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AT A GLANCE

2025 Issue 6 at a Glance:

Esteemed colleagues,

In our last issue of 2025, the Turkish Journal of Ophthalmology brings together a wide variety of current studies that contribute directly to clinical practice in areas ranging from corneal and ocular surface diseases to glaucoma, from anterior segment surgery to rare retinal pathologies.

In the original research section, an experimental study by Özgür et al. titled "Evaluation of a New Potential Bevacizumab Biosimilar in Corneal Neovascularization" presents noteworthy findings on the effectiveness of anti-VEGF treatments, as well as their accessibility and cost-effectiveness (See pages 299-304).

In their study titled "Clinical Outcomes of Different Surgical Techniques in Limbal Stem Cell Deficiency", İçer et al. examined the long-term clinical outcomes of various relevant surgical techniques and emphasized the importance of individualizing the surgical approach according to the etiology and degree of corneal involvement (See pages 305-313).

In the field of glaucoma, a study titled "Surgical Success and Predictive Factors in Patients Undergoing Gonioscopy-Assisted Transluminal Trabeculotomy" by Gümüş Akgün et al. provides a valuable clinical perspective on the increasing interest in minimally invasive glaucoma surgeries (See pages 314-320).

A study by Gürpınar and Arıtürk titled "Anterior Segment OCT Imaging of Bleb Morphological Changes as Predictors of Success After Bleb Needling" reveals the role of objective imaging methods in postoperative follow-up (See pages 321-328).

In a study titled "Comparison of Microvascular and Electrophysiological Findings of Normal-Tension Glaucoma and Chronic Non-Arteritic Ischemic Optic Neuropathies", Koru Toprak et al. elucidate the pathophysiological differences between these two clinical pictures, which can be challenging in differential diagnosis (See pages 329-335).

Also in this issue, Gümüş Akgün et al. present a study titled "Refractive Results and Complications of Lensectomy in Simple Extreme Microphthalmos Cases" that will contribute to forming more realistic surgical expectations in this rare but difficult-to-manage patient group (See pages 336-340).

In the review section, an article titled "Decision-Making in Keratoprosthesis: Navigating Device Selection in Complex Ocular Scenarios" by Agarwal et al. addresses current information on device selection in complex ocular surface cases from an experience-based perspective, serving as a guide for treatment strategy planning in patients with advanced disease (See pages 341-349).

In the letters to the editor section, an article by Özyol focuses on the pharmacological pinhole approach to the treatment of presbyopia, which has gained increasing attention in recent years. Within a historical framework ranging from pilocarpine to aceclidine, this treatment option is examined in the light of current debates. As the search for non-surgical treatments for presbyopia continues to gain momentum, this article is a special resource that provides both a historical perspective and a reminder of the current approaches applied in clinical practice (See pages 350-351).

In the same section, Ural Fatihoğlu et al. present the first genetically confirmed case of *KCNV2*-associated retinopathy in Türkiye, making a notable contribution in the field of rare retinal diseases (See pages 352-356).

We believe that this issue not only provides up-to-date and evidence-based answers to the problems encountered in clinical practice but will also strengthen the culture of scientific discourse. We extend our heartfelt appreciation to all of our authors, reviewers, and colleagues, and wish you enjoyable, fruitful reading and a healthy, hopeful, and peaceful new year.

On behalf of the Editorial Board,

Sait Eğrilmez, MD

Original Article

Evaluation of a New Potential Bevacizumab Biosimilar in Corneal Neovascularization

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Abstract

Objectives: To compare the antiangiogenic effects of bevacizumab and a new potential bevacizumab biosimilar (anti-human VEGF GU01) on suture-induced corneal neovascularization (CNV) in rabbits.

Materials and Methods: CNV was induced in the right eyes of 15 rabbits by placing 7-0 black silk suture in the corneal stroma (3 mm wide and 1-1.5 mm from the superior limbus). All sutures were removed on day 7, and the rabbits were randomly divided into three groups. An injection of 0.1 mL balanced salt solution (control group), 2.5 mg/0.1 mL bevacizumab (bevacizumab group), or 2.5 mg/0.1 mL of anti-human VEGF GU01 (potential bevacizumab biosimilar group) was administered subconjunctivally. After suturing, standard corneal images were obtained with a surgical microscope on day 7 (pre-injection) and day 14 (7 days post-injection) to analyze the CNV area, which was calculated in square millimeters using the ImageJ program. On day 14, all animals were sacrificed and corneal specimens were analyzed histopathologically by hematoxylin-eosin staining.

Results: On day 14, the percent reduction in CNV area was significantly greater in the bevacizumab and bevacizumab biosimilar groups compared to the control group (control: 24.6%, bevacizumab: 82.2%, biosimilar: 83.4%; $p<0.05$). There was no statistically significant difference between the bevacizumab and biosimilar groups with respect to the CNV regression rates ($p>0.05$).

Conclusion: This experimental study showed that the potential bevacizumab biosimilar anti-human VEGF GU01 was as effective as subconjunctival bevacizumab in the treatment of CNV.

Keywords: Bevacizumab, bevacizumab biosimilar, anti-human VEGF GU01, corneal neovascularization

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The study was presented at 2nd International Safiye Ali Congress on Multidisciplinary Studies in Health Sciences (September 30 to October 2, 2022-Online) and its abstract was published in the congress abstract book.

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Introduction

Maintaining corneal transparency is one of the main requisites for clear vision.[1] Stress and hypoxia associated with various causes (infection, inflammation, ischemia, degeneration, trauma, or limbal stem cell deficiency) can lead to the pathological growth of blood vessels in the cornea, causing loss of transparency. This condition is called corneal neovascularization (CNV).[2]

CNV is treated using surgical and medical methods with varying degrees of success.[3,4] These treatments aim both to prevent the formation of new vessels (focusing on the underlying etiology and pathophysiology) and to induce regression of existing pathological vessels.[5] Vascular endothelial growth factor (VEGF), a key mediator of vascular development, has been shown to play an important role in CNV formation.[6] Thus, VEGF inhibition can mitigate the condition.

There are several well-known anti-VEGF agents, such as ranibizumab (Lucentis; Genentech, USA), bevacizumab (Avastin; Genentech, USA) and aflibercept (Eylea; Bayer, Germany), that have been trialed or used in the treatment of CNV.[7] Among these agents, topical or subconjunctival bevacizumab is one of the most commonly used treatments for CNV, despite being an

off-label indication.[8] While other anti-VEGFs are also effective in the treatment of CNV, they are less frequently prescribed due to high cost. Biosimilar molecules have been developed to facilitate access to anti-VEGF agents.[9,10] To this end, the immunology laboratory of our university developed the novel anti-VEGF monoclonal antibody anti-human VEGF GU01, a potential bevacizumab biosimilar (with support from the Ministry of Science, Industry and Technology within the scope of project no: 0192-SanTez-2013-1).[11] Anti-human VEGF GU01 is a mouse-derived monoclonal immunoglobulin G antibody produced with the hybridoma method using the HiTrap Protein G HP clone and purified by fast protein liquid chromatography.[11]

The aim of this study was to evaluate the effect of anti-human VEGF GU01 in reducing CNV.

Materials and Methods

Approval for this study was obtained from Gazi University Animal Care Ethics Committee (project no: G.Ü.ET-15.025, date: 17/04/2015). The study was conducted with 15 healthy young New Zealand rabbits weighing between 2.5 and 3 kg.

Before the procedures, topical proparacaine HCl 0.5% (Alcaine; Alcon, USA) was instilled into the eyes. Under general anesthesia (intramuscular ketamine 50 mg/kg and xylazine 5 mg/kg), 7-0 black silk sutures were placed in the right eye of each rabbit under a surgical microscope. All sutures were placed through the mid-stroma, located central to the upper limbus in an area 1-1.5 mm long and 3 mm wide, by the same researcher (M.C.Ö.). Topical moxifloxacin eye drops (Vigamox, Alcon, Fort Worth, Texas, USA) were applied to the eyes twice a day for one week for infection prophylaxis. After 7 days, adequate CNV formation was observed in all eyes and the sutures were removed under general anesthesia.

Following suture removal, the 15 rabbits were randomly divided into three groups. The control group received 0.1 mL of balanced salt solution; the bevacizumab group received 2.5 mg/0.1 mL bevacizumab (Avastin 100 mg/4 mL; Genentech, USA); and the biosimilar group received 2.5 mg/0.1 mL anti-human VEGF GU01 (10 mg/0.4 mL; Gazi University Immunology Laboratory; Ankara, Türkiye) administered subconjunctivally (Table 1). The injections were administered using a 30-gauge needle, from the upper quadrant, 1 mm from the limbus (M.C.Ö.).

A surgical microscope (Möller-Wedel FS 3000, Haag Streit, Germany) with mounted recording system (Avermedia software, Taiwan) were used for imaging. The area of CNV was displayed at a magnification of 16x and quantified in square millimeters using the ImageJ program (Wayne Rasband, Research Services Branch, National Institutes of Health, Bethesda, MD, USA) on day 7 (pre-injection) and 14 (7 days after injection). To standardize area calculations, an image of a ruler at 16x magnification was obtained with the surgical microscope. A 1-mm line marked on the standard ruler image was loaded into the ImageJ program and recorded as 1 mm for numerical analyses. On each photograph, the neovascularized region was demarcated using the program's cursor. CNV areas calculated before treatment were accepted as 100%, and the percent reduction in this area was determined 1 week after treatment. These measurements were performed by an investigator blinded to the treatment groups (A.Ö.). Afterwards, all animals were sacrificed and the right eyes were enucleated. The corneal regions where CNV was located were excised, keeping the limbal region intact. Half of each tissue was stored in formaldehyde for 24 hours and embedded in paraffin, then stained with hematoxylin-eosin for histopathological evaluation. The other tissue halves were sent to the immunology laboratory for immunohistochemical examination with CD31 stain, which is an endothelial cell marker. Slides with 4-µm sections were photographed and evaluated under a microscope at 200x magnification.

Statistical Analysis

The sample size of the study was determined based on the number of animals used in similar experimental models in the field. An a priori power analysis was not performed. The SPSS program (version 22, IBM, USA) was used for statistical analysis. As the data distribution and sample number were not sufficient for parametric analyses, the Kruskal-Wallis test was used for comparisons of pre-treatment and post-treatment CNV areas, and the Mann-Whitney U test was used to compare percent regression in CNV area post-treatment. p values <0.05 were considered significant.

Results

On day 7 after suturing, sufficient CNV induction was observed in all eyes. The mean CNV area in the control, bevacizumab, and biosimilar groups was 2.59 ± 0.34 mm^2, 2.37 ± 0.40 mm^2, and 2.36 ± 0.44 mm^2, respectively. There was no significant difference in initial CNV area between the groups ($p>0.05$) (Figures 1 and 2). No keratitis or other suture-related complications were observed.

After treatment, the mean CNV regression rate was significantly higher in the bevacizumab ($82.2\%\pm3.0\%$) and biosimilar ($83.4\%\pm3.8\%$) groups compared to the control group ($24.6\%\pm3.9\%$) ($p<0.05$). There was no statistically significant difference in CNV regression rate between the bevacizumab and biosimilar groups ($p>0.05$) (Figures 1 and 3). In hematoxylin-eosin staining, a large number of vessels were observed in the control group, while almost no vessels were observed in the bevacizumab and biosimilar groups (Figure 4). Immunohistochemical evaluation could not be performed due to insufficient CD31 staining.

Table 1. The study groups and treatments administered

Control group (n=5)	0.1 mL balanced salt solution
Bevacizumab group (n=5)	2.5 mg/0.1 mL bevacizumab
Biosimilar group (n=5)	2.5 mg/0.1 mL anti-human VEGF GU01

VEGF: Vascular endothelial growth factor

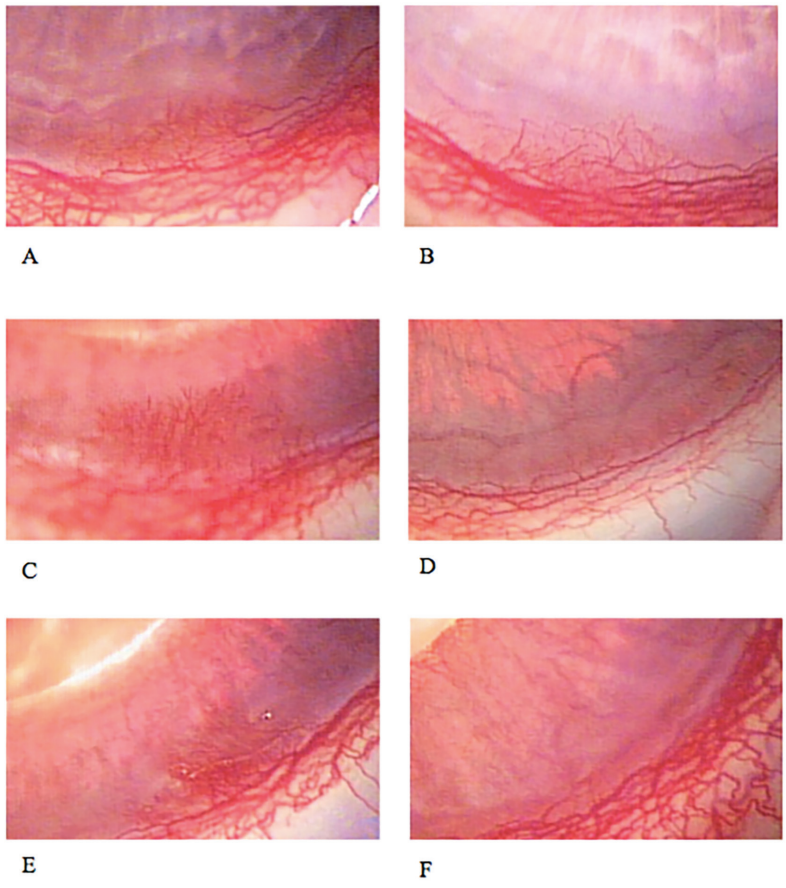

Figure 1. Appearance of corneal neovascularization before treatment (day 7, immediately after suture removal) and after treatment (day 14). A) Pre-treatment control group. B) Post-treatment control group. C) Pre-treatment bevacizumab group. D) Post-treatment bevacizumab group. E) Pre-treatment biosimilar group. F) Post-treatment biosimilar group

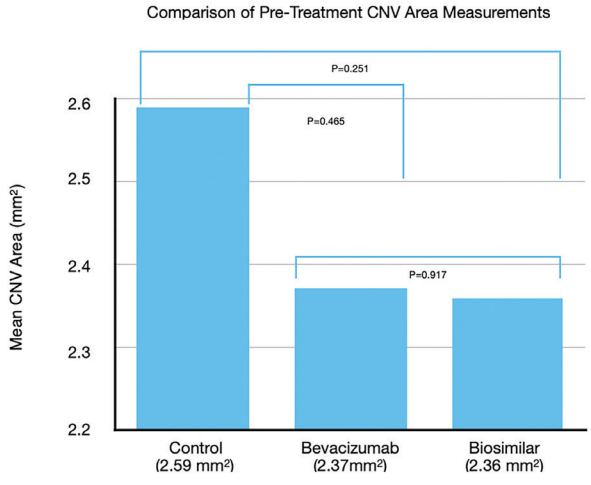

Figure 2. Corneal neovascularization (CNV) areas on day 7 after suturing. p values were calculated using the Kruskal-Wallis test. There was no statistically significant difference between the groups

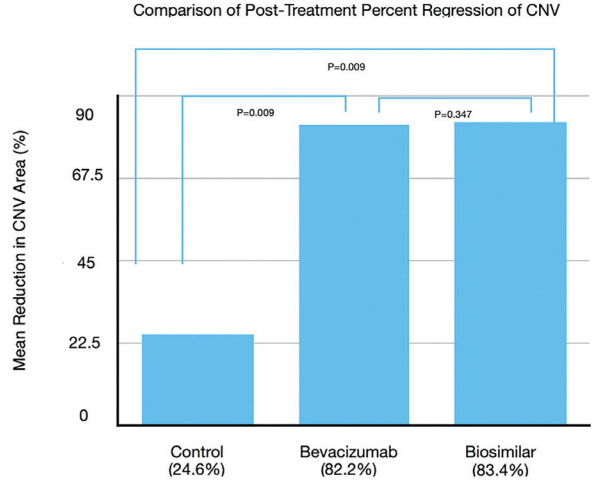

Figure 3. Percent regression of corneal neovascularization (CNV) areas 7 days after treatment. p values were calculated using the Mann-Whitney U test. CNV area decreased significantly more in the bevacizumab and biosimilar groups than in the control group. There was no statistically significant difference in CNV regression between the bevacizumab and biosimilar groups

