

Surgeons frequently abstain from caffeine during procedures to minimize tremors and avoid any detrimental effects on their work. This is especially true for delicate microsurgical activities like vitreoretinal surgery, which require fine manual dexterity. Research has shown that caffeine use before surgery may have a deleterious impact on surgical performance, particularly in inexperienced surgeons.[96,97] However, another study suggested that caffeine had no appreciable impact on surgical performance.[98] Propranolol, on the other hand, was linked to better results.[96,98,99]

Practical Implications

The effects of caffeine on various eye diseases present conflicting findings, making it a challenge to provide clear recommendations. While there is evidence of a protective effect against cataracts, its impact on other ocular diseases is unclear.

Increased intraocular pressure from caffeine appears clinically insignificant for glaucoma progression. Caffeine cessation is not routinely recommended for non-glaucomatous or glaucomatous patients, but those genetically susceptible to glaucoma should be advised to consume caffeine conservatively (e.g., less than 180 mg per day).

Recent research suggests caffeine is not a substantial risk factor for dry eye disease. However, stopping caffeine intake a few hours before surgery should be recommended to reduce the chances of dry eye and increased intraocular pressure during the procedure, minimizing potential complications.

Microsurgeons may also benefit from abstaining from caffeine before surgery to decrease tremors and lower the risk of complications.

Conclusion

Caffeine, a widely consumed psychoactive substance, warrants caution due to its potential effects on the eye. Further research is needed, especially concerning ocular diseases with conflicting findings such as AMD and myopia.

Recent studies suggest that the caffeine metabolite 7-MX could offer a more promising treatment for myopia, showing no signs of mortality or toxicity compared to caffeine. Additionally, there are indications that caffeine may provide protection against wet AMD. Therefore, further research should include investigating these effects, given the current uncertainty surrounding the impact of caffeine on myopia and AMD.

Moreover, additional research should explore the different components of coffee, the effects of roasting, and the method of beverage preparation. These factors may contribute to the variable development of eye diseases. Coffee, the primary source of caffeine, contains several other physiologically active substances derived from coffee beans and those produced during processing by roasting. Roasted coffee beans harbor bioactive substances known to be harmful to the eyes, such as furfural and its derivatives, formaldehyde, and acrolein.[100] It is difficult to rule out the possibility that differences in these constituent levels between different coffee brands and preparation techniques could factor in the disparities in reported intraocular pressure findings among coffee drinkers.

In conclusion, it is imperative to schedule routine, periodic eye exams to detect and treat eye illnesses early on and to visit an ophthalmologist as soon as possible if one is suffering any visual or eye-related issues.

Methods of Literature Search

The literature search was done from November 2023 to January 2024, using electronic databases including Google

Scholar and PubMed, by searching the following keywords: caffeine and eye, caffeine and cataract, caffeine and glaucoma, caffeine and dry eye, caffeine and myopia, caffeine and eye health in pediatrics, caffeine effects on choroidal thickness, caffeine mechanism of action, caffeine and surgical performance, caffeine effects on retina, caffeine on diabetic retinopathy. An extensive search was performed and all relevant articles were retrieved. Most were written in the English language and the timeline of published articles ranged from 1984 to 2023.

Ethics

Authorship Contributions

Surgical and Medical Practices: A.A., A.L.R., P.P.C., J.C., Concept: A.A., A.L.R., P.P.C., J.C., Design: A.A., A.L.R., P.P.C., J.C., Data Collection or Processing: A.A., A.L.R., J.C., Analysis or Interpretation: A.A., A.L.R., P.P.C., Literature Search: A.A., J.C., Writing: A.A., A.L.R., P.P.C., J.C.

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Case Report

Partial Lateral Rectus Avulsion Due to Cat Scratch

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Abstract

Isolated rectus muscle rupture due to trauma without globe damage is extremely rare. The most commonly affected muscle is the medial rectus, while the least affected is the lateral rectus. The oblique muscles are much less affected by trauma because they are protected by the surrounding bone structures. Eye movements should be assessed after evaluating the integrity of the globe and performing a detailed eye examination. The most appropriate treatment should be provided as soon as possible after the degree of damage is determined. Especially in animal-related injuries, rabies prophylaxis should be overlooked in addition to tetanus. Here we present a 37-year-old male patient with partial lateral rectus avulsion due to cat scratch.

Keywords: Lateral rectus avulsion, cat scratch, strabismus

Introduction

Isolated traumatic extraocular muscle avulsion without globe damage is extremely rare.[1,2,3,4,5,6] It usually presents as a decrease in eye movement in the direction of the affected muscle, and at least one rectus muscle is observed to be completely damaged.[5,6,7,8] However, if partial damage has occurred, there may be no significant impact on eye movements. Here we describe an isolated partial lateral rectus avulsion due to cat scratch.

Case Report

A 37-year-old male patient presented to the emergency department on October 23 after a cat scratch to his left eye. The trauma had occurred approximately 1 hour before presentation, and the patient had no history of systemic or eye disease. He was given a tetanus vaccine in the emergency room. However, he refused rabies vaccination because he was scratched by his pet cat, which was vaccinated against rabies.

In the ophthalmological examination, visual acuity was 20/20 in both eyes. The patient was orthophoric in the primary gaze position and his eye movements were free in all directions. Right eye examination findings were normal. In the left eye, an approximately 2-mm laceration was observed in the lateral bulbar conjunctiva, corresponding to the lateral rectus insertion region, and a pink-white tissue was protruding from the wound (Figure 1). This tissue was tightly adhered to the globe. Orbital computed tomography (CT) revealed no pathological findings.

The patient was admitted for surgery on the same night. During the surgery, it was observed that a 22-mm-long piece of the lateral rectus muscle had been pulled through the conjunctival laceration (Figure 2). The remaining superior three-quarters of the lateral rectus muscle was intact, and globe integrity was preserved. The severed muscle piece was excised (Figure 3). Histopathological examination of the tissue confirmed it was striated muscle. The patient used antibiotic (moxifloxacin hydrochloride 0.5%; Vigamox, Alcon, Fort Worth, TX, USA) and steroid (fluorometholone acetate 0.1%; Flarex, Alcon, Fort

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Worth, TX, USA) drops 4 times a day for 1 week postoperatively.

The day after surgery, the patient was orthophoric in the primary position and there was no limitation in eye movements. The patient was checked at 1 week and 1 month postoperatively, and no change in the examination findings was observed.

Discussion

Although isolated rectus muscle damage due to trauma is rare, the most commonly affected muscle is the medial rectus, followed by the inferior rectus.[1,7] This has been attributed to these muscles' closer proximity to the corneoscleral limbus and Bell's phenomenon.[1,6] In Bell's phenomenon, the medial rectus and inferior rectus come to the fore as the eye reflexively moves upward and outward. The oblique muscles are damaged much less frequently because they are well protected by the surrounding tissues.

Figure 1. A 2-mm laceration in the left lateral bulbar conjunctiva with a pink-white tissue protruding from the wound

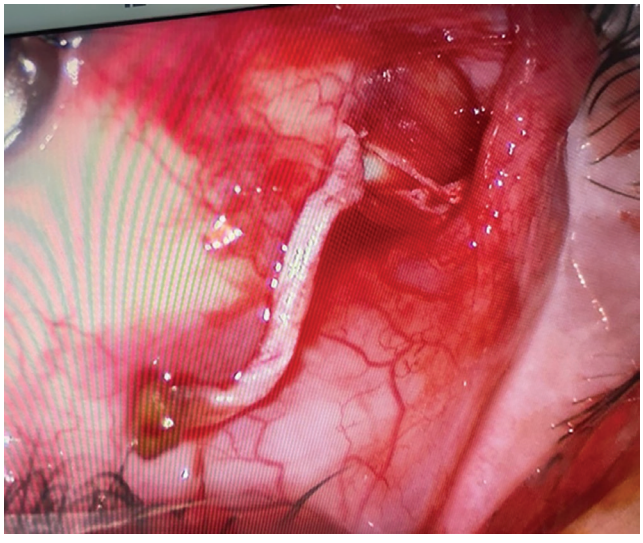

Figure 2. A piece of lateral rectus muscle 22 mm long and 3 mm wide piece protruded from the conjunctival laceration and was tightly adhered at the insertion site. The remaining superior three-quarters of the lateral rectus muscle was intact

Visual acuity, fundus examination, and globe integrity should be evaluated carefully in patients with traumatic extraocular muscle injuries. When necessary, a detailed evaluation of the damaged muscle can be performed with tests such as magnetic resonance imaging and high-resolution CT. We performed orbital CT to better evaluate extraocular structures, the condition of the muscle we thought was damaged, and the presence of a foreign body, but this examination is not mandatory in every patient. In addition, the oculocardiac reflex is an important aid in correctly identifying muscle tissue during the operation.[1]

Although there is no consensus on the optimal timing of surgical treatment after injury for a good recovery, Minguini et al.[1] performed repair within 1-3 days and achieved successful results. As we thought an earlier intervention would lead to better motor and sensory recovery, we performed surgery 5 hours after the injury.

In another patient with partial lateral rectus avulsion due to a cat scratch, Williams et al.[5] observed that the muscle piece was detached from the posterior point of origin and attached to the globe at the anterior insertion region, as in our patient. This suggests that the anterior insertion is not the weakest attachment point of the lateral rectus muscle.

Since the medial rectus muscle does not attach to the surrounding tissues, in case of total rupture, it moves further back and is very difficult to find.[1,9] If it is ruptured from the posterior origin region, as in our case, repair is difficult and the ruptured part can be excised. If other muscles are torn from their insertion site, they do not go back too far due to their adhesion to the surrounding tissues and can be easily found and sutured instead.