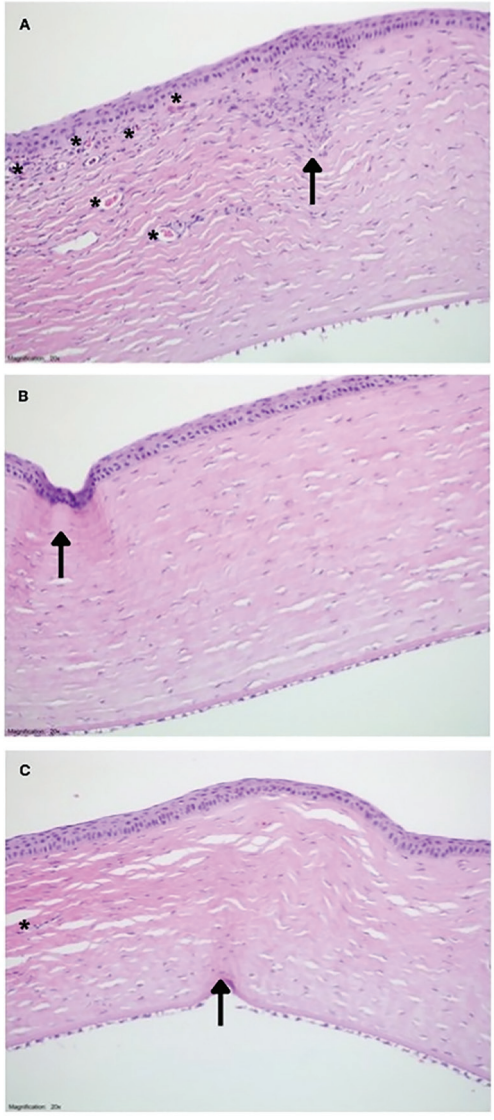

Figure 4. Histopathology images: A) Control group: signs of inflammation in the suture area (arrow) and erythrocyte-containing vessels (asterisks) in the stroma. B) Bevacizumab group: signs of inflammation in the suture area (arrow) but no erythrocyte-containing vessels in the stroma. C) Biosimilar group: signs of inflammation in the suture area (arrow) and minor erythrocyte-containing vessels (asterisk) in the stroma

Discussion

The term biosimilar is used for substances that are very similar to biological agents but not identical in terms of efficacy, safety, and purity. The increasing use of biosimilar drugs reduces drug costs and facilitates patient access to medication. However, the production of biosimilars is a complex process. Minor structural differences in the manufacturing process can significantly alter effectiveness and safety.[9] In our study, we investigated the effectiveness of anti-human VEGF GU01, a potential bevacizumab biosimilar produced in our immunology laboratory, in an experimental CNV model.[11]

There are currently no commercially available ophthalmic preparations of bevacizumab, and the preparation process for ocular use varies from country to country. While the drug is manufactured in single bottles containing 4 mL or 16 mL, ocular use requires tiny doses prepared in syringes. This user-dependent drug preparation introduces the risk of contamination. Cases of severe endophthalmitis and vision loss following bevacizumab injection have been reported in different parts of the world.[12,13,14]

In 1998, Yatoh et al.[15] demonstrated that VEGF inhibition prolonged graft survival in mice, leading to many experimental and clinical studies on the effect of bevacizumab on CNV. Experimental studies were generally conducted with suture-induced CNV models. The CNV created in these models is more compatible with the CNV that occurs in humans, both pathophysiologically and in appearance.[16,17] In the light of this information, we used the suture-induced CNV model in our study.

The duration of CNV is an important factor in treatment selection. While medical treatment can be more effective during active vessel formation (i.e., stages of new CNV development), surgical interventions such as fine needle diathermy have been shown to be more effective in stages where mature vessels develop (i.e., when CNV becomes chronic).[18,19] An important factor in this difference is thought to be pericytes that cover the vessels within the first two weeks of CNV development, thereby reducing their susceptibility to pharmacological agents.[5] Lin et al.[18] examined the timing of anti-VEGF therapy in the treatment of CNV and observed that early anti-VEGF treatment was beneficial, whereas late anti-VEGF treatment had no regressive effect on CNV. In our study, treatment was applied in the early period. Our results demonstrated more than 80% regression in CNV area on day 14 both in the bevacizumab- and anti-human VEGF GU01-treated groups.

The suture-induced CNV model was preferred for this study because it is both easy to create and highly similar to the pathophysiology of CNV in humans. However, more aggressive and permanent neovascularizations can be observed in clinical practice, especially in cases such as chemical burns and limbal stem cell deficiency. Therefore, evaluating the efficacy of anti-human VEGF GU01 in such demanding models may be important in terms of revealing the true clinical potential of the drug.[17]

There is no consensus on the dose and frequency of subconjunctival bevacizumab administration for the treatment of CNV. In a 24-patient study, single doses of 2.5 and 5 mg subconjunctival bevacizumab were found to have a similar effect on CNV regression.[20] In another experimental study involving 100 rats, comparable effects were observed with 1 mg, 5 mg, and 25 mg subconjunctival bevacizumab in the treatment of CNV.[21] In our study, we administered the drug at a dose of 2.5 mg. We did not repeat injections in our study because the half-life of subconjunctival bevacizumab was shown to be between 1.8 and 2.8 weeks in rabbits.[22]

Corneal transplantation is the most successful of all organ transplants, with a success rate of 90%.[23] However, when surgery

is performed in an inflamed or vascularized recipient bed, this rate can fall to 20-40%.[24] Bevacizumab is one of the most commonly used anti-VEGF agents in the treatment of CNV. Dekaris et al.[25] administered 25 mg/0.5 mL subconjunctival and 25 mg/mL topical bevacizumab postoperatively to evaluate the benefit to graft survival after penetrating keratoplasty in 50 eyes considered high-risk for surgery. After three years of follow-up, graft transparency was preserved in 70% of the patients.

Aside from increased proangiogenic growth factors, extracellular matrix remodeling also plays an important role in CNV. Matrix metalloproteinases (MMP), especially MMP-2 and MMP-9, facilitate the invasion of new vessels by destroying the basement membrane and stromal structure. These enzymes, secreted by inflammatory cells and activated epithelial/stromal cells, may increase the effect of angiogenic factors such as VEGF and support the progression of vascularization. Although MMP levels were not directly evaluated in our study, the suppression of neovascularization by the biosimilar VEGF inhibitor indirectly suggests that MMP activity may also have decreased.[26,27]

Study Limitations

One of the main limitations of this study is the small number of animals in the experimental groups. The use of five animals per group may limit the statistical power and generalizability of the results obtained. Although post-hoc power analysis indicated sufficient study power (>95%), advanced-phase experimental and clinical studies with larger samples would allow a more robust evaluation of the effectiveness of anti-human VEGF GU01. Another limitation of our study is that staining with CD31 antibody, which is used to evaluate corneal vascularization at the immunohistochemical level, was unsuccessful. A possible reason for this is that the cold chain was disrupted during transport or storage of the CD31 antibody. Temperature-sensitive antibodies such as CD31 must be stored at a constant temperature in the range of 2-8 °C to maintain biological activity. Any disruption in the cold chain may adversely affect the staining result by reducing the antibody's ability to bind to the target antigen. Therefore, immunohistochemical analysis could not be performed in our study, and the results were obtained only by clinical and histopathological evaluation. Considering this technical problem in future studies, the use of alternative vascular endothelial markers such as CD34 or von Willebrand factor in addition to CD31 may be considered. In addition, analyzing levels of proangiogenic and angiogenic molecules would have strengthened the study.

Conclusion

The evidence suggests that the widespread use of bevacizumab in corneal surgeries will increase surgical success. Once phase studies are completed, anti-human VEGF GU01, a potential bevacizumab biosimilar, has the potential to increase surgical success rates in high-risk penetrating keratoplasties. This experimental study is the first in the literature to document subconjunctival administration of anti-human VEGF GU01.

Ethics

Ethics Committee Approval: Approval for this study was obtained from Gazi University Animal Care Ethics Committee (project no: G.Ü.ET-15.025, date: 17/04/2015).

Informed Consent: Not applicable (animal study).

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Declarations

Authorship Contributions

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

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Original Article

Clinical Outcomes of Different Surgical Techniques in Limbal Stem Cell Deficiency

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Abstract

Objectives: This study aimed to evaluate the long-term outcomes of limbal stem cell deficiency (LSCD) treated with various limbal stem cell transplantation (LSCT) techniques.

Materials and Methods: This retrospective study included 32 eyes of 29 patients who underwent LSCT. Clinical evaluation was performed based on preoperative and postoperative best corrected visual acuity (BCVA, logarithm of the minimum angle of resolution [logMAR]), degree of corneal neovascularization, extent of corneal involvement, and clarity of the central visual axis. Human leukocyte antigen (HLA) compatibility in allograft recipients was assessed via HLA tissue typing. The Kruskal-Wallis and Wilcoxon tests were used to compare variables between groups.

Results: A total of 84.4% (n=27) of the eyes had LSCD secondary to chemical injury. Median preoperative and postoperative BCVA (logMAR) values were 2.1 and 1.8 (p=0.01) in the conjunctival limbal allograft (CLAL) group (n=22; 18 living-related, 4 deceased donors), 0.9 and 0.7 (p=0.11) in the conjunctival limbal autograft (CLAU) group (n=4), and 2.1 and 1.3 (p=0.04) in the simple limbal epithelial transplantation (SLET) group (n=6; 3 autografts, 3 allografts), respectively. There was no statistically significant difference in BCVA improvement between groups. Median clinical scores improved from 10 to 6 in the CLAL group (p<0.001), from 7 to 4 in the CLAU group (p=0.11), and from 10 to 3 in the SLET group (p=0.03). Preoperatively, a statistically significant difference in clinical scores was observed only between the CLAU and SLET groups (p=0.029); however, no significant difference was found between groups postoperatively. HLA compatibility was 75% in 15 eyes that received living-related CLAL, and 100% in all 3 eyes that underwent allogeneic SLET.

Conclusion: Different LSCT techniques may be applied in LSCD depending on the underlying etiology and extent of involvement. Favorable outcomes can also be achieved with allogeneic approaches when HLA compatibility is ensured.

Keywords: Limbal stem cell deficiency, limbal stem cell transplantation, simple limbal epithelial transplantation, conjunctival limbal allograft, conjunctival limbal autograft

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Introduction

Limbal stem cells (LSCs) are adult stem cells that differentiate into corneal epithelium, playing a critical role in maintaining the integrity and transparency of the corneal surface.[1] The Vogt palisades within the limbal region are densely populated with LSCs and provide the specialized microenvironment necessary for their survival and function. In addition, LSCs are located within limbal epithelial crypts and pits, contributing to the formation of a functional barrier between the cornea and conjunctiva.[2,3,4]

Direct damage to LSCs and/or disruption of their niche leads to limbal stem cell deficiency (LSCD). The loss of limbal barrier function allows conjunctival epithelial cells to migrate onto the corneal surface, resulting in ocular surface instability. Neovascularization within the corneal epithelium and stroma compromises corneal transparency, potentially causing significant visual impairment or blindness.[5,6] Moreover, LSCD is often associated with a deficiency of goblet cells, which further

contributes to ocular surface deterioration through impaired tear film function.

LSCD can be classified as either primary or secondary. Primary LSCD arises from genetic or congenital conditions such as *PAX6* mutations and aniridia,[7,8] congenital epidermal dysplasia,[9,10] dyskeratosis congenita,[11] and xeroderma pigmentosum.[12] In contrast, secondary LSCD is typically acquired and may result from chemical or thermal injuries,[13] cicatrizing disorders such as mucous membrane pemphigoid,[14] Stevens-Johnson syndrome,[15,16] or graft-versus-host disease.[17] Additional causes include ocular surgeries, radiation, cryotherapy, systemic chemotherapy,[18] and drug-induced toxicity, commonly associated with agents like mitomycin C, 5-fluorouracil, antiglaucoma medications, or sulfur mustard.[19,20] Iatrogenic factors such as ocular surgical interventions and contact lens wear also contribute to the development of secondary LSCD.[21]

The management of LSCD varies according to disease severity, stage, and underlying etiology, and may involve medical, surgical, or combined therapeutic approaches. Medical therapy is the first-line treatment, as optimizing the ocular surface supports residual stem cell function in partial LSCD and enhances graft survival in surgical cases. Surgical intervention focuses on restoring LSCs, typically via autologous or allogeneic limbal stem cell transplantation (LSCT). The choice of LSCT technique (e.g., keratolimbal or conjunctival limbal graft, simple limbal epithelial transplantation [SLET], and cultivated limbal epithelial transplantation [CLET]) depends on the extent of disease and donor availability.

In 1989, Kenyon and Tseng[22] reported the successful transplantation of conjunctival limbal autografts (CLAU) from the healthy contralateral eye in patients with unilateral LSCD. However, the relatively large grafts (typically harvested in two segments spanning 2-3 clock hours) pose a risk of iatrogenic LSCD in the donor eye. As an alternative, excellent long-term clinical outcomes have been reported with the *ex vivo* expansion of LSCs harvested from a small biopsy of the healthy or a donor eye that is cultured on various substrates and subsequently transplanted onto the affected eye.[23,24] Another surgical option is SLET, which uses a 2x2 mm limbal tissue sample divided into 6-10 small fragments and placed on an amniotic membrane-covered cornea with fibrin glue. This approach enables *in vivo* expansion of cells without the need for *ex vivo* laboratory culturing.[25] Due to the minimal tissue requirement, the risk to the donor site is negligible. SLET can be performed using either autologous or allogeneic grafts.

In cases of bilateral total LSCD, allogeneic tissue is required for LSCT. The donor is typically either deceased or a living relative of the patient.[26,27] However, allografts require long-term systemic immunosuppression, and the survival rate of transplanted cells is generally inferior to that of autologous grafts.[28] An alternative approach in such cases is the transplantation of cultivated autologous oral mucosal epithelial cells. While this technique has shown success in stabilizing the ocular surface, the degree of visual improvement achieved is often suboptimal.[29,30]

This study aimed to evaluate the long-term clinical outcomes of LSCD cases managed with various LSCT techniques.

Materials and Methods

This retrospective study evaluated 32 eyes of 29 patients with LSCD of various etiologies who underwent LSCT between January 2010 and January 2023 at the Department of Ophthalmology, Eskisehir Osmangazi University Faculty of Medicine. The study was approved by the Clinical Research Ethics Board of Eskişehir Osmangazi University (number: E-25403353-050.99-2400074876, subject: 2024-102, decision number: 47, decision date: 19.03.2024) and adhered to the ethical principles of the Declaration of Helsinki.

Data collected included patients' demographic characteristics, LSCD etiology and severity, biomicroscopic and fundus examination findings, best corrected visual acuity (BCVA), age at the time of surgery, surgical technique, and any additional procedures. For cases involving allogeneic transplantation, human leukocyte antigen (HLA) typing results were also analyzed. BCVA was recorded in logarithm of the minimum angle of resolution (logMAR) units.

Pre- and postoperative corneal evaluations included assessment of the damaged corneal area, degree of neovascularization, and clarity of the central visual axis using the clinical grading system described by Aravena et al.[31] (Figure 1 and 2A). For area of damage, the cornea was divided into four quadrants perpendicular to the axis with the largest involvement and graded from 1 to 4 based on the extent of involvement. Corneal neovascularization was scored by dividing the cornea into four areas and assigning a grade of 1 to 4 according to the number of areas involved. For central optical axis clarity, a score of 2 was given if the axis was opaque, and 0 if it was clear. The total score was calculated as the clinical severity score. In cases of LSCD secondary to chemical burns, we also applied the Roper-Hall classification for corneal

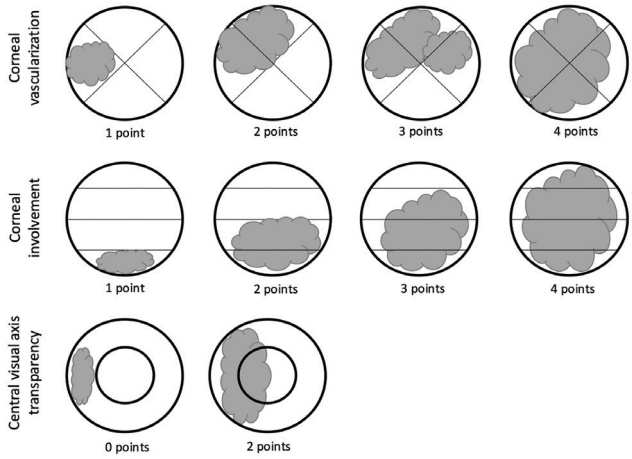

Figure 1. Representative diagram of the clinical grading system used in limbal stem cell deficiency. The diagram illustrates the evaluation criteria for limbal involvement by clock hours (top panel), corneal surface area involvement (middle panel), and central visual axis involvement (bottom panel)[31]

haze and limbal ischemia, as well as the Dua classification, which provides a more detailed assessment based on extent of limbal involvement (in clock hours) and percentage of conjunctival involvement (Figure 2B, C).[32,33] A postoperative improvement of at least 0.2 logMAR units in BCVA was considered a successful outcome. In patients who underwent allogeneic LSCT, HLA matching was evaluated between the recipient and related donors for HLA-A, B, C, DR, and DQ loci.

Three surgical techniques were employed for LSCT: conjunctival limbal allograft (CLAL), CLAU, and SLET. All procedures were performed by the same surgeon (N.Y.).

Conjunctival Limbal Allograft and Autograft Surgery

For donor tissue preparation, conjunctival limbal grafts were harvested from the 12 and 6 o'clock positions, each spanning approximately 2 clock hours, ensuring that the total graft size did not exceed 6 clock hours. The incision began from the conjunctival side and extended 1 mm into the cornea from the limbus to include stem cells. The tissue was dissected and transferred into balanced salt solution (BSS). After harvesting from both areas, the donor sites were partially closed using two 10-0 nylon sutures without excessive tension. In the recipient eye, a 360-degree conjunctival peritomy was performed, and any symblepharon was lysed. Abnormal corneal epithelium and fibrovascular pannus were carefully removed without damaging the underlying stroma. The graft segments were sutured to the area of LSCD using 10-0 nylon sutures.

Simple Limbal Epithelial Transplantation

For autologous or allogeneic SLET, a 2-mm limbal tissue was obtained from the superior limbus. The incision extended from the conjunctiva 1 mm into the cornea to include stem cells. The tissue was then placed in BSS. The recipient site was prepared similarly with a 360-degree peritomy and symblepharon release, if present. Abnormal corneal epithelium and pannus were removed without stromal damage. A human amniotic membrane (basement membrane side facing upward) was placed over the cornea and adjacent bare sclera and secured using fibrin glue. The membrane was gently flattened with a spatula to avoid folds. The limbal tissue was cut into 6-10 small pieces using Vannas scissors and placed in a circular pattern over the mid-peripheral cornea (epithelial side up). The correct orientation of the small graft fragments can be determined by the pigmentation and/or smooth surface of the epithelial side, as well as the presence of whitish fibrous strands on the stromal side. Care was taken to ensure that no tissue fragments were placed over the pupillary area or the limbus. Each tissue fragment was fixed with a drop of fibrin glue, and after polymerization, a large-diameter bandage contact lens was applied.

A threshold of logMAR 2.0 (≈ counting fingers at 1 meter) was defined as the lower limit of functional visual acuity, and keratoplasty was indicated when visual acuity remained worse than this level due to persistent stromal opacity.

Preoperative and Postoperative Management

All patients received topical 0.1% dexamethasone sodium phosphate (Dexa-Sine SE, Liba Laboratories, İstanbul, Türkiye) and/or 0.05% cyclosporine A (Restasis, Allergan, Irvine, CA, USA), together with artificial tears containing polyvinyl alcohol-povidone (Refresh single dose, Allergan, Irvine, CA, USA) and/or sodium hyaluronate (Eyestil, SIFI S.p.A., Catania, Italy) and/or carbomer (Thilo-Tears SE, Alcon/Thilo Pharma, Freiburg, Germany), prior to surgery. In selected cases, vitamin A ointment (VitA-POS, Ursapharm GmbH, Saarbrücken, Germany) was also applied preoperatively. In patients with acquired LSCD, LSCT was performed at least one year after the causative event. Postoperatively, all patients received a standardized topical regimen consisting of an antibiotic, a corticosteroid, and cyclosporine. Preservative-free topical antibiotics (netilmicin [Netira, SIFI S.p.A., Catania, Italy] or moxifloxacin [Vigamox, Alcon Laboratories, Fort Worth, TX, USA]) were administered four times daily for one month. Topical 0.1% dexamethasone sodium phosphate, initiated at a frequency of 6-8 times daily, was progressively tapered and discontinued within 6-12 months. Topical 0.05% cyclosporine A, prescribed at a dosage of 2-4 times daily, was maintained for a minimum duration of one year. In addition, patients undergoing allogeneic transplantation received systemic cyclosporine (Sandimmun Neoral, Novartis Pharma AG, Basel, Switzerland) at a dose of 3-5 mg/kg/day, targeting blood levels of 100-200 ng/mL, which was continued for at least one year.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM, Inc., Armonk, NY, USA). Normality testing with the Shapiro-Wilk and Kolmogorov-Smirnov tests indicated that the variables were not normally distributed. Descriptive statistics for numerical variables were expressed as

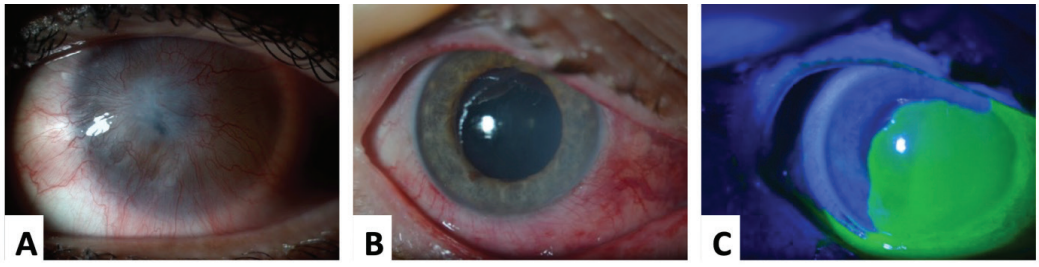

Figure 2. A) An eye that developed limbal stem cell deficiency following chemical injury, with a score of 12 according to the Aravena classification.[31] B, C) An eye in the acute stage of chemical injury, classified as stage III according to the Roper-Hall classification and grade IV according to the Dua classification

median (range). The Kruskal-Wallis test was used to compare numerical variables between groups, and the Wilcoxon test was used for pre- and postoperative comparisons within groups. A p value <0.05 was considered statistically significant.

Results

The median age of patients was 35.5 years (2-62 years), and 75% were male. The majority of eyes (n=27; 84.4%) developed LSCD secondary to chemical injuries. Three eyes had hereditary dyskeratosis, one had long-standing bullous keratopathy, and one had a history of corneal infection. CLAL was performed in 22 eyes, CLAU in 4 eyes, and SLET in 6 eyes (3 autografts and 3 allografts). Overall, 8 of 32 eyes (25%) required keratoplasty for visually significant stromal opacity: 2 eyes underwent simultaneous penetrating keratoplasty (PK) at the time of LSCT, 5 eyes underwent PK at a mean of 4.8 years post-LSCT (range: 4 months to 15 years), and 1 eye received deep anterior lamellar keratoplasty 12 years after CLAL. The median follow-up period was 60 months (12-108 months). Pre- and postoperative images of three eyes that underwent CLAL or SLET are shown in Figure 3.

Among eyes with LSCD secondary to chemical burns, 7 were classified as Stage 3 and 20 as Stage 4 according to the Roper-Hall classification. Based on the Dua classification, 3 eyes were grade IV, 5 were grade V, and 19 were grade VI. In the CLAL group (n=17), Roper-Hall classification identified 5 eyes as stage 3 and 12 as Stage 4, whereas Dua classification identified 1 eye as grade IV, 4 as grade V, and 12 as grade VI. In the CLAU group (n=4), 2 eyes were stage 3 and 2 were stage 4 by Roper-Hall; according to Dua classification, 2 were grade IV, 1 was grade V, and 1 was grade VI. In the SLET group (n=6), all eyes were stage 4 based on Roper-Hall, and all were grade VI based on Dua classification (Table 1).

Preoperative and postoperative median BCVA values were 2.1 (0.52-2.8) and 1.8 (0.22-2.8) logMAR for the CLAL group, 0.9 (0.7-2.8) and 0.7 (0.52-2.3) logMAR for the CLAU group, and 2.1 (1.8-2.3) and 1.3 (0.52-2.3) logMAR for the SLET group, respectively (Figure 4). There was no statistically significant difference in preoperative and postoperative BCVA between the groups. However, a significant improvement in visual acuity was observed within the CLAL group (p=0.01) and the SLET group (p=0.04). Although the CLAU group showed an improvement

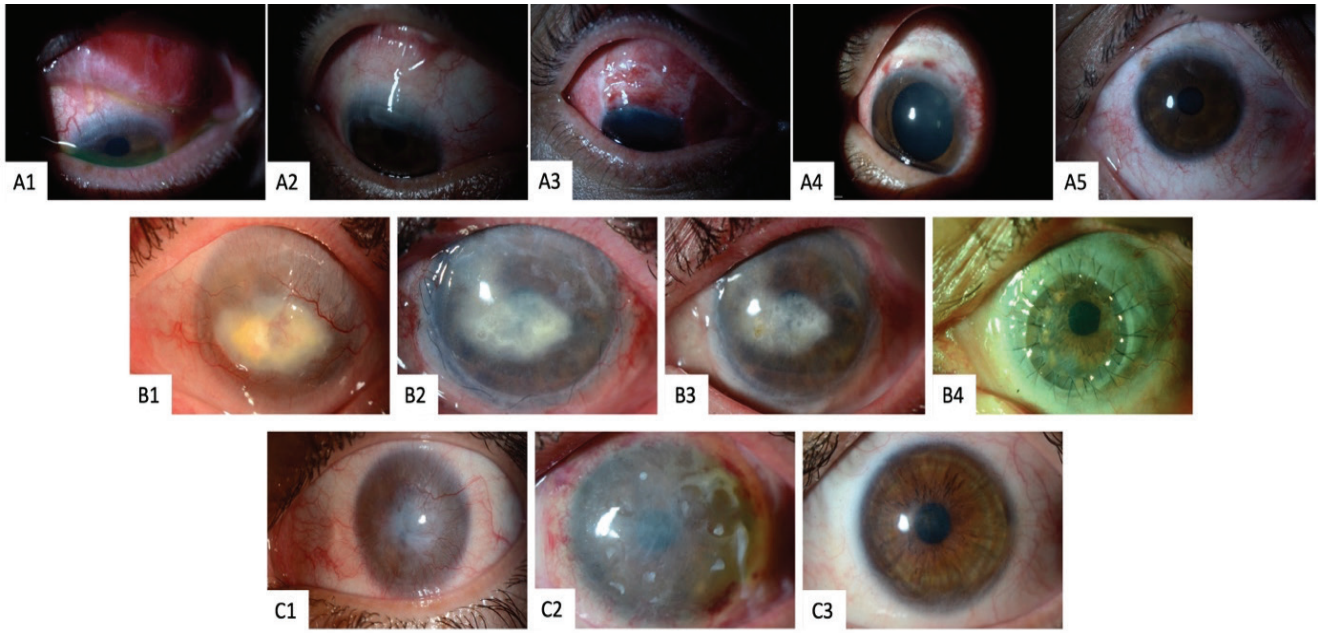

Figure 3. A1-5) A patient with a history of chemical injury and associated symblepharon. Symblepharon release and conjunctival limbal allograft (CLAL) were performed. Clear cornea achieved one year after bilateral living-related CLAL. B1-4) A patient with a history of chemical injury who underwent CLAL. Twelve years later, deep anterior lamellar keratoplasty was performed. C1-3) A patient who underwent simple limbal epithelial transplantation. Postoperatively, corneal haze decreased, neovascularization regressed, and the visual axis was cleared

Table 1. Preoperative severity distribution in patients with limbal stem cell deficiency secondary to chemical injury

Group (eyes)	Roper-Hall classification		Dua classification			Clinical score[31] median (range)
	Stage 3	Stage 4	Grade IV	Grade V	Grade VI	
CLAL (n=17)	5	12	1	4	12	10 (6-10)
CLAU (n=4)	2	2	2	1	1	7 (4-10)
SLET (n=6)	0	6	0	0	6	10 (10-10)

CLAL: Conjunctival limbal allograft, CLAU: Conjunctival limbal autograft, SLET: Simple limbal epithelial transplantation

in visual acuity, the change did not reach statistical significance (p=0.11). The overall success rate, defined as improvement in visual acuity, was 31.3%. By group, success rates were 36.4% for CLAL and 33.3% for SLET, whereas no improvement in visual acuity was observed in the CLAU group (0%).

The median clinical scores improved from 10 (6-10) to 6 (1-10) in the CLAL group, from 7 (4-10) to 4 (3-4) in the CLAU group, and from 10 (10-10) to 3 (1-7) in the SLET group (Figure 5). Although all groups demonstrated postoperative clinical improvement, the change was statistically significant in the CLAL (p<0.001) and SLET (p=0.03) groups, while it did not reach statistical significance in the CLAU group (p=0.11). A statistically significant difference in preoperative clinical scores was observed only between the CLAU and SLET groups (p=0.029), whereas no significant difference was found among the groups postoperatively (p>0.05).

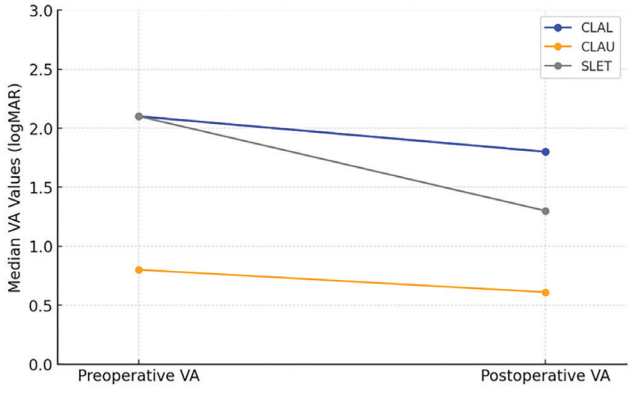

Figure 4. Changes in preoperative and postoperative median visual acuity (VA) in the conjunctival limbal allograft (CLAL), conjunctival limbal autograft (CLAU), and simple limbal epithelial transplantation (SLET) groups
logMAR: Logarithm of the minimum angle of resolution

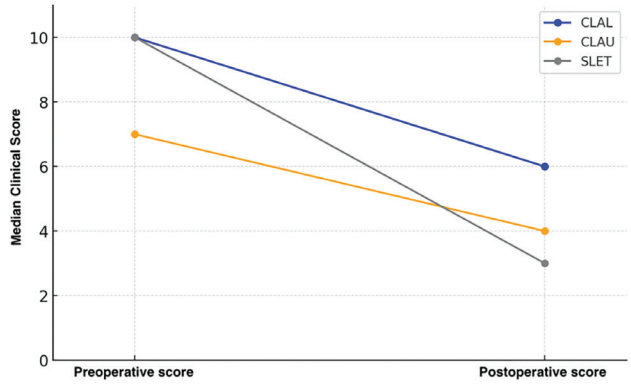

Figure 5. Changes in median preoperative and postoperative clinical scores in the conjunctival limbal allograft (CLAL), conjunctival limbal autograft (CLAU), and simple limbal epithelial transplantation (SLET) groups

Postoperative complications were observed in several cases. LSC graft failure developed in two eyes, which subsequently presented with persistent epithelial defects that were managed with autologous serum therapy. Conjunctivalization occurred in two eyes. Keratitis developed in two eyes: one following autologous serum application and the other presenting as crystalline keratopathy. In addition, glaucoma developed in two eyes, both of which were treated with Ahmed glaucoma valve implantation. None of the donors developed conjunctivalization or iatrogenic LSCD. A localized subconjunctival hemorrhage following biopsy occurred in 22 of 28 living donor eyes (78.6%) and resolved spontaneously in all cases. The wound site exhibited complete healing within one week, with no evidence of refractive changes in the donor.