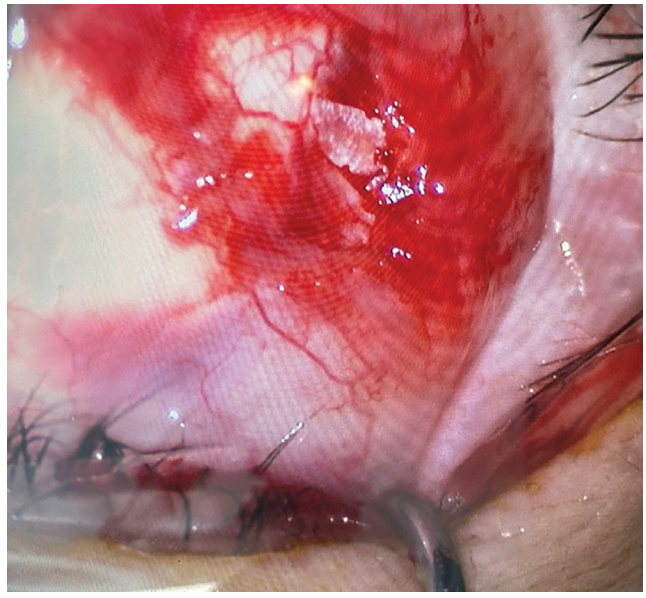

Figure 3. The severed muscle piece was excised

The first treatment option is to reattach the severed muscle or tendon ends. If suitable ends cannot be found, it may be necessary to transfer from adjacent rectus muscles.[6] However, care must be taken during this process, because if one muscle is avulsed and the other two muscles are completely transferred, the blood supply to all three rectus muscles will be impaired. While this can sometimes be done in younger patients, it would be more appropriate to perform partial muscle transfer (such as the Jensen procedure or Nishida transposition surgery with vessel sparing) in children and patients over the age of 50.[6] Vessel-sparing Nishida transposition surgery is more preferred today. Even if patients with partial lateral rectus avulsion exhibit no postoperative impairment of eye movements, regular follow-up should be performed because eye movements may deteriorate in the future due to decreased or lost function in the remaining intact muscle.

After injury, care must be taken in terms of tetanus and rabies prophylaxis. It is known that most animal-related traumas are caused by pets.[10]

Isolated traumatic rectus muscle rupture is an extremely rare condition. Globe integrity and eye movements should be evaluated quickly and the most appropriate treatment provided as soon as possible. When the avulsed muscle piece is large, it may cause restriction in eye movements and eye misalignment. Therefore, repair should always be the first choice, and excision should be considered if this is not possible. Tetanus prophylaxis should definitely be questioned, and rabies prophylaxis should not be overlooked in animal injuries.

Ethics

Informed Consent: Obtained.

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Pulsatile Proptosis and Sphenoid Wing Dysplasia with no Evidence of Neurofibromatosis Type 1: A Case Report and Review of the Literature

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Abstract

In this study, we aimed to present a rare case of pulsatile proptosis due to sphenoid wing dysplasia without the features of neurofibromatosis type 1 (NF1). A 17-year-old male patient presented with swelling in the superotemporal region of the right eye. Physical examination revealed facial asymmetry with a pulsatile, ill-defined, soft lesion with in the superotemporal region of the right orbit associated with pulsatile proptosis, downward dystopia, and hypotropia. Computer tomography imaging to establish a differential diagnosis showed temporal lobe herniation secondary to sphenoid wing dysplasia. The patient was assessed for NF1, which is most commonly associated with sphenoid wing dysplasia, but no evidence supporting the diagnosis was found. Patients presenting with proptosis should be carefully examined for pulsation and murmurs, and a trauma history should be investigated. Radiological imaging should be used to facilitate the differential diagnosis, and the current clinical condition should be managed with a multidisciplinary approach.

Keywords: Dystopia, exophthalmos, neurofibromatosis type 1, pulsatile proptosis, sphenoid wing dysplasia

Introduction

Proptosis is defined as one or both eyes bulging forward.[1] It can result from different conditions such as infectious, inflammatory, vascular, and neoplastic conditions. Differential diagnosis is critical since it may risk vision and even life.

Encephalocele is one of the causes of proptosis. Encephaloceles are acquired or congenital herniations of meninges and brain parenchyma through a structural cranial bone defect. Traumatic intraorbital encephalocele, though rare, is the most common type and arises from orbital roof fractures caused by blunt trauma. Congenital cases are often linked with sphenoid dysplasia, which is most frequently associated with neurofibromatosis type 1 (NF1).[2,3] Sphenoid dysplasia-related encephaloceles cause ocular symptoms such as dystopia, strabismus, and optic disc pressure. NF1 is a hereditary neurocutaneous disorder. Instances of sphenoid dysplasia occurring without associated NF1 features are rare.[4]

The aim of this article is to present a rare case of non-NF1-related pulsatile proptosis and review of literature.

Case Report

A 17-year-old male patient presented to the eye clinic with a pulsating lesion in the superotemporal region of the right orbit persisting for 5 years. Macroscopic examination revealed facial asymmetry with a pulsatile, ill-defined, soft lesion in the superotemporal region of the right orbit, and no audible bruit was detected.

The patient exhibited downward dystopia, 10 prism diopters of hypotropia in primary position, and proptosis of the right eye (Figure 1). Eye movements were restricted upward in the right eye but free in other directions. Suppression was observed in the Worth 4-dot test and Schober's test.