HLA tissue typing data were available for 15 eyes that underwent CLAL, with a mean compatibility rate of 75% (range: 50%-100%). In contrast, all 3 eyes that underwent allogeneic SLET had 100% HLA compatibility. Figure 6 shows the distribution of compatibility percentages across HLA subgroups. Using the median value of 67% as the cut-off, HLA compatibility above 67% was defined as high (n=7, median 100%, range 71%-100%) and 67% or below as low (n=8, median 62%, range 50%-67%) in the CLAL group. In the high-compatibility group, significant improvement was observed in both visual acuity (1.2 to 0.52, p=0.03) and clinical scores (8 to 5, p=0.04), whereas in the low-compatibility group, improvement was limited to clinical scores only (9.5 to 7, p=0.03), with no significant improvement in visual acuity (2 to 2, p=0.5).

Discussion

The long-term outcomes of CLAL, CLAU, and SLET (both autograft and allograft) surgical techniques were evaluated in patients with LSCD of various etiologies. A significant improvement in both visual acuity and clinical scores was observed in patients who underwent CLAL and SLET.

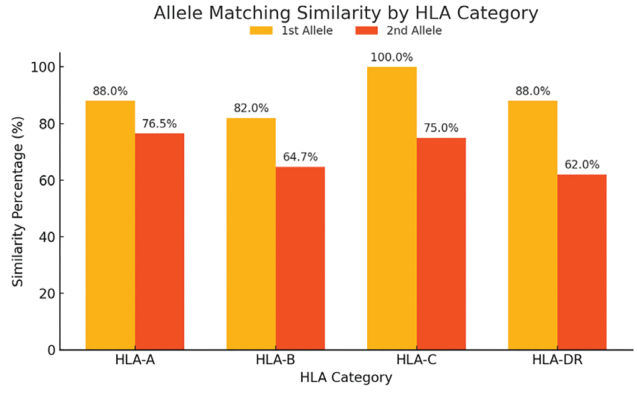

Figure 6. Human leukocyte antigen (HLA) compatibility percentages by HLA subgroups

Although the CLAU group demonstrated a slight postoperative improvement in visual acuity and clinical condition, these changes were not statistically significant. A significant difference in clinical scores was observed only between the CLAU and SLET groups preoperatively, whereas no significant differences were detected among the other groups preoperatively or among all groups postoperatively.

Severe trauma or inflammation of the limbus may result in LSCD, clinically characterized by progressive corneal neovascularization, conjunctivalization, and scarring of the corneal surface, ultimately leading to epithelial dysfunction and corneal blindness.[34] In such cases, treatment is directed toward promoting regeneration of the corneal epithelium and restoring corneal transparency. Early-stage LSCD secondary to limbal niche dysfunction may be managed medically without the need for surgical intervention.[35] However, LSCT is the mainstay of treatment in advanced LSCD.

The CLAU technique, first introduced in 1989, requires a healthy fellow eye. Using an autograft eliminates the risk of graft rejection and the need for systemic immunosuppression but also introduces the risk of iatrogenic LSCD in the donor eye.[36] The CLAL technique, while requiring larger graft tissue and systemic immunosuppressive therapy, remains one of the most commonly preferred approaches in the management of bilateral LSCD. Tran et al.[37] reported significant improvement in visual acuity by postoperative month 12 compared with baseline, particularly in traumatic and toxic cases undergoing allogeneic LSCT. However, their study did not address HLA matching. HLA matching between donor and recipient in CLAL procedures has been shown to improve surgical success rates.[38] In this study, the significant clinical improvement observed in the CLAL group may be attributable to the high degree of HLA compatibility (mean match rate of 75%). In the CLAL group, higher HLA compatibility (above 67%) was associated with significant improvements in both visual acuity and clinical scores, whereas lower compatibility (≤67%) led to improvement only in clinical scores, without a corresponding gain in visual acuity. These findings suggest that the degree of HLA compatibility may play a critical role in determining functional outcomes after allogeneic LSCT, particularly with regard to visual recovery.

In 1997, Pellegrini et al.[23] introduced the CLET technique, which involves *ex vivo* expansion of limbal tissue from a healthy eye to generate a transplantable epithelial sheet. Although clinically effective in restoring the ocular surface, CLET is associated with high costs and necessitates access to a clinical-grade laboratory. In 2012, Sangwan et al.[25] introduced the SLET technique, which combines the advantages of both CLAU and CLET while avoiding many of their limitations. SLET requires minimal donor tissue (under 1 clock hour), obviates the need for cell culture, and does not necessitate systemic immunosuppression. These advantages have contributed to its widespread adoption in the management of LSCD. Additionally, SLET incorporates amniotic membrane transplantation, which supports stem cell proliferation via its growth factors.[39] In this study, amniotic membrane transplantation was performed in all SLET patients.

Although SLET is widely employed as a single-stage treatment for unilateral LSCD, successful outcomes have also been reported in bilateral cases using allogeneic grafts.[40,41] However, systemic immunosuppression is necessary to maintain graft viability. In this cohort, three of six eyes treated with SLET had bilateral LSCD and consequently received allogeneic grafts. To minimize the risk of graft rejection, donor-recipient HLA compatibility was assessed preoperatively, and only donors with 100% HLA match were selected. SLET is known to have a relatively short learning curve and is easily reproducible.[42] However, it may be insufficient as a standalone procedure in cases of severe symblepharon, in which additional conjunctival grafting is often required. While Arora et al.[43] reported no significant difference in symblepharon scores between SLET and CLAU at six months, other studies have identified preoperative symblepharon as a risk factor for SLET failure.[42,44]

A review comparing different LSCT techniques reported comparable anatomical success rates among SLET, CLET, CLAL, and keratolimbal allograft (KLAL) procedures, whereas another review evaluating three different techniques suggested that postoperative clinical outcomes were superior in SLET and CLAU compared to CLET.[45,46] Although KLAL and CLET were not performed in this study, the clinical outcomes of three different surgical approaches were evaluated. Postoperative clinical scores were comparable across the three groups. Significant improvements in visual acuity and clinical scores were observed in eyes treated with CLAL and SLET, whereas the CLAU group showed only mild improvements that did not reach statistical significance. This may be attributed to the smaller sample size in the CLAU group and the relatively better baseline condition of eyes in this group. The median preoperative clinical score was 7 in the CLAU group, compared with 10 in the CLAL group and 10 in the SLET group.

In a study investigating the treatment of chemical burns, the most common cause of LSCD, patients with low-grade injuries benefited significantly from medical therapy, amniotic membrane transplantation, limbal grafting, and subsequent keratoplasty, whereas those with severe injuries were more prone to failure despite all available treatment modalities.[47] For advanced LSCD, surgical restoration of LSCs is required, and the choice of LSCT technique is of critical importance, depending on factors such as disease laterality, availability of donor tissue, and the need for systemic immunosuppression. In cases of unilateral LSCD, the most effective treatment method is SLET, which can also be applied in bilateral cases using grafts from HLA-compatible first-degree relatives. SLET is advantageous due to its minimal tissue requirements and the absence of the need for immunosuppression in autologous cases. In unilateral cases, CLAU can also be performed without the need for immunosuppression, although it carries the risk of iatrogenic LSCD in the donor eye. However, CLAL grafts are more easily obtainable, either from living or deceased donors. Nevertheless,

both necessitate lifelong systemic immunosuppression, and harvesting from a living donor also carries the risk of iatrogenic LSCD. CLET provides an alternative by expanding a small limbal biopsy *ex vivo* to generate an epithelial sheet, thereby reducing donor-site morbidity. However, it requires specialized laboratory facilities, is costly, and outcomes may vary due to differences in culture methods and potential loss of limbal niche cells.

Complications associated with various LSCT procedures share common features such as conjunctivalization and persistent epithelial defects, but also differ in certain aspects, particularly with respect to the adverse effects of systemic immunosuppression in allografts.[48] Due to the large graft size required, CLAU carries the risk of iatrogenic LSCD in the donor eye, which has been clinically documented.[49] Attempts to reduce graft size have been made to minimize this risk, but these smaller grafts have been associated with lower success rates and higher complication rates.[50] Delayed epithelial healing and persistent epithelial defects are among the most common complications after CLAU, often necessitating management such as amniotic membrane transplantation; in severe cases, corneal melting and perforation may still occur.[36,51] Donor site safety remains a concern, as long-term follow-up has revealed corneal ectasia and vascularization in some cases following CLAU.[52] In bilateral ocular surface damage, limbal allograft transplantation is indicated, but carries an inevitable risk of immunological failure and graft rejection.[53] Postoperative glaucoma has been reported in 26-32% of cases, and bacterial keratitis rates range between 8% and 14%.[54,55] By contrast, donor site complications after SLET appear to be minimal. Subconjunctival hemorrhage is relatively frequent but resolves spontaneously. The most prevalent complication in recipients is focal recurrence of pannus, which can be observed without intervention if stable, or effectively managed with repeat SLET, with or without conjunctival autografting.[44,56] Other reported issues include progressive conjunctivalization, symblepharon, and graft loss or detachment, which may contribute to recurrence and failure.[57,58] Rare complications such as epithelial hyperplasia, recurrent corneal neovascularization, and persistent epithelial defects have also been described.[58,59] In this cohort, postoperative complications included persistent epithelial defects, conjunctivalization, keratitis, and glaucoma requiring Ahmed valve implantation. Donor eyes remained largely safe, with no cases of conjunctivalization or iatrogenic LSCD. Localized subconjunctival hemorrhage occurred in 78.6% and resolved spontaneously, and all wounds healed within one week without refractive changes.

Study Limitations

One of the main limitations of this study is the small sample size and the unequal distribution of patients among the LSCT groups. Additional sources of heterogeneity include differences in mean age across groups, varying etiologies of LSCD, and discrepancies in preoperative clinical scores. These factors may limit both the generalizability and the objectivity of comparisons between surgical techniques. In particular, differences in LSCD severity prior to surgery may hinder accurate assessment of the relative efficacy of each technique. Postoperative clinical scores were similar between the CLAU and SLET groups. However, the lower preoperative scores and the smaller number of patients in the CLAU group may explain why a significant improvement was observed in the SLET group but not in the CLAU group. Nonetheless, application of the CLAU technique in a larger number of patients with more severe preoperative disease may still yield meaningful clinical benefits comparable to other techniques. Postoperative outcomes of LSCT may also vary depending on the underlying etiology and stage of LSCD, particularly in terms of inflammation and epithelialization rates.[60] Thus, comparisons between surgical techniques are likely to be more reliable and objective in cases with similar etiologies and baseline clinical scores. Another important limitation of this study is that some patients underwent keratoplasty either concurrently with or following LSCT. In such cases, the contribution of keratoplasty to clinical improvement cannot be excluded, potentially confounding the interpretation of outcomes attributed solely to LSCT.

Conclusion

Different LSCT techniques may be applied in the management of LSCD depending on the underlying etiology and whether the condition is unilateral or bilateral. Favorable outcomes have also been reported with allogeneic techniques, particularly when HLA compatibility is achieved. Among the available methods, the SLET technique appears to offer certain advantages over others due to its minimal tissue requirement, technical simplicity, and reproducibility.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Board of Eskişehir Osmangazi University (number: E-25403353-050.99-2400074876, subject: 2024-102, decision number: 47, decision date: 19.03.2024) and adhered to the ethical principles of the Declaration of Helsinki.

Informed Consent: Since it was a retrospective study, informed consent was not obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: N.Y., Concept: N.Y., S.M.İ., O.Ö., Design: N.Y., S.M.İ., O.Ö., Data Collection or Processing: N.Y., S.M.İ., O.Ö., Analysis or Interpretation: N.Y., S.M.İ., O.Ö., Literature Search: N.Y., S.M.İ., O.Ö., Writing: N.Y., S.M.İ., O.Ö.

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Original Article

Surgical Success and Predictive Factors in Patients Undergoing Gonioscopy-Assisted Transluminal Trabeculotomy

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Abstract

Objectives: This retrospective study aimed to evaluate the one-year surgical success of gonioscopy-assisted transluminal trabeculotomy (GATT) and identify prognostic factors influencing surgical outcomes in eyes diagnosed with open-angle glaucoma.

Materials and Methods: A total of 225 eyes (214 patients) treated with GATT between March 1, 2018, and June 1, 2024, were included in the study. Preoperative and postoperative data were analyzed. Complete surgical success (Criterion A) was defined as having an intraocular pressure (IOP) between 5 and 18 mmHg or at least a 30% reduction in IOP without the need for additional surgery. Overall success referred to achieving the same IOP with or without glaucoma medications. Surgical failure was defined as IOP >18 mmHg or <5 mmHg, significant vision loss, or the need for additional surgical intervention.

Results: The mean age of patients was 64.4±11.9 years, and the mean axial length (AL) was 24.0±2.0 mm. The mean preoperative IOP was 26.7±7.3 mmHg, which decreased to 14.3±6.5 mmHg at 12 months postoperatively ($p<0.05$). The rate of complete success according to Criterion A was 41.3%, while the rate of overall success was 87.6%. Multivariate analysis revealed that higher preoperative IOP (odds ratio [OR]: 1.07; $p=0.02$), longer AL (OR: 1.3; $p<0.01$), and postoperative IOP spikes (OR: 5.18; $p<0.01$) were significantly associated with surgical failure. Patients who underwent circumferential (360°) GATT had significantly higher success rates compared to those who received hemi-GATT (OR: 4.69; $p=0.01$). Glaucoma stage, presence of pseudoexfoliation glaucoma, history of prior trabeculectomy, and vitrectomy were not significantly associated with surgical outcomes ($p>0.05$ for all).

Conclusion: GATT is an effective and safe surgical option for various types of glaucoma. Higher preoperative IOP, longer AL, and postoperative IOP spikes increase the risk of surgical failure, whereas circumferential GATT is associated with improved success rates. GATT can also be considered as a potential alternative for patients with prior glaucoma surgery or advanced-stage glaucoma.

Keywords: Open-angle glaucoma, surgical success, gonioscopy-assisted transluminal trabeculotomy

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Introduction

Glaucoma is a leading cause of irreversible blindness.[1] While medical treatment is the initial approach in managing glaucoma, surgical intervention should be considered when intraocular pressure (IOP) cannot be controlled with maximal medical treatment. Trabeculectomy continues to be regarded as the gold standard surgical procedure for treating glaucoma.[2] However, it is associated with potential intraoperative and postoperative complications, including bleb-related problems, suprachoroidal hemorrhage, and ocular hypotony, which in some cases may necessitate additional surgical intervention during the postoperative period.

Minimally invasive glaucoma surgery (MIGS) has steadily gained recognition as a safer operative alternative to trabeculectomy, while also enabling a swifter postoperative recovery.[3] Gonioscopy-assisted transluminal trabeculotomy (GATT) is an increasingly common surgical option for managing open-angle glaucoma (OAG).[4] Reports indicate that GATT can achieve success rates as high as 80% in patients with OAG.[4,5] Elucidating the prognostic factors that moderate

surgical outcomes remains essential. Therefore, in this study we investigated predictors of operative success in suture-based GATT surgery.

Materials and Methods

This retrospective review included patients who underwent GATT surgery for OAG between 1 March 2018 and 1 June 2024 and completed at least 12 months of postoperative follow-up. All participants provided written informed consent for the use of their data in accordance with the principles outlined in the Declaration of Helsinki. This study received ethical approval from the University of Health Sciences Hamidiye Scientific Research Ethics Committee (decision date: 15/5/2025, decision number: 11/37).