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On examination, the patient's direct and consensual light reflexes were normal, bilateral visual acuity was 20/20 and intraocular pressures were within normal limits. Anterior segment and fundus examination findings were normal (Figure 2). Optical coherence tomography, retinal nerve fiber layer analysis, and visual field examination revealed no pathology.

In contrast-free orbital computer tomography, the right greater wing of the sphenoid bone appeared dysplastic (Figure 3). There was a distinct extra-axial cerebrospinal fluid space in the right temporal fossa, and herniation of the temporal lobe into the orbit markedly displaced the superior oblique muscle. The patient was evaluated for NF1, but there were no findings that satisfied the diagnostic criteria other than sphenoid wing dysplasia. The patient also had no family history of NF1. The family was referred for genetic counseling and no specific feature was identified.

Consultations with the plastic and reconstructive surgery and neurosurgery departments were sought for the patient. Orbital roof reconstruction was recommended by the neurosurgery team. However, the patient declined surgical treatment. He is currently continuing follow-up in the strabismus unit.

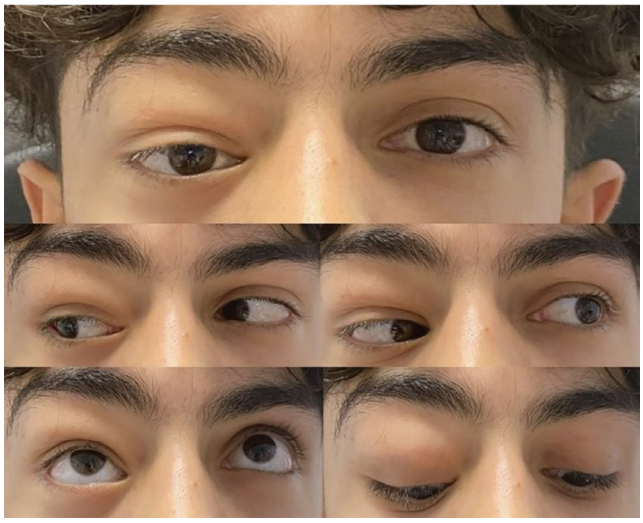

Figure 1. Downward dystopia and minimal limitation in upward movement

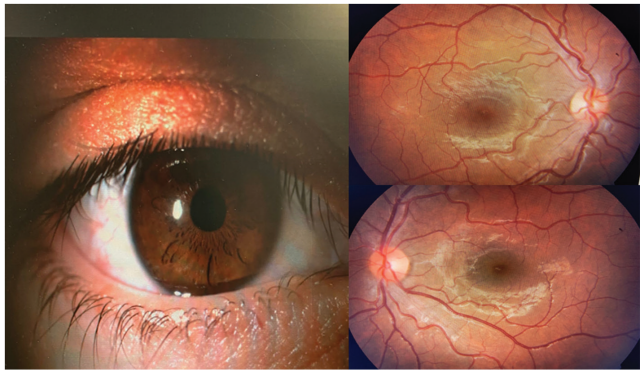

Figure 2. Anterior segment and fundus examination findings were normal

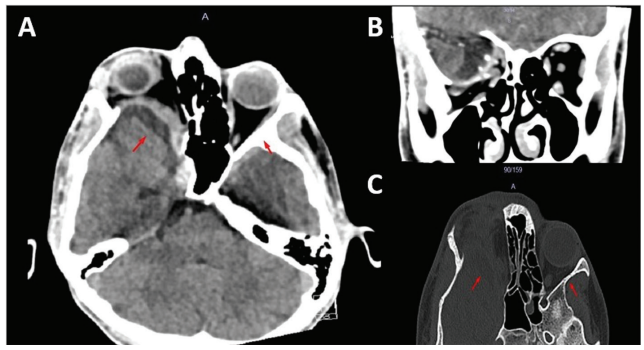

Figure 3. In panels A and C, the positions of the sphenoid wings are indicated by red arrows. While the sphenoid wing is observed on the right, there is a dysplastic appearance on the left. The coronal section in panel B shows herniation of the temporal lobe into the right orbit

Discussion

In this report, we present a rare instance in which a patient presented with pulsatile proptosis and diagnosed with sphenoid wing dysplasia despite having no clinical evidence of NF1.

Proptosis refers to the forward protrusion of one or both eyes from the orbit. This condition arises due to an increase in the contents within the fixed anatomical structure of the bony orbit.[5] The reflection of cerebrospinal fluid pulsations into the orbit due to a defect in the orbital roof is termed pulsatile proptosis. Pulsatile proptosis is observed in conditions such as carotid-cavernous fistula, arteriovenous malformation, and encephalocele secondary to sphenoid wing dysplasia or orbital roof fracture.[6,7] A differential diagnosis can be made through physical examination, anamnesis (including trauma history, chemosis, epibulbar venous congestion, and the absence of a bruit), and radiological imaging. Our patient had pulsatile proptosis but no trauma history, chemosis, epibulbar venous congestion, or bruit.