Each patient underwent preoperative assessments including IOP, cup-to-disc ratio, number of glaucoma medications used, best corrected visual acuity, retinal nerve fiber layer (RNFL) thickness, axial length (AL), and glaucoma type (primary or secondary). Intraoperative and postoperative data included the extent of GATT (360° circumferential or 180° hemispheric [hemi]), presence of postoperative fibrin reaction, presence and timing of IOP spikes, presence and duration of hyphema, as well as any intraoperative or postoperative complications.

Peripapillary RNFL thickness was measured after pupil dilation, using a Spectralis optical coherence tomography (OCT) device (Heidelberg Engineering, Heidelberg, Germany). Visual field tests were conducted using the Humphrey Visual Field Analyzer (HFA II 750; Carl Zeiss Meditec Inc., Dublin, CA, USA) with the 30-2 Swedish Interactive Thresholding Algorithm. Mean deviation (MD) values were documented and used to stratify glaucoma severity: mild disease corresponded to an MD greater than -6 decibels, moderate disease to an MD between -6 and -12 decibels, and severe disease to an MD below -12 decibels.

Complete success was defined as attaining an IOP greater than 5 mmHg and ≤18 mmHg (Criterion A), greater than 5 mmHg and ≤15 mmHg (Criterion B), or a reduction of at least 30% from baseline IOP, without requiring additional glaucoma medications or further surgical intervention. Overall success was defined as achieving the same IOP targets, either with or without the use of glaucoma medications. Surgical failure was defined as an IOP above the target range specified by Criterion A or B, or below 5 mmHg, a complete loss of visual acuity due to glaucoma progression or surgical complications, or the need for additional glaucoma surgeries, including trabeculectomy, seton implantation, or cyclodestructive procedures.

Surgical Technique

All surgeries were performed by four glaucoma specialists following a standardized surgical technique, in accordance with the institution's established protocols, as outlined below:

GATT: A temporal main incision was made with a 23-gauge blade, after which 1.6% sodium hyaluronate was injected into the anterior chamber. A tangential side-port incision was then created with the same 23-gauge blade in the superonasal or inferonasal quadrant to allow introduction of the polypropylene suture. To visualize the nasal angle, the surgical microscope and the patient's head were tilted in opposite directions, and a Swan-Jacob goniolens was used. Through the temporal incision, a 1-2 mm goniotomy was performed with the 23-gauge blade to expose Schlemm's canal (SC). The tip of a 5-0 polypropylene suture was cauterized to create a blunt end, introduced into the SC with 23-gauge microforceps, and advanced around the canal. For circumferential GATT, the distal portion of the suture was grasped and the proximal end was pulled to accomplish a complete 360° circumferential goniotomy. For 180° hemi-GATT, the suture was advanced only 180 degrees and then pulled to complete the procedure. Afterwards, the suture was removed.

Postoperative Follow-up

Postoperatively, patients were prescribed a two-week course of moxifloxacin 0.5% eye drops (Moxai; Abdi İbrahim Pharmaceuticals, İstanbul, Türkiye) five times daily, as well as topical prednisolone acetate 1% eye drops (Pred Forte; Allergan, Irvine, CA, USA) six times per day for the first two weeks and then progressively tapered over the subsequent four weeks.

Statistical Analysis

All statistical analyses were conducted using SPSS version 20.0® for Windows (IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was applied to assess the normality of data distribution. Continuous variables were summarized as means ± standard deviations or as medians with interquartile ranges, as appropriate. Independent t-tests were used to assess differences in continuous variables between groups, while categorical variables were analyzed using two-sided chi-square tests. Potential risk factors for failure were identified in univariate analyses, and variables with $p<0.05$ were included in the multivariate analysis to identify prognostic factors. A p value of <0.05 was considered statistically significant.

Results

A total of 225 eyes from 214 patients (142 males, 72 females) were included in the study. Among the patients, the mean age was 64.4±11.9 years, and the mean AL was 24.0±2.0 mm. The mean follow-up time was 18.6±7.0 months (range, 12-48). Of the eyes, 118 (52.4%) were phakic and 107 (47.6%) were pseudophakic. Phacoemulsification (phaco)-combined surgery was performed in 9 eyes (4%). The indication for surgery was primary OAG (POAG) in 69 eyes (30.7%), pseudoexfoliation glaucoma (PEXG) in 103 eyes (45.8%), uveitic glaucoma in 16 eyes (7.1%), pigment dispersion syndrome in 4 eyes (1.8%), secondary glaucoma after intraocular surgery in 30 eyes (13.3%), steroid responder glaucoma in 2 eyes (0.9%), and traumatic glaucoma in 1 eye (0.4%, Table 1).

One eye (0.4%) had previously undergone penetrating keratoplasty, 29 eyes (12.9%) had a history of prior vitrectomy, 43 eyes (19.1%) had previously undergone trabeculectomy, 1 eye (0.4%) had a prior Ahmed glaucoma valve implantation, and 1 eye (0.4%) had undergone goniotomy (Table 1).

Change in Intraocular Pressure and Success

Preoperatively, the mean IOP was 26.7±7.3 mmHg, and the patients used an average of 3.6±1.1 glaucoma medications. At 12 months postoperatively, the mean IOP had decreased to 14.3±6.5 mmHg (p<0.05), with a corresponding decrease in the average number of medications to 1.5±1.5 (p<0.05). According to Criterion A, complete success (IOP controlled without the use of glaucoma medications) was observed in 93 eyes (41.3%), whereas 197 eyes (87.6%) achieved overall success and 28 eyes (12.4%) were considered surgical failures. According to Criterion B, complete success was observed in 75 eyes (33.3%), overall success in 173 eyes (76.9%), and surgical failure in 52 eyes (23.1%).

Predictors of Surgical Outcome

Factors related to decreased likelihood of success in univariate analysis were: previous vitrectomy (overall success 75.9%, compared to 89.3% in eyes without vitrectomy, p=0.06; odds ratio [OR]: 2.65, 95% confidence interval [CI]: 1.01-6.94, p=0.04), higher preoperative IOP (OR: 1.07, 95% CI: 1.02-1.13, p=0.01), longer AL (OR: 1.35, 95% CI: 1.16-1.57, p<0.01), and postoperative IOP spike (overall success 73.2%, compared to 94.2% in eyes without spike, p<0.01; OR: 5.89, 95% CI: 2.51-13.83, p<0.01). In contrast, circumferential trabeculotomy was associated with increased likelihood of surgical success (overall success 90.5% in 360° GATT vs. 64% in 180° GATT, p<0.01; OR: 5.36, 95% CI: 2.09-13.77, p<0.01) (Tables 2 and 3).

Complete surgical success was achieved in 12% and overall success in 64% in the hemi-GATT group. In contrast, in the circumferential GATT group, complete success was observed in 45% and overall success in 90.5% (p=0.01 for both). The mean number of glaucoma medications was 2.76±1.4 in the hemi-GATT group and 1.4±1.4 in the circumferential GATT group (p=0.01). The distribution of glaucoma types between the two surgical groups was not statistically significant (p=0.6).

In the multivariate regression model, preoperative IOP, AL, presence of postoperative IOP spike, and the extent of trabeculotomy were found to be related to final surgical success (Table 4). Lower preoperative IOP and shorter AL were associated with a higher chance of surgical success (adjusted OR: 1.07; 95% CI: 1.01-1.13; p=0.02 and adjusted OR: 1.30; 95% CI: 1.09-1.58; p<0.01, respectively). The occurrence of an IOP spike increased the likelihood of surgical failure fivefold (adjusted OR: 5.18; 95% CI: 1.6-15.69; p<0.01), while circumferential trabeculotomy increased the likelihood of surgical success by 4 times (adjusted OR: 4.69; 95% CI: 1.56-14.18; p=0.01).

Complications

Postoperative complications included fibrin reaction in 65 eyes (28.9%), hyphema in 114 eyes (50.7%), and intravitreal hemorrhage in 12 eyes (5.3%). A total of 29 eyes (12.9%) received subconjunctival dexamethasone for fibrin reaction, of which 5 were phaco-combined cases. Anterior chamber washout was performed in 9 eyes (4%) due to prolonged hyphema, and vitrectomy was performed in 1 eye (0.4%) due to intravitreal

Table 1. Baseline demographic and clinical characteristics of patients undergoing gonioscopy-assisted transluminal trabeculotomy

Age (years), mean ± SD	64.4±11.9
Median (IQR)	67 (58.5-73.0)
BCVA (Snellen decimal), mean ± SD	0.32±0.28
Median (IQR)	0.3 (0.05-0.5)
IOP (mmHg), mean ± SD	26.7±7.3
Median (IQR)	26 (22-30)
Number of glaucoma medications, mean ± SD	3.6±1.1
Median (IQR)	4 (3-4)
Cup-to-disc ratio, mean ± SD	0.85±0.2
Median (IQR)	0.9 (0.8-1.0)
RNFL thickness (µm), mean ± SD	64.3±18.7
Median (IQR)	62 (50-76)
Axial length (mm), mean ± SD	24.0±2.0
Median (IQR)	23.4 (23.0-24.2)
Type of glaucoma, n (%)	
Primary OAG	69 (30.7)
Secondary OAG	156 (69.3)
PEX	103 (45.8)
Post-IO surgery	30 (13.3)
Uveitic	16 (7.1)
PDS	4 (1.8)
Steroid responder	2 (0.9)
Traumatic glaucoma	1 (0.4)
Glaucoma stage, n (%)	
Mild	43 (19.1)
Moderate	47 (20.9)
Severe	135 (60)
Previous surgeries, n (%)	
Trabeculectomy	43 (19.1)
Vitrectomy	29 (12.9)
Keratoplasty	1 (0.4)
Goniotomy	1 (0.4)
AGV implantation	1 (0.4)
Extent of GATT, n (%)	
360° circumferential	200 (88.9)
180° hemi-GATT	25 (11.1)
Postoperative fibrin reaction, n (%)	65 (28.9)
Presence of IOP spike, n (%)	71 (31.6)
Timing of IOP spike (days postop), mean ± SD	12.7±12.5
Median (IQR)	8 (1-22)
Mean IOP during spike (mmHg), mean ± SD	32.9±6.7
Median (IQR)	30 (28-38)
Presence of hyphema, n (%)	114 (50.7)
Duration of hyphema (days), mean ± SD	7.9±8.9
Median (IQR)	5 (2-10)

SD: Standard deviation, IQR: Interquartile range, BCVA: Best-corrected visual acuity, IOP: Intraocular pressure, RNFL: Retinal nerve fiber layer, OAG: Open-angle glaucoma, PEX: Pseudoexfoliation syndrome, PDS: Pigment dispersion syndrome, IO: Intraocular, AGV: Ahmed glaucoma valve, GATT: Gonioscopy-assisted transluminal trabeculotomy, postop: Postoperative

Table 2. Results of univariate logistic regression analysis of factors associated with surgical success		
	p value	**OR (95% CI)**
Preoperative IOP	**0.01**	1.07 (1.02-1.13)
Axial length	**<0.01**	1.35 (1.16-1.57)
Glaucoma stage	0.5	1.46 (0.46-4.5)
Previous vitrectomy	**0.04**	2.65 (1.01-6.94)
Pseudoexfoliation glaucoma	0.3	0.62 (0.27-1.41)
Previous trabeculectomy	0.15	1.9 (0.79-4.81)
Extent of trabeculotomy	**<0.01**	5.36 (2.09-13.77)
IOP spike	**<0.01**	5.89 (2.51-13.83)
Postoperative fibrin reaction	0.18	0.49 (0.18-1.37)
Postoperative hyphema	0.9	0.97 (0.44-2.14)
Lens status	0.78	1.12 (0.51-2.47)
IOP: Intraocular pressure, OR: Odds ratio, CI: Confidence interval		

hemorrhage. An IOP spike was observed in 71 eyes (31.6%) at a mean of 12.7±12.5 days, with a mean IOP of 32.9±6.37 mmHg. Transient hypotony was observed in 9 eyes (4.0%), none of which persisted beyond postoperative month 3.

Discussion

Traditional glaucoma surgeries such as tube implantation and trabeculectomy have long been associated with a considerable risk of serious complications.[6] In recent years, conjunctiva-sparing techniques have become increasingly popular in glaucoma surgery to reduce the risk of major complications. These methods are classified as MIGS by the European Glaucoma Society.[7] GATT is a minimally invasive, ab-interno cannulation of the SC that opens the trabecular meshwork (TM) and SC wall to improve aqueous outflow.[8] It provides effective IOP control in primary and secondary OAG, uveitic glaucoma, steroid-induced glaucoma, and pediatric as well as juvenile glaucoma,

Table 3. Relationships between baseline characteristics, predictive factors, and postoperative outcomes			
	Overall success (Criterion A), n (%)	**Number of AGM (mean ± SD)**	**Complete success (Criterion A), n (%)**
Preoperative IOP ≥30 mmHg <30 mmHg	 52 (77.6) 145 (91.8) **p<0.001**	 1.8±1.5 1.46±1.5 p=0.11	 17 (25.4) 76 (48.1) **p<0.001**
Axial length ≥26 mm <26 mm	 6 (66.6) 191 (90.4) **p=0.01**	 2.7±1.6 1.43±1.4 **p=0.001**	 2 (22.2) 91 (43.1) p=0.12
Glaucoma stage Mild Moderate Severe	 38 (88.4) 40 (85.1) 119 (88.1) p=0.9	 1.3±1.5 1.4±1.5 1.6±1.5 p=0.35	 22 (51.2) 21 (44.7) 50 (37.0) p=0.1
Previous vitrectomy + -	 22 (75.9) 175 (89.3) p=0.06	 1.93±1.5 1.5±1.5 p=0.15	 9 (31.0) 84 (42.9) p=0.3
Pseudoexfoliation glaucoma + -	 93 (90.3) 104 (85.2) p=0.3	 1.49±1.5 1.6±1.5 p=0.5	 47 (45.6) 46 (37.7) p=0.3
Revious trabeculectomy + -	 35 (81.4) 162 (89.5) p=0.2	 1.88±1.7 1.47±1.4 p=0.1	 16 (37.2) 77 (42.5) p=0.6
Extent of trabeculotomy Hemi-GATT Circumferential	 16 (64) 181 (90.5) **p=0.001**	 2.76±1.4 1.4±1.4 **p<0.001**	 3 (12) 90 (45) **p=0.00**1
IOP spike + -	 52 (73.2) 145 (94.2) **p<0.001**	 2.2±1.4 1.3±1.4 **p<0.001**	 13 (18.3) 80 (51.9) **p<0.001**
Comparisons were made between subgroups using chi-square or Fisher's exact test, with a significance threshold of p<0.05 AGM: Antiglaucoma medications, SD: Standard deviation, IOP: Intraocular pressure, GATT: Gonioscopy-assisted transluminal trabeculotomy			

Table 4. Results of multivariate logistic regression of factors associated with surgical success

	p value	OR (95% CI)
Preoperative IOP	**0.02**	1.07 (1.01-1.13)
Axial length	**0.004**	1.30 (1.09-1.58)
Previous vitrectomy	0.71	0.79 (0.23-2.67)
Extent of trabeculotomy	**0.01**	4.69 (1.56-14.18)
IOP spike	**<0.001**	5.18 (1.60-15.69)

IOP: Intraocular pressure, OR: Odds ratio, CI: Confidence interval

making it a versatile option for a broad range of patients.[8] Since its introduction, some prognostic factors influencing surgical outcomes have been identified.[9,10,11] However, our study examined the largest cohort and the most diverse spectrum of cases among the studies conducted to date.

Previous studies suggest that GATT effectively lowers IOP and decreases reliance on glaucoma medications.[4,9,12,13] At 1-year follow-up, we noted a marked decrease in both IOP and the required number of glaucoma medications, achieving an overall success rate of 87.6%. We found that higher preoperative IOP, longer AL, and the occurrence of postoperative IOP spikes negatively impacted the success of GATT. In contrast, circumferential-GATT was associated with better outcomes compared to hemi-GATT. Furthermore, our analysis did not show any association between success and the presence of PEXG, prior trabeculectomy, or glaucoma stage.

One of the key factors influencing the success of procedures like GATT, which bypass trabecular resistance, is proper functioning of the distal outflow pathway. However, there is currently no easy, objective, and non-invasive method to assess distal outflow function preoperatively. As a result, it remains challenging to predict which patients are more likely to experience surgical failure. Therefore, identifying clinical risk factors is crucial for enhancing patient selection and outcomes.