Sphenoid wing dysplasia is characterized by hypoplasia or total absence of the greater or lesser wing of the sphenoid bone. It leads to the expansion of the orbit and middle cranial fossa, causing herniation of the temporal lobe into the orbit.[4] Pulsatile proptosis is observed as a result. Although it can be seen as an isolated deformity, it most commonly occurs in association with NF1.

Sphenoid wing dysplasia is one of the major diagnostic criteria for NF1, and is considered a pathognomonic finding for the disease. Between 5% and 12% of NF1 patients have signs of sphenoid wing dysplasia.[4] NF1 is an autosomal dominant inherited disorder that arises from a mutation of a gene of chromosome 17q11.2.[8] NF1 diagnostic criteria include: >6 cafe-au-lait macules, >2 neurofibromas, freckling in axillary or inguinal regions, optic pathway glioma, >2 iris Lisch nodules or choroid abnormalities, distinctive osseous lesion (such as sphenoid dysplasia, pseudoarthrosis of a long bone), presence of a heterozygous pathogenic NF1 variant. NF1 is characterized by the presence of two or more of the diagnostic criteria.[9] In our patient, there were no findings that satisfied the diagnostic criteria other than sphenoid wing dysplasia, and there was no family history of NF1.

Upon reviewing the literature, we found that only 5 patients with sphenoid wing dysplasia did not have evidence of NF1. Among these, one patient was diagnosed with myofibroma, another with craniofacial fibrous dysplasia, and the other three patients had isolated bone defects, similar to our case.[4,10,11] Table 1 summarizes case reports of sphenoid wing dysplasia in the literature.[4,10-32]

In the literature, there are publications reporting orbital roof reconstruction with a titanium mesh and/or bone graft in the treatment, although they are limited in number. Surgeries performed early after diagnosis have been shown to have a more successful visual prognosis.[10,12]

In conclusion, history of trauma should not be overlooked in the differential diagnosis of pulsatile lesions around the orbit,

Table 1. Case reports of sphenoid wing dysplasia with pulsatile proptosis in the literature are summarized by article title, patient sex and age, and etiology

Age (years)	Sex	Etiology	Article[ref#]
7	M	Isolated bone defect	Sphenoid wing dysplasia: report of 3 cases[10]
36	M	NF1	
19	M	Craniofacial fibrous dysplasia	
43	M	NF1	Traumatic brain injury, bulging eyeball, and skin lumps[13]
19	F	NF1	Acute enophthalmos after lumbar puncture in a patient with type 1 neurofibromatosis related sphenoid wing dysplasia[14]
14	M	NF1	Symptomatic enophthalmos due to sphenoid wing dysplasia appearing over 12 years in a patient with neurofibromatosis type 1: a case report and literature review[15]
Unknown	Unknown	NF1 (4 cases)	Reconstruction of sphenoid wing dysplasia in neurofibromatosis type 1 patients: an evolving technique[16]
41	F	NF1	Pulsating proptosis and heavy eye syndrome precipitated by neurofibromatosis type 1: a case report[17]
25	F	NF1	Computer-aided three-dimensional virtual surgical planning in complex skull base reconstruction for sphenoid wing dysplasia in neurofibromatosis type 1[18]
18	M	Isolated bone defect	Sphenoid wing dysplasia in the absence of neurofibromatosis: Diagnosis and management of a novel phenotype[4]
20	M	NF1	Neuroimaging findings of extensive sphenoethmoidal dysplasia in NF1[19]
59	F	NF1	Imaging findings of jugular foramen meningocele in a neurofibromatosis type 1 patient[20]
1 week	M	Myofibroma	Sphenoid dysplasia: a rare presentation of infantile myofibroma[21]
38	F	NF1	A multidisciplinary approach to sphenoid wing dysplasia presenting with pulsatile proptosis in neurofibromatosis type 1: a rare case report[22]
9	M	NF1	Evidence of neurofibromatosis type 1 in a multi-morbid Inca child mummy: a paleoradiological investigation using computed tomography[23]
2	M	NF1	Sphenoid wing dysplasia with pulsatile exophthalmos in neurofibromatosis type 1[24]
13	F	NF1	Sphenoid wing dysplasia and plexiform neurofibroma in neurofibromatosis type 1[25]
57	F	NF1	Ipsilateral sphenoid wing dysplasia, orbital plexiform neurofibroma and fronto-parietal dermal cylindroma in a patient with segmental neurofibromatosis[26]
1 month	M	NF1	A rare case of primary congenital glaucoma in combination with neurofibromatosis 1: a case report[27]
55	F	NF1	Increased ocular pulse amplitude associated with unilateral dysgenesis of the orbital roof[11]
55	F	Isolated bone defect	
15	M	NF1	Treatment of sphenoid dysplasia with a titanium-reinforced porous polyethylene implant in orbitofrontal neurofibroma: report of three cases[28]
18	M	NF1	
25	M	NF1	
6	M	NF1	Orbital reconstruction for pulsatile exophthalmos secondary to sphenoid wing dysplasia[12]
7	M	NF1	Reconstruction of skull base defects in sphenoid wing dysplasia associated with neurofibromatosis 1 with titanium mesh[29]
21	F	NF1	
30	F	NF1	Reconstruction of the sphenoid wing in a case of neurofibromatosis type 1 and complex unilateral orbital dysplasia with pulsating exophthalmos[30]
25	M	NF1	Reconstruction of sphenoid wing dysplasia with pulsating exophthalmos in a case of neurofibromatosis type 1 supported by intraoperative navigation using a new skull reference system[31]
15 months	F	NF1	Cranio-orbital-temporal neurofibromatosis: are we treating the whole problem?[32]