Greater preoperative IOP demonstrated an inverse association with surgical success in our study. As there are no studies in the current literature evaluating the association between preoperative IOP and surgical success rates, the underlying mechanism of surgical failure remains speculative and cannot be thoroughly discussed. However, although a ≥30% reduction in IOP, our primary criterion for surgical success, was achieved in cases with high preoperative IOP, most of these eyes remained above the target IOP levels during follow-up. Furthermore, eyes with a preoperative IOP of <30 mmHg demonstrated higher rates of both complete and overall surgical success, suggesting a more favorable postoperative outcome in our study. The need for additional surgical intervention was significantly higher, indicating a higher rate of surgical failure among eyes with high baseline IOP (≥30 mmHg). Our results indicate that eyes with high preoperative IOP have notably lower success rates following GATT surgery.

It has been previously proposed that advanced stages of glaucoma may lead to structural distortion of the collector channels, SC, and TM, potentially compromising aqueous outflow.[14] This condition has been thought to negatively affect the outcomes of surgeries involving the SC. However, in our study, we observed that glaucoma stage, whether mild, moderate or advanced, did not have an impact on surgical outcome. Grover et al.[15] indicated that eyes with an MD worse than -15 had a low likelihood of successful GATT due to possible atrophy of the collector channels. However, Aktas et al.[16] observed no direct association between glaucoma severity and surgical success among patients with advanced glaucoma. They concluded that while SC-based MIGS procedures may not be ideal for advanced-stage glaucoma, this limitation may not apply to circumferential angle surgeries such as GATT.[16] The results of our study, as well as previous studies, indicate that GATT is effective in advanced-stage glaucoma as well.[13,16,17]

High myopia has also been suggested as a contributing factor to collector channel distortion.[13,14] An elongated AL may lead to structural changes in the SC and TM.[18] A study assessing the efficacy of Kahook dual-blade trabeculotomy reported lower success rates in eyes with long AL and suggested that surgeries targeting the TM and SC may be less effective in such eyes.[19] Consistent with previous findings, our results demonstrated that higher AL correlated with lower surgical success and a greater need for glaucoma medication.

Our analysis showed that the occurrence of postoperative IOP spikes is a contributing factor to surgical failure and greater need for glaucoma medications following GATT. Postoperative inflammation, peripheral anterior synechiae, and fibrotic closure of the TM have been suggested as potential causes of postoperative IOP spikes.[20] Our findings support those of Shi et al.,[21] who also reported that postoperative IOP spikes contribute to surgical failure.

We observed higher overall and complete surgical success rates and a lower average number of glaucoma medications in eyes that underwent circumferential GATT compared to those that underwent hemi-GATT. These findings indicate that circumferential GATT provides better IOP control and medication independence. A study comparing 360° GATT with the 90° ab-interno needle goniectomy found that 360° GATT produced a greater, more sustained reduction in IOP and achieved higher long-term success rates. The authors attributed these superior outcomes to GATT's full circumferential trabeculotomy, which removes resistance along the entire SC.[22] Alagoz et al.[23] noted that over prolonged follow-up, the trabecular flap re-approximated portions of the incision site, leading to a closed cleft appearance on gonioscopy, which was further supported by anterior segment OCT findings. Peripheral anterior synechiae also mainly formed in the regions where the cleft appeared closed, suggesting a potential role of postoperative tissue adhesion in limiting long-term outflow. In their study, with a follow-up of up to 78 months, the median extent of the open cleft was longer in the circumferential GATT group than in the hemi-GATT group. As portions of the treated TM may gradually re-close over time and compromise long-term efficacy, a complete 360° trabeculotomy should be the primary goal in the GATT procedure.

Studies evaluating the success of GATT in patients with a history of previous unsuccessful incisional glaucoma surgery have reported satisfactory success rates, showing that GATT represents a safe and efficacious surgical option for managing refractory OAG.[5,24] In one such study, Wang et al.[24] reported that 82.1% of these eyes had an IOP of ≤18 mmHg at 24 months postoperatively. Consistent with previous reports, our findings indicated that prior trabeculectomy was not significantly associated with worse surgical outcomes following GATT. Given the increased risk of bleb fibrosis after repeated filtering surgeries,[25] GATT presents a potentially valuable alternative approach in patients with prior surgical failure.[24]

Some studies have reported higher success rates in the PEXG group.[4,12] However, others indicate that this advantage diminishes after 6 months, with outcomes becoming comparable to those in POAG.[9,10] Our analysis likewise indicated that PEXG had no statistically significant effect on surgical outcomes at one year.

Secondary glaucoma is a common complication following vitrectomy, ranging from 8.4% to 14.8% after vitreoretinal procedures.[26] However, there is a lack of data in the literature regarding the success of MIGS procedures targeting the SC in vitrectomized eyes. Nonetheless, previous studies on vitrectomized patients with secondary glaucoma have shown that GATT is both effective and safe.[27,28] In our study, we found that a history of vitreoretinal surgery did not significantly affect the success of GATT. Since the success of trabeculectomy is often limited by conjunctival scarring in eyes with a history of vitrectomy, GATT may serve as a viable alternative, provided that gonioscopic evaluation confirms a favorable angle anatomy.

Trabeculectomy, the most frequently performed conventional glaucoma surgery, carries a considerable risk of complications, including ocular hypotony, hypotony maculopathy, choroidal detachment, suprachoroidal hemorrhage, and bleb-related problems such as infections and endophthalmitis.[29] In our study group, 4% of patients experienced transient hypotony which lasted 3 months. None of the other complications related to trabeculectomy were encountered.

The most common complication associated with GATT has been reported as transient hyphema, which may occur in up to 55% of cases during or after GATT surgery.[8,30] In our study, the most frequently observed complication was hyphema, occurring in 50.7% of cases.

In a study evaluating GATT outcomes in POAG and PEXG, 19.4% of the overall cohort experienced a fibrin reaction.[31] Notably, fibrin formation was observed in all eyes that underwent phaco-combined GATT.[31] In our study, fibrin reaction was observed in 28.9% of the eyes, including 5 of the 9 eyes that underwent phaco-combined GATT. We believe several factors may have contributed to the relatively high rate of fibrin reaction. First, circumferential GATT was performed in 88.9% of cases. Additionally, in eyes with clotted hyphema, the coagulum was also counted as fibrin for the purpose of complication analysis.

Zeng et al.[32] reported that IOP spikes occurred in about 40% of patients with OAG. Consistent with the previous reports, we observed IOP spikes in 31.6% of cases, and this was found to be associated with surgical failure.

Study Limitations

The primary limitations of this study are its retrospective design and the comparatively small sample sizes in specific subgroups. Moreover, the heterogeneity of glaucoma etiologies within the study population may introduce confounding factors. However, this diversity reflects the spectrum of patients commonly encountered in real-world glaucoma practice and thus adds value by providing clinically relevant, real-life data. Further prospective studies involving more diverse and balanced subgroup distributions are needed to validate these findings.

Conclusion

In conclusion, higher preoperative IOP, longer AL, and the occurrence of postoperative IOP spikes were negatively associated with surgical success, whereas circumferential GATT was associated with more favorable outcomes than hemi-GATT. Since our analysis showed no significant association between surgical success and the presence of PEXG, prior trabeculectomy, history of pars plana vitrectomy, or glaucoma stage, GATT should be considered a valuable surgical option in eyes with a history of trabeculectomy or vitrectomy, as well as in cases across all stages of glaucoma.

Ethics

Ethics Committee Approval: This study received ethical approval from the University of Health Sciences Hamidiye Scientific Research Ethics Committee (decision date: 15/5/2025, decision number: 11/37).

Informed Consent: All participants provided written informed consent for the use of their data in accordance with the principles outlined in the Declaration of Helsinki.

Declarations

Authorship Contributions

Surgical and Medical Practices: G.G.A., N.A., İ.Ç., Ç.A., Concept: G.G.A., N.A., T.Y., Design: G.G.A., N.A., T.Y., Data Collection or Processing: G.T., B.S.Y., Analysis or Interpretation: G.G.A., G.T., İ.Ç., Ç.A., T.Y., Literature Search: G.G.A., B.S.Y., G.T., Writing: G.G.A., N.A.

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Original Article

Anterior Segment OCT Imaging of Bleb Morphological Changes as Predictors of Success After Bleb Needling

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Abstract

Objectives: To determine the bleb morphology and anterior segment changes after needling in trabeculectomy patients with filtration failure by anterior segment-optical coherence tomography (AS-OCT), and to identify morphological predictors of success.

Materials and Methods: Thirty-two eyes of 32 patients who underwent trabeculectomy with mitomycin C and experienced filtration failure underwent bleb needling with subconjunctival 5-fluorouracil injection. AS-OCT imaging was performed before and at several time points up to 6 months post-needling. Intraocular pressure (IOP), anterior chamber depth, and bleb height and width were measured. Complete success was defined as achieving IOP ≤19 mmHg without medication, and qualified success as IOP ≤19 mmHg with medication at 6 months.

Results: The mean age of the patients was 61.7±7.8 years (range, 44-76), and the mean interval between trabeculectomy and needling was 6.6±6.1 months (range, 1-26). IOP was 27.70±5.11 mmHg preoperatively (preop), 18.32±7.51 mmHg at 1 month, and 20.90±7.03 mmHg at 6 months. The decrease in IOP was statistically significant (p=0.015 and p=0.397, respectively). Bleb width was 3.74±0.67 mm preop, 4.16±0.55 mm at 1 month, and 3.9±0.49 mm at 6 months (p=0.001 and p=0.047, respectively). Bleb height was 0.45±0.16 mm preop, 0.41±0.11 mm at 1 month, and 0.40±0.11 mm at 6 months (p=0.812 and p=0.249, respectively). The success rate of needling was 75% at 1 month and 40.6% at 6 months. There were significant differences in age, preop IOP, and bleb height after needling between indistinct and encapsulated blebs. Choroidal effusion developed in 3 patients and resolved with medical treatment. Ahmed glaucoma valve implantation was performed in 6 patients who could not reach the target IOP.

Conclusion: AS-OCT imaging provides an objective and reproducible evaluation of bleb morphological changes after needling. Reduced bleb height, particularly in encapsulated blebs, and increased microcyst density observed on AS-OCT predict successful aqueous humor drainage. Incorporating AS-OCT assessments into clinical practice could improve postoperative management by enabling early detection of bleb dysfunction and guiding timely interventions.

Keywords: Anterior segment OCT, bleb dysfunction, needling, glaucoma, trabeculectomy

Introduction

Trabeculectomy remains the gold standard surgical approach for lowering intraocular pressure (IOP) in patients unresponsive to maximal medical therapy. Its long-term efficacy depends on the sustained function of a filtering bleb. However, postoperative scarring due to fibroblast proliferation and extracellular matrix deposition often compromises bleb functionality. Antimetabolites such as mitomycin C (MMC) and 5-fluorouracil (5-FU) are routinely used to inhibit fibrotic remodeling and enhance surgical success.[1]

Despite these adjunctive strategies, bleb failure remains a prevalent complication, particularly in eyes with encapsulated or indistinct blebs. Encapsulation has been reported in 13-29% of cases, and approximately 20% of trabeculectomy patients eventually require bleb needling revision.[2,3] Bleb needling has emerged as a minimally invasive, cost-effective outpatient intervention to restore aqueous outflow by mechanically disrupting subconjunctival fibrosis and reestablishing bleb functionality.

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Bleb morphology provides valuable insight into filtration efficacy. Conventional assessment methods, such as slit-lamp biomicroscopy and grading systems like the Indiana Bleb Appearance Grading System and Moorfields Bleb Grading System, are limited by their subjective nature and inability to visualize internal structures.[4,5] Advances in anterior segment imaging have introduced high-resolution, non-contact modalities like anterior segment optical coherence tomography (AS-OCT), which enables the detailed visualization of internal bleb morphology, including bleb height, width, microcysts, and the scleral flap.[6]

The present study aimed to use AS-OCT parameters to evaluate morphological changes in blebs after needling revision for failed trabeculectomy and identify imaging biomarkers predictive of successful treatment outcomes.

Material and Methods

Study Design and Participants

This prospective observational study included 32 eyes of 32 patients who underwent trabeculectomy with MMC (Misintu; Koçsel Pharmaceuticals, Kocaeli, Türkiye) between January 2018 and October 2023. Patient age, gender, type of glaucoma, and time between surgery and needling were recorded. Bleb filtration failure was defined clinically as elevated IOP (>19 mmHg), increased vascularization, indistinct bleb margins, subconjunctival scarring, or Tenon cyst formation (encapsulated bleb). In patients who underwent needling within the first month after trabeculectomy, the indication was either persistent filtration failure despite maximal tolerated medical therapy or early encapsulation characterized by rapid fibrotic thickening of the bleb wall. Patients with prior glaucoma drainage device implantation or insufficient follow-up were excluded. Slit-lamp examination and AS-OCT were used to classify blebs into two morphological subtypes: 1) indistinct blebs, characterized by low elevation, poorly defined margins, and minimal microcystic appearance, and 2) encapsulated blebs, which were elevated, thick-walled, well-demarcated, and hyperreflective on AS-OCT.

Needling Procedure

All patients underwent bleb needling performed under topical anesthesia (0.5% proparacaine: Alcaine; Alcon, Puurs, Belgium) in a sterile setting. A 26-gauge needle was introduced through the conjunctiva approximately 5 mm temporal to the bleb, and adhesions were dissected in multiple directions beneath the conjunctiva and over the scleral flap. Adequate filtration was confirmed when the bleb was observed to be elevated and expanded. Subsequently, 0.1 mL (5 mg) of 5-FU (Fluorouracil-Koçak 5000 mg/100 mL; Koçak Pharmaceuticals, İstanbul, Türkiye) was injected subconjunctivally in the superior quadrant (Figure 1).

Imaging and Data Collection

Data were recorded before needling (preoperative) and at 1 hour, 1 week, 1 month, and 6 months post-needling (postoperative). IOP was measured by Goldmann applanation tonometry. Anterior chamber depth (ACD) was measured by the same clinician using a Zeiss IOL Master (Carl Zeiss Meditec, Dublin, CA, USA). AS-OCT was recorded with a Heidelberg Spectralis OCT (Heidelberg Engineering Inc., Heidelberg, Germany) in a 400x400 µm scan area resolution. AS-OCT images were captured horizontally for bleb width and vertically for bleb height. The immediate post-injection period was avoided to minimize the effect of transient microcyst inflation from 5-FU. To ensure standardization, all OCT scans were obtained by the same experienced operator using a predefined imaging protocol. Baseline images were used as a reference to reproduce the scan location at each visit, and the patient's fixation was aligned identically at every examination. Bleb height and bleb width were quantified using the OCT device software. Bleb height was defined as the vertical length of the subconjunctival fluid space at the corneal base. Bleb width was defined as the horizontal length between the medial and lateral edges of the subconjunctival fluid cavity (in millimeters), including the bleb wall (Figure 2).

Reproducibility

All AS-OCT measurements were taken by a clinician masked to the IOP outcomes (A.G.). A second independent examiner (N.A.), also masked to the clinical data, repeated the measurements in a randomly selected subset of 15 eyes to evaluate interobserver reliability. Intraobserver reproducibility was assessed by repeating measurements twice at an interval of one month. Intraclass correlation coefficients (ICCs) were calculated to determine both intraobserver and interobserver reliability.

Definition of Success

In this study, surgical success was defined using a target IOP cutoff of ≤19 mmHg, which was selected as a stricter and more clinically relevant threshold than commonly used values. This cutoff aligns with the clinical practice of aiming to maintain IOP within the high teens, particularly in early- to moderate-stage glaucoma, as suggested by recent staging-oriented guidelines.[7] Complete success was defined as achieving an IOP ≤19 mmHg without medication at 6 months. Qualified success was defined as achieving IOP ≤19 mmHg with glaucoma medication. Failure was defined as IOP >19 mmHg despite treatment or the need for additional glaucoma surgery. The final success rate was calculated as the proportion of patients who achieved the target IOP without needing medication at 6-month follow-up relative to the total number of patients.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ondokuz Mayis University Clinical Research Ethics Committee (approval number: OMÜ KAEK 2023/116, date: 27.04.2023). Although the study protocol was registered and approved by the institutional review board as a retrospective observational study, data collection was performed prospectively. Ethical approval for the analysis of patient data was obtained during the data collection period.

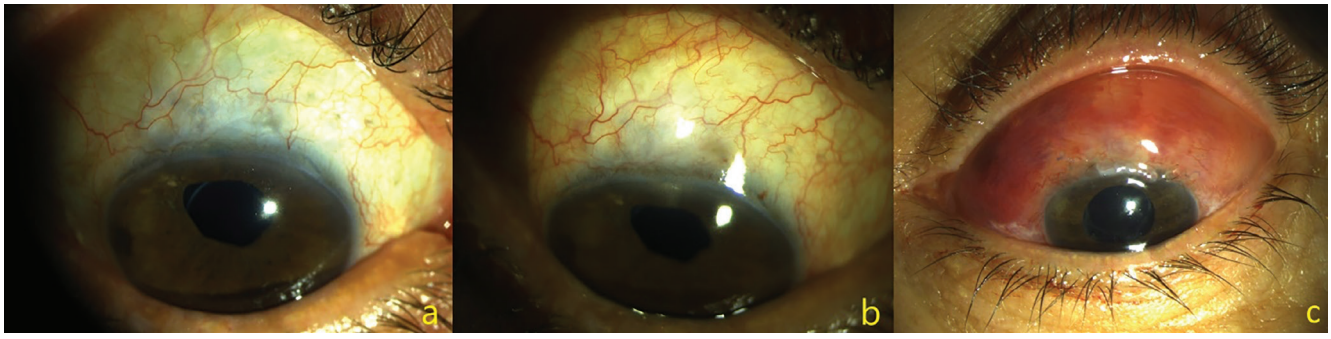

Figure 1. a) Appearance of an indistinct bleb before needling. b) Five days after needling, there is bleb elevation due to aqueous humor outflow. c) Appearance of the bleb 1 hour after needling. Aqueous humor outflow and subconjunctival injection of 5-fluorouracil resulted in diffuse bleb dilatation. The anterior chamber volume was preserved

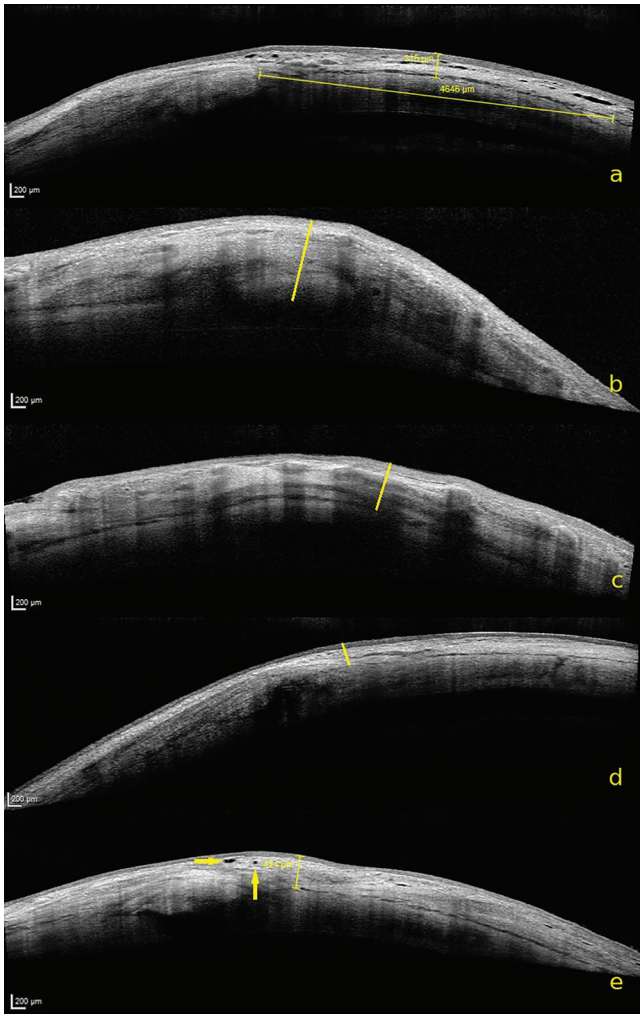

Figure 2. Measuring bleb height and width in micrometers with AS-OCT (yellow lines). The vertical distance based on the sclera indicates the bleb height. a) Bleb width was determined as the horizontal distance between the two edges of the bleb wall, which contained significant cysts. b) Encapsulated bleb before needling. c) Encapsulated bleb after needling. d) Indistinct bleb before needling. e) Indistinct bleb after needling. Note the decrease in postoperative height in the encapsulated bleb (yellow lines) and increase in postoperative height and number of microcysts (arrows) in the indistinct bleb

AS-OCT: Anterior segment-optical coherence tomography

Written informed consent was obtained from all participants prior to enrollment and before any study-related procedures.

Statistical Analysis

All statistical analyses were performed using the SPSS 26 statistical program (Armonk, NY: IBM Corp). No formal sample size calculation was performed; this was an exploratory prospective observational study. The clinical and bleb morphology parameters before and after needling were compared between indistinct and encapsulated blebs using the independent samples t-test and the Mann-Whitney U test. Dependent groups were compared using the Wilcoxon signed-rank test and paired samples t-test. For repeated measurements across time points, repeated-measures analysis of variance (ANOVA) or Friedman test for non-parametric data was additionally applied to account for intra-subject variability. Categorical variables were analyzed using Pearson's chi-square test. A value of $p<0.05$ was considered significant.

Results

The mean age of the study participants (15 females, 17 males) was 61.1±7.8 years (range, 44-76). Glaucoma subtypes included primary open-angle glaucoma (n=11), pseudoexfoliative glaucoma (n=8), narrow-angle glaucoma (n=4), uveitic glaucoma (n=6), and glaucoma secondary to intravitreal silicone oil (n=3). The mean interval between trabeculectomy and bleb needling was 6.6±6.1 months (range, 1-26). All patients had uncontrolled IOP despite maximal medical therapy before the needling procedure. Seventeen patients presented with indistinct blebs, while 15 had encapsulated blebs. Eleven patients had early filtration failure (≤3 months), and 21 had late filtration failure (>3 months) (Table 1).

The mean IOP significantly decreased from 27.7±5.11 mmHg preoperatively to 11.61±6.13 mmHg postoperatively, then gradually increased to 20.9±7.03 mmHg at 6 months. According to Friedman's test, the overall difference in IOP across time points was statistically significant ($p=0.001$). Pairwise comparisons with Bonferroni correction revealed significant reductions in IOP from preoperative to postoperative 1 hour, 1 week, and 1 month ($p<0.05$), whereas the difference between preoperative and 6-month values was not statistically significant

(p=0.397) (Figure 3). The success rate was 75% at 1 month and 40.6% at 6 months post-needling.

Regarding measurement reproducibility, intra-observer ICCs for AS-OCT were 0.969 for bleb height and 0.920 for bleb width. Inter-observer ICCs were 0.988 for bleb height and 0.943 for bleb width.

The mean ACD was 3.26±0.57 mm preoperatively and decreased to 2.90±0.44 mm postoperatively. Repeated-measures ANOVA revealed a significant overall change in ACD over time (p=0.001). Post-hoc pairwise analysis showed a significant reduction at postoperative 1 hour compared to baseline (p=0.001) but no significant differences at later follow-up visits (all p>0.05) (Table 1).

AS-OCT analysis showed a significant increase in bleb width, from 3.74±0.67 mm preoperatively to 3.90±0.49 mm at 6 months. Friedman's test revealed a significant overall difference in bleb width across time points (p=0.001). Pairwise analysis indicated significant increases from baseline at postoperative 1 hour, 1 week, and 1 month (all p<0.01), and the 6-month value remained significantly higher than baseline (p=0.047).

Bleb height changed significantly, initially increasing from 0.45±0.16 mm before needing to 0.47±0.17 mm at 1 hour after needling, then gradually decreasing to 0.40±0.11 mm at 6 months (RM-ANOVA: F=3.897, p=0.021, η^2=0.140). However, post-hoc pairwise comparisons with Bonferroni correction did not reveal significant differences from baseline at any individual follow-up time point (all p>0.05). Table 1 shows the bleb height, width, ACD, and IOP values recorded at the follow-up points.

Subgroup analysis by bleb morphology revealed that patients with indistinct blebs had a significantly higher mean age than those with encapsulated blebs (65.3±5.4 vs. 56.1±7.3 years, p=0.001). Gender distribution, glaucoma subtype, and time to needling did not differ significantly between the groups. However, pre-needling IOP was lower in the indistinct bleb group (24.73±3.22 mmHg) compared to the encapsulated bleb group (30.67±4.78 mmHg, p=0.001). Post-needling IOP values were similar between groups at all time points.

The success rate was slightly higher in the indistinct bleb group than in the encapsulated bleb group (82.4% vs. 66.7% at 1 month; 41.2% vs. 40.0% at 6 months). Bleb height was consistently greater in encapsulated blebs across all time points (Table 2).

Table 3 demonstrates that preoperative IOP correlated significantly with bleb height (r=0.59, p=0.002) and width (r=0.42, p=0.036). No significant correlations were observed at postoperative 1 hour or 1 month. At 6 months, IOP was negatively correlated with bleb width (r=-0.52, p=0.010), while the correlation with bleb height was not significant.

Choroidal effusion developed in three patients on the fifth postoperative day and resolved with medical therapy. Six patients who failed to achieve target IOP despite needling and adjunctive medical therapy subsequently underwent Ahmed glaucoma valve implantation.

Discussion

Trabeculectomy remains the cornerstone surgical technique for effectively lowering IOP in glaucoma patients unresponsive to medical or laser therapies.[8] The long-term success of trabeculectomy primarily depends on the sustained function of the filtering bleb, which can be compromised by subconjunctival fibrosis. Antimetabolites such as MMC and 5-FU are widely used to suppress postoperative scarring and maintain bleb

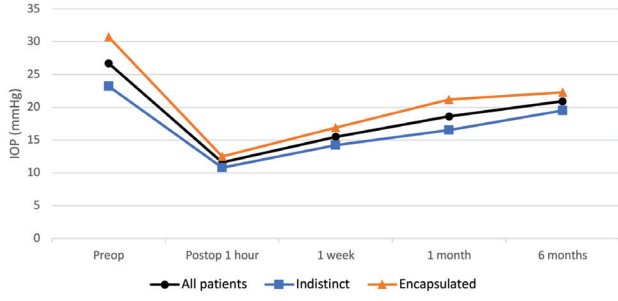

Figure 3. Intraocular pressures (IOP) according to follow-up times

Table 1. Comparison of bleb parameters, anterior chamber depth, and intraocular pressure changes during follow-up compared to baseline

Variables	Preop	Postop 1 hour	Postop 1 week	Postop 1 month	Postop 6 months	p
IOP	27.70±5.11	11.61±6.13	15.55±8.2	18.65±7.51	20.9±7.03	**0.001[a]**
p[b]		**0.015**	**0.001**	**0.015**	0.397	
ACD (mm)	3.26±0.57	2.90±0.44	3.24±0.59	3.52±0.5	3.24±0.41	**0.001[a]**
p[b]		0.726	0.998	0.159	0.988	
Bleb width (mm)	3.74±0.67	4.30±0.88	4.29±0.60	4.16±0.55	3.90±0.49	**0.001[a]**
p[b]		**0.001**	**0.006**	**0.001**	**0.047**	
Bleb height (mm)	0.45±0.16	0.47±0.17	0.43±0.13	0.41±0.11	0.40±0.11	**0.021[c]**
p[d]		0.989	0.999	0.812	0.249	

Statistically significant results (p<0.05) are indicated in bold. [a]Friedman's test, comparison across all time points; [b]Wilcoxon signed-rank test with Bonferroni correction, pairwise comparisons to preop; [c]Repeated measures ANOVA, comparison across all time points; [d]Bonferroni-corrected t-tests, pairwise comparisons to preop. IOP: Intraocular pressure, ACD: Anterior chamber depth, Preop: Preoperative, Postop: Postoperative

functionality.[9] However, fibrosis and subsequent bleb failure can still occur despite these adjunctive treatments.

Bleb needling revision, a minimally invasive outpatient procedure, can restore aqueous humor outflow by mechanically disrupting subconjunctival adhesions beneath the bleb wall.[10,11] In our study, needling targeted adhesions over the scleral flap without penetrating the anterior chamber. AS-OCT was employed to monitor these structural changes objectively, and it demonstrated excellent reproducibility, as evidenced by the high ICCs (ICC ≥0.92).

The success rates of bleb needling vary significantly in the literature due to differences in patient populations, study methodologies, antimetabolite usage, and the criteria used to define success. In our study, the success rates at 1 and 6 months post-needling were 75% and 40.6%, respectively. Previous studies have yielded variable results, with Ewing and Stamper[12] reporting a high success rate of 91.7%, Shah et al.[13] reporting 77.7% success in pediatric patients, and Shin et al.[14] indicating a cumulative success rate of 45% at 1 year (declining to 28% at 4 years). Rotchford and King[15] observed that the success rate decreased from 64.2% at 6 months to 13% at 48 months, while Tsai et al.[16] reported success rates of approximately 70% at 6 months. The variability among these findings underscores the complexity of bleb needling outcomes and the importance of clearly defined success criteria.

The morphological characteristics of filtration blebs provide critical insights into their functional status. Functional blebs typically exhibit slight elevation, minimal conjunctival vascularization, and the presence of microcysts, whereas non-functional blebs demonstrate intense vascularization, encapsulation, and limited microcystic features.[4] In our study, encapsulated blebs consistently exhibited higher bleb heights and were associated with lower initial success rates compared to indistinct blebs. Younger patient age was significantly correlated with encapsulated blebs and poorer outcomes, aligning with prior research indicating increased fibrosis in younger individuals.[17]

Advanced imaging modalities such as ultrasound biomicroscopy, confocal microscopy, and particularly AS-OCT have transformed bleb evaluation by providing detailed and objective visualization of internal bleb structures.[18,19,20] AS-OCT is a non-contact method that provides high-resolution cross-sectional images of anterior segment structures. Leung et al.[21] classified blebs based on their OCT appearance, describing functional blebs as having fluid-filled cavities and diffuse microcysts with moderate reflectivity. Similarly, Kawana et al.[22] evaluated bleb drainage pathways, bleb wall microcysts, and the scleral flap using three-dimensional OCT imaging and described functional blebs as exhibiting a fluid-filled cavity with diffuse microcysts in the bleb wall. Guthoff et al.[23] correlated cystic elevation on AS-OCT with higher IOP and demonstrated that needling effectively reduced cyst height.

In our study, AS-OCT analysis revealed a significant increase in bleb width immediately post-needling, followed by a gradual decline. These findings reflect the transient nature of needling effects and suggest the potential need for repeated interventions. Conversely, bleb height significantly decreased, particularly in encapsulated blebs, suggesting the effective disruption of subconjunctival fibrosis and improved aqueous drainage. Persistently elevated bleb height after needling may serve as a predictor of filtration failure, thereby necessitating alternative surgical approaches such as glaucoma drainage implants.

ACD typically decreases postoperatively due to improved aqueous outflow. Although an initial decrease in ACD was observed immediately post-needling in our study, subsequent measurements showed no significant long-term change. This outcome is consistent with the findings of Lenzhofer et al.[24], who suggested that there is no direct association between ACD and surgical success.

Recent studies further support the prognostic value of AS-OCT-based morphometrics in evaluating filtering bleb function and postoperative IOP control. A 2023 study by Sun et al.[25] demonstrated that AS-OCT-derived Wuerzburg Bleb Classification System scores showed significant correlations with IOP at multiple postoperative intervals (1, 2, 3, 6, and 12 months), and that specific features such as microcyst presence were strong predictors of surgical success ($p<0.05$). Likewise, a recent cross-sectional analysis using sweptsource AS-OCT found that internal bleb reflectivity, maximal bleb height, and pixel intensity metrics effectively discriminated functioning versus failing blebs with high diagnostic accuracy (area under the curve ≥0.75).[26]

Our findings complement this emerging evidence. We observed a significant positive correlation between preoperative IOP and bleb height ($r=0.59$, $p=0.0018$) and width ($r=0.42$, $p=0.036$), suggesting that filtering blebs in eyes with higher baseline IOP are initially larger. Additionally, the negative correlation between IOP and bleb width at 6 months ($r=-0.52$, $p=0.010$) demonstrates the importance of sustained bleb patency (reflected by maintained width) for long-term IOP control. These results highlight the dynamic prognostic implications of AS-OCT-based bleb metrics and support their integration into postoperative monitoring protocols for more targeted intervention.