M: Male, F: Female, NF1: Neurofibromatosis type 1

and radiological imaging should be utilized to aid diagnosis. Additionally, findings related to NF1, which are closely linked to the patient's symptoms, should be thoroughly examined, and genetic counseling should be provided to the patient.

Ethics

Informed Consent: Obtained.

Authorship Contributions

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

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Case Report

Conjunctival Collagen Cross-Linking for the Treatment of Leaking Avascular Cystic Bleb

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Abstract

Trabeculectomy is a primary surgical procedure used to reduce intraocular pressure (IOP) in patients with glaucoma. Despite its effectiveness, it can lead to significant complications, including hypotony, choroidal effusion, blebitis, and bleb leaks. Bleb leaks require prompt medical or surgical intervention to prevent severe complications such as blebitis and bleb-associated endophthalmitis. In recent years, the indications for collagen cross-linking (CCL) have expanded beyond corneal ectatic diseases to include various ocular conditions such as keratitis and leaking blebs. Here, we present the case of a 70-year-old male patient with a leaking avascular cystic bleb. Following treatment with a combination of conjunctival CCL, topical gentamicin, a dorzolamide/timolol combination, and a therapeutic contact lens, the patient experienced cessation of bleb leakage and an increase in IOP.

Keywords: Bleb leak, collagen cross-linking, trabeculectomy

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Introduction

Trabeculectomy is a commonly performed surgical procedure aimed at reducing intraocular pressure (IOP) in patients with glaucoma.[1] Despite its efficacy in lowering IOP and preserving vision, trabeculectomy is associated with several potential complications.[2] Among these, bleb leaks are particularly concerning due to their potential to cause serious complications such as blebitis and bleb-associated endophthalmitis.[3] These complications necessitate timely and effective management, either medically or surgically, to prevent further morbidity.

Collagen cross-linking (CCL) is a minimally invasive procedure designed to strengthen the cornea by using a combination of riboflavin and ultraviolet A (UVA) light to induce cross-links between collagen fibers. This process enhances the cornea's mechanical stability and resistance to deformation. Over recent years, the therapeutic applications of CCL have significantly expanded beyond its initial use in treating corneal ectatic disorders.[4] CCL is now being investigated for its efficacy in managing a variety of ocular conditions, including infectious keratitis and leaking blebs.[5,6]

In this case report, we present a 70-year-old male patient who developed a leaking avascular cystic bleb following trabeculectomy. The patient's management included conjunctival CCL combined with a regimen of topical antibiotics, hypotensive eye drops, and the use of a therapeutic contact lens (TCL). By documenting the cessation of bleb leakage and the subsequent increase in IOP following this multimodal treatment approach, this case report underscores the potential utility of CCL in addressing bleb leaks.

Case Report

A 70-year-old male patient was admitted to the glaucoma department for routine evaluation. His medical history was unremarkable for systemic diseases. However, his ocular history included a trabeculectomy performed on the left eye seven years

prior. Best corrected visual acuity was 0.7 in the right eye and 0.4 in the left, as measured with Snellen chart. IOP readings were 14 mmHg in the right eye and 7 mmHg in the left.

Anterior segment examination of the right eye revealed a pseudophakic eye with no other significant findings. In the left eye, a notable avascular cystic bleb was present at the 12 o'clock position, along with pseudophakia. The bulbar conjunctiva in the superior region was hyperemic, and prominent scleral vessels were observed nasally to the avascular cystic bleb. The conjunctiva adjacent to the bleb exhibited limited mobility. Anterior chamber depth was normal, and the cornea was clear. Fluorescein staining revealed pinpoint leakage from the avascular cystic bleb (Figure 1A). The bleb leak was located approximately 2 mm from the limbus. Anterior segment optical coherence tomography showed fluid-containing cystic spaces (Figure 2). Fundus examination revealed a total cup-to-disc ratio in both eyes, with no signs of maculopathy related to bleb leakage.

Initially, the circumstances and risks associated with the patient's left eye, as well as all available treatment options, were comprehensively explained to the patient. Following an in-depth discussion, a medical regimen was implemented, which included the application of a TCL with a base curve of 8.6 mm and a diameter of 14.5 mm, topical gentamicin (Gentagut, Bilim Pharmaceuticals, İstanbul, Türkiye), and a combination of dorzolamide/timolol (Tomec, Abdi İbrahim, İstanbul, Türkiye). After applying the TCL, its coverage of the bleb leak was assessed and confirmed. The patient was monitored daily, but no improvement in the severity of bleb leakage was observed by the end of the third day.

Following a collaborative decision with the patient, conjunctival CCL was performed to address the bleb leakage. A 0.1% hypotonic riboflavin solution containing 1.1% hydroxypropyl methylcellulose without dextran (MedioCROSS M, PeschkeMeditrade GmbH, Germany) was applied to the bleb's anterior surface at 1-minute intervals for 5 minutes. Subsequently, accelerated CCL treatment was conducted with 3 minutes of UVA irradiation at 30 mW/cm^2 using the CRS-X cross-linker (Yuratek, Türkiye) (Figure 3). A sponge was used to protect the cornea during the procedure. Post-treatment, topical gentamicin drops were continued not only to prevent infection but also to irritate the bleb surface, thereby stimulating epithelial proliferation. Treatment with combination dorzolamide/timolol was also extended to mitigate bleb leakage. A TCL (base curve: 8.6 mm, diameter: 14.5 mm) was applied for additional protection and support.

The patient was closely monitored after treatment, and the signs and symptoms of bleb-related infection were explained in detail to the patient. On the first postoperative day, a decrease in bleb leakage intensity was noted. Two weeks after CCL treatment, there was no observable bleb leakage (Figure 1B), and IOP had increased to 11 mmHg. No ocular complications or bleb leakage were detected during the 2.5-month follow-up.

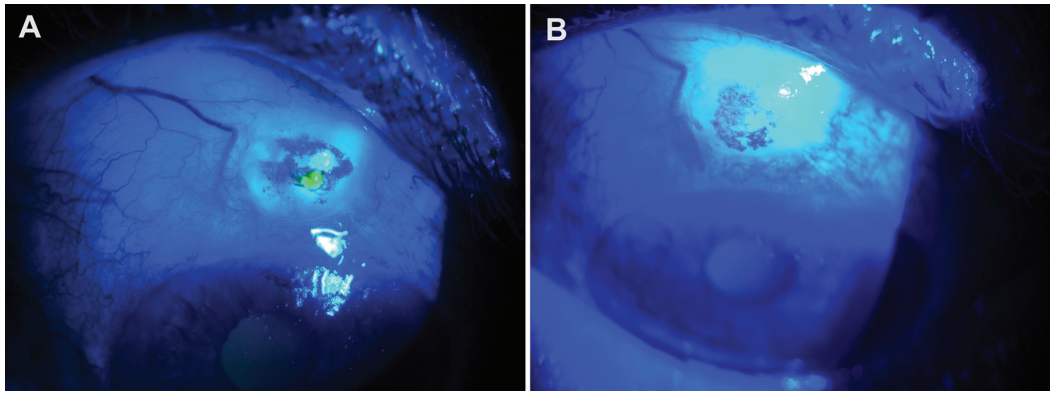

Figure 1. Visualization of pinpoint leakage from avascular cystic bleb upon contact with fluorescein paper (A). Resolution of bleb leakage observed two weeks after conjunctival collagen cross-linking treatment (B)

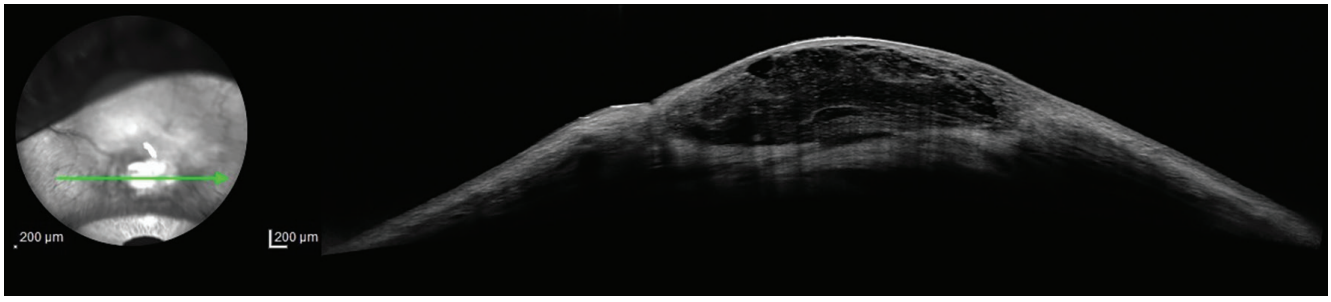

Figure 2. Anterior segment optical coherence tomography showing cystic spaces within the bleb

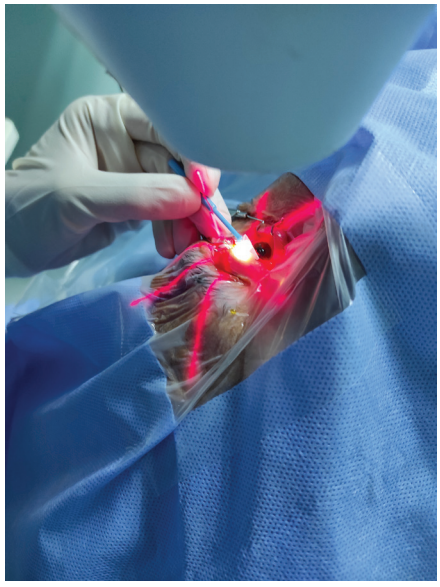

Figure 3. Accelerated conjunctival collagen cross-linking treatment utilizing the CRS-X cross-linker (Yuratek, Türkiye). A sponge was employed to safeguard the cornea during the procedure

Discussion

Despite many complications, trabeculectomy remains one of the most common surgical procedures performed for patients with glaucoma.[7] One such complication is bleb leakage, which can be detected in both the early and late postoperative periods. Early leakage is generally related to surgical technique and insufficient conjunctival healing. In contrast, late bleb leakage is often caused by the use of antimetabolites, such as mitomycin C.[7] Early detection and management of bleb leakage are essential to prevent serious complications including bleb-related infection and hypotony.

Bleb leakage can be managed through both medical and surgical treatments. Medical treatment options include aqueous suppressants, prophylactic antibiotics, direct pressure patching, and the use of bandage contact lenses. Surgical interventions to address leaking blebs encompass autologous blood injection, compression sutures, cyanoacrylate glue application, and conjunctival advancement procedures.[8] Medical management is typically the initial approach in cases where the bleb leak is minor, free of infection, and the patient exhibits stable visual acuity and IOP, with no prior history of bleb-related infection. Surgical intervention is generally considered when a bleb leak fails to respond to medical management, is severe enough to induce complications, or if the patient has a history of recurrent bleb-related infections. A frequently utilized surgical technique is conjunctival advancement, which entails the excision of unhealthy bleb tissue and the subsequent coverage of the filtration site with a flap of healthy conjunctival tissue harvested from the region posterior to the bleb. Additionally, conjunctival CCL has recently emerged as an effective modality for the treatment of bleb leaks.[6] One advantage of this technique is the potential enhancement of conjunctival strength and stability through the reinforcement of the collagen structure, which may subsequently reduce the risk of future leakage.

There is a limited body of research investigating the impact of conjunctival CCL on bleb leakage. Choy et al.[9] conducted a study wherein they treated 5 patients experiencing bleb leakage with conjunctival CCL, employing a protocol involving 30 minutes of UVA application. They reported that all patients demonstrated complete healing within a timeframe ranging from 1 to 4 weeks after treatment. Upon follow-up, this effect persisted for an average duration of 33.5±10.2 weeks following the cessation of bleb leakage.[9] In another study conducted by Wang and Harasymowycz[6], a cohort of 7 patients presenting with bleb leakage underwent treatment involving 30 minutes of riboflavin loading followed by 30 minutes of UVA irradiation at 2 mW/cm^2. While complete resolution was observed in 5 patients, bleb leakage persisted in 2 individuals.[6] A prior case report documented the cessation of bleb leakage in a 60-year-old male patient after undergoing two consecutive CCL treatments.[10] However, another author reported achieving bleb stabilization for 4 years with a single session of conjunctival CCL treatment.[11] As a result, despite the demonstrated effectiveness of conjunctival CCL in treating bleb leakage, clear criteria for patient selection and specific treatment protocols for CCL remain elusive. Therefore, additional studies are essential to delineate the precise role of CCL within the spectrum of therapeutic options for this condition.

In the present case report, accelerated CCL treatment was administered (3 minutes of UVA irradiation at 30 mW/cm^2). The rationale for selecting this treatment option included a stable eye with no complications, a lack of response to initial medical therapy, and restricted conjunctival mobility. Remarkably, cessation of bleb leakage was observed within two weeks after treatment. However, it should be noted that this treatment approach was combined with adjunctive therapies including topical gentamicin, dorzolamide/timolol combination, and TCL application. Although combined treatment was applied, it is believed that conjunctival CCL played a major role in reducing bleb leakage, as a significant decrease in the intensity of bleb leakage was detected on postoperative day 1. In comparison to other studies, we employed an accelerated CCL protocol that was notably shorter in duration. Similarly, Lázaro-Rodríguez et al.[11] also adopted this protocol (Avedro accelerated crosslinking) and reported prolonged stabilization of the bleb. Therefore, it can be inferred that accelerated conjunctival CCL treatment, involving 3 minutes of UVA irradiation at 30 mW/cm^2, represents an effective and safe treatment protocol for managing bleb leakage. However, it should be noted that the short follow-up duration is a limitation of this study. Although the long-term effect of conjunctival CCL has been shown, further studies are necessary to evaluate the use of CCL.

In conclusion, conjunctival CCL appears to be a viable treatment modality for managing leaking blebs. When combined with adjunctive topical treatments and TCL application, bleb

leakage can be effectively managed in a non-invasive, safe, and expeditious manner. Hence, it is prudent to consider conjunctival CCL as an initial therapeutic option before resorting to surgical intervention for managing bleb leakage. Nevertheless, there exists a necessity for further comprehensive studies aimed at discerning the most effective treatment options and identifying suitable candidates for conjunctival CCL in the management of bleb leaks.

Ethics

Informed Consent: Obtained.

Authorship Contributions

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

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