Study Limitations

The present study has several limitations. First, the patient cohort was heterogeneous in terms of glaucoma subtype, and the number of cases in the indistinct and encapsulated bleb groups was relatively small. Second, the inclusion of uveitic glaucoma may have introduced bias, as intraocular inflammation can alter wound healing and subconjunctival fibrosis, potentially affecting the response to needling. Nevertheless, we included these patients to better reflect the heterogeneity encountered in real-world clinical practice. Future studies with larger, more homogeneous cohorts, particularly those focusing exclusively on non-inflammatory glaucomas, are needed to clarify these effects. Additionally, further research should investigate advanced AS-OCT parameters, including bleb wall reflectivity, microcyst density, scleral flap visualization, and internal bleb architecture,

Table 2. Comparison of demographic, clinical, and morphological parameters between indistinct and encapsulated bleb types			
Variables	**Indistinct (n=17)**	**Encapsulated (n=15)**	**p value**
Age (years), mean ± SD	65.3±5.4	56.1±7.3	**0.001[a]**
Gender, n			
Female	6	9	0.162[b]
Male	11	6	
Glaucoma type, n			
Primary open-angle glaucoma	7	4	0.524[b]
PEX glaucoma	5	3	
Narrow-angle glaucoma	1	3	
Uveitic glaucoma	2	4	
Secondary to silicone oil injection	2	1	
Time to bleb dysfunction, n (%)			
Early (≤3 months)	5 (29.4)	6 (40)	0.529[b]
Late (>3 months)	12 (70.6)	9 (60)	
Time between surgery and needling (months), mean ± SD	5.7±4.4 (1-14)	7.7±7.4 (1-26)	0.711[b]
Success, n (%)			
1 month	14 (82.4)	10 (66.7)	
6 months	7 (41.2)	6 (40)	
IOP (mmHg), mean ± SD			
Preop	24.73±3.22	30.67±4.78	**0.001[a]**
Postop 1 hour	10.75±7.17	12.53±5.34	0.379[b]
Postop 1 week	14.25±7.95	16.93±8.51	0.373[a]
Postop 1 month	16.53±6.25	21.21±8.32	0.095[a]
Postop 6 months	19.47±5.40	22.33±8.31	0.305[b]
ACD (mm), mean ± SD			
Preop	3.11±0.56	3.45±0.56	0.173[b]
Postop 1 hour	2.91±0.51	2.90±0.36	0.950[a]
Postop 1 week	3.27±0.72	3.21±0.43	0.711[b]
Postop 1 month	3.59±0.54	3.45±0.47	0.719[b]
Postop 6 months	3.31±0.48	3.10±0.19	0.312[a]
Bleb width (mm), mean ± SD			
Preop	3.74±0.84	3.75±0.47	0.975[a]
Postop 1 hour	4.49±1.12	4.10±0.49	0.211[a]
Postop 1 week	4.32±0.68	4.27±0.55	0.822[a]
Postop 1 month	4.21±0.65	4.11±0.43	0.909[b]
Postop 6 months	4.05±0.57	3.75±0.51	0.182[a]
Bleb height (mm), mean ± SD			
Preop	0.34±0.09	0.59±0.13	**0.001[b]**
Postop 1 hour	0.40±0.17	0.56±0.14	**0.001[b]**
Postop 1 week	0.38±0.12	0.50±0.12	**0.002[b]**
Postop 1 month	0.37±0.12	0.45±0.11	**0.017[b]**
Postop 6 months	0.34±0.05	0.48±1.07	**0.001[b]**

Statistically significant results ($p<0.05$) are indicated in bold. [a]Independent samples t-test, [b]Mann-Whitney U test, [c]Chi-square test. IOP: Intraocular pressure, PEX: Pseudoexfoliative, ACD: Anterior chamber depth, Preop: Preoperative, Postop: Postoperative

Table 3. Correlation between intraocular pressure and bleb morphological parameters at different time points (Pearson correlation analysis)

IOP		Bleb height	Bleb width
Preop	r	0.59	0.42
	p	**0.002**	**0.036**
Postop 1 hour	r	0.22	0.08
	p	0.254	0.674
Postop 1 week	r	-0.18	-0.05
	p	0.361	0.801
Postop 6 months	r	-0.31	-0.52
	p	0.118	**0.010**

Statistically significant results ($p<0.05$) are indicated in bold. IOP: Intraocular pressure, Preop: Preoperative, Postop: Postoperative

to establish their value as predictive biomarkers for bleb function and needling success.

Conclusion

AS-OCT imaging provides objective and reproducible insights into morphological bleb changes after needling. In our study, reduced bleb height (particularly in encapsulated blebs) and increased bleb width were associated with improved aqueous outflow and short-term procedural success. Incorporating AS-OCT into postoperative follow-up may help predict bleb functionality, identify early signs of failure, and guide timely re-intervention, ultimately improving long-term surgical outcomes.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ondokuz Mayis University Clinical Research Ethics Committee (approval number: OMÜ KAEK 2023/116, date: 27.04.2023).

Informed Consent: Informed consent was obtained from all subjects prior to their participation in the study.

Declarations

Authorship Contributions

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

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

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Original Article

Comparison of Microvascular and Electrophysiological Findings of Normal-Tension Glaucoma and Chronic Non-Arteritic Ischemic Optic Neuropathies

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Abstract

Objectives: To compare microvascular alterations in the optic nerve head between non-arteritic anterior ischemic optic neuropathy (NAION) and normal-tension glaucoma (NTG) and assess the correlation between vascular density (VD) and pattern electroretinography (PERG) changes.

Materials and Methods: Patients with NTG and NAION underwent comprehensive ophthalmologic examinations, including optic coherence tomography angiography and PERG imaging. Demographic and clinical data were collected, and groups were matched for age, intraocular pressure, mean deviation, and global retinal nerve fiber layer thickness.

Results: The study included 25 eyes from the NAION group, 24 eyes from the NTG group, and 30 eyes from the control group. VD was significantly lower in the peripapillary, inferior hemi, inferior temporal, and temporal inferior regions in NAION patients compared to NTG patients (p=0.004, p=0.003, p=0.002, p=0.006, respectively). Analysis of PERG parameters revealed that the P50 amplitudes in both NAION and NTG patients were lower than those in the control group (p=0.001, p=0.012, respectively). A statistically significant difference between the NAION and NTG groups was observed only in N95 amplitude (p=0.035). N95 amplitude emerged as the most sensitive discriminator, while inferior temporal VD was the most specific discriminator. VD correlated with P50 latency, P50 amplitude, and N95 amplitude (p<0.050 for all).

Conclusion: Our findings highlight the diagnostic value of peripapillary vessel density and PERG parameters in distinguishing NAION from NTG. The observed correlations between PERG and VD suggest a complementary role for these measures in evaluating retinal ganglion cell function and microvascular alterations.

Keywords: Non-arteritic ischemic optic neuropathy, normal-tension glaucoma, optic coherence tomography angiography, pattern electroretinogram

Introduction

Glaucoma and non-arteritic anterior ischemic optic neuropathy (NAION) are the two most common causes of irreversible optic nerve damage. NAION is characterized by sudden vision loss and optic disc edema during the acute phase, which progresses to a chronic phase marked by optic disc pallor and thinning of the retinal nerve fiber layer (RNFL).[1] NAION has been associated with decreased blood flow in the short posterior ciliary artery, the primary vessel supplying the optic nerve head (ONH).[2] Normal-tension glaucoma (NTG) differs from other types of glaucoma in both its pathophysiological and clinical characteristics. Although the cause remains a subject of debate, it is suggested that chronic retinal ganglion cell loss in NTG occurs in conjunction with reduced perfusion of the ONH.[3,4] Although the mechanisms of retinal nerve fiber damage in NAION and NTG differ, detecting the underlying cause of damage during the chronic period can be difficult. Both optic disc changes and visual field alterations may mimic each other.

Recently, optical coherence tomography angiography (OCTA) has found increasing utility as a non-invasive method enabling observation of capillary circulation in the peripapillary

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region. Several studies using OCTA have demonstrated a decrease in vascular density (VD) in patients with NAION and open-angle glaucoma when compared to normal subjects.[5,6,7,8] Pattern electroretinography (PERG) is a sensitive method for evaluating retinal ganglion cell function. It has been observed that PERG amplitudes are reduced in NAION and NTG compared to normal subjects, indicating retinal ganglion cell damage in both NAION and NTG.[9,10]

The study aims to identify and compare the microvascular changes occurring in the ONH in NAION and NTG, as well as to determine the correlation between VD and PERG changes.

Materials and Methods

Patients diagnosed with NTG and NAION at a tertiary eye care center between May and October 2022 were included in this prospective cross-sectional study. The study was conducted in accordance with the Helsinki Declaration after obtaining approval from the Balıkesir University Faculty of Medicine Ethics Committee (decision number: 2022/101, date: 28.09.2022). Written informed consent was obtained from all patients.

All patients underwent a comprehensive ophthalmologic examination, including assessment of best corrected visual acuity (BCVA) using a Snellen chart, measurement of intraocular pressure with Goldman applanation tonometry, slit-lamp biomicroscopic examination, measurement of central corneal thickness, and dilated fundus examination. Additionally, all patients underwent standard automated perimetry (Humphrey visual field analyzer, Carl Zeiss Meditec, Dublin, CA, 24-2 Swedish Interactive Threshold Algorithm Standard Strategy), RNFL thickness measurement by optical OCT (AngioVue, Optovue Inc., Fremont, CA), OCTA (AngioVue, Optovue Inc., Fremont, CA) for peripapillary angiography, and PERG measurements (Monpack One, Metrovision, France).

Inclusion criteria for the study were as follows: spherical equivalent between -6.0 diopters (D) and +3 D, cylindrical equivalent <2 D, axial length <25 mm, presence of open angles on gonioscopy, and at least two reliable visual field tests. Exclusion criteria included systemic medication use, history of antiglaucoma medication use prior to NTG diagnosis, presence of pathologies causing media opacity (e.g., cataract, vitreous hemorrhage), and history of intraocular surgery.

A diagnosis of NTG was established in patients with compatible glaucomatous defects in the optic disc, visual field, and open anterior chamber angles, with intraocular pressure measurements on different days <18 mmHg. NAION diagnosis was defined by sudden painless vision loss, optic disc edema, presence of compatible visual field defects, and exclusion of arteritic causes. Patients with chronic phase NAION, defined as occurring at least 6 months after resolution of optic disc edema, were included in the study.

The healthy control group consisted of volunteers who did not have any ocular symptoms, no history of intraocular surgery, intraocular pressure <18 mmHg, and no visual field defects. The NTG, NAION, and control groups were matched based on age, intraocular pressure, mean deviation (MD), and global RNFL thickness. Matching was performed within ±5 years for age, ±1 mmHg for intraocular pressure, ±1 dB for MD, and ±15 µm for global RNFL thickness.

All participants underwent OCTA imaging of the peripapillary region using a 4.5x4.5 mm^2 scan pattern (Figure 1). The operational mechanism of the device has been explained elsewhere.[11] VD was calculated as the ratio of the area covered by small vessels extending from the optic disc boundary within a 1000 µm-wide elliptical area to the total area. Segmentation of the device was based on the area between the inner limiting membrane and the posterior boundary of the RNFL. VD was measured inside the disc as a whole and in the peripapillary region, the superior and inferior hemifields, and the nasal superior, nasal inferior, inferior nasal, inferior temporal, temporal inferior, temporal superior, superior nasal, and superior temporal sectors. Peripapillary RNFL thickness was also measured using the same device. We selected only images with a scanning quality of more than 7 and no motion-related artifacts.

PERG recordings were obtained in a room isolated from magnetic fields and sound. Briefly, electrical responses were

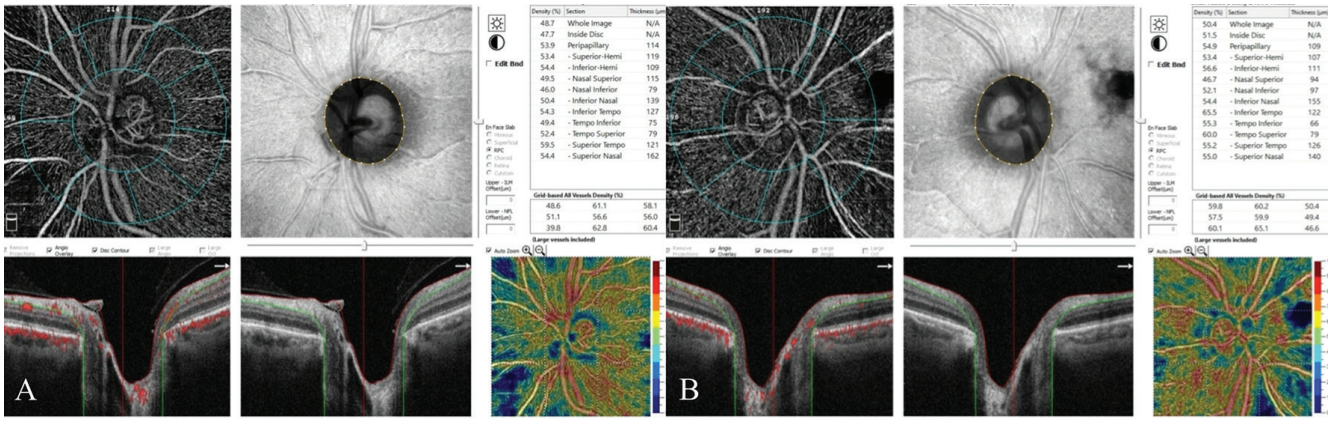

Figure 1. Representative optical coherence tomography angiography and optic nerve head (ONH) analysis outputs from (A) a patient with non-arteritic anterior ischemic optic neuropathy and (B) a patient with normal-tension glaucoma. Peripapillary vessel density and peripapillary retinal nerve fiber layer thickness were evaluated in the peripapillary annulus and inside-disc region, across 8 sectors, and in the superior/inferior hemifields using the ONH analysis software (Angio DiscVue)

recorded using five Dawson-Trick-Litzkow electrodes: one electrode for each eye was attached to the lower eyelid to face the cornea, and two reference electrodes were attached to the outer canthi of both eyes. A grounding electrode was placed on the forehead. We conducted the test under scotopic conditions at a distance of 30 cm, following 2 minutes of light adaptation under binocular vision with near-distance correction. Participants were instructed to focus on a red spot located at the center of a chessboard pattern displayed on the screen, and four PERG recordings were obtained for each eye and averaged. We expressed the results as a graph containing recorded electrical responses and analytical data about selected peak amplitudes. Amplitudes and latencies were recorded for the N35, P50, and N95 waves (peaks). Further details were provided in a separate study.[12]

Statistical Analysis

Normal distribution of the data was assessed using the Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation for normally distributed variables and as number and percentage for categorical variables. Categorical data were analyzed using the chi-square test, while continuous variables were evaluated using one-way analysis of variance (ANOVA). Group differences were further assessed using Tukey's post-hoc multiple comparison test. Correlations between parameters were analyzed using Pearson's correlation coefficient. The discriminative ability of various parameters for group differentiation was evaluated using receiver operating characteristic (ROC) analysis. All statistical analyses were performed using SPSS 25.0 software, with a p value of <0.05 considered statistically significant.

Results

The study included 30 eyes each from the NAION, NTG, and control groups. Five patients from the NAION group and six patients from the NTG group were excluded from the study due to inability to match RNFL thicknesses and visual field MD values. Table 1 presents the demographic and clinical characteristics of the participants. There were no significant differences between the groups in terms of age, gender, intraocular pressure, and MD (p>0.05).

The optic disc parameters of OCTA are shown in Table 2. VD was lower in NAION patients compared to the healthy control group in all regions except the inside disc (p<0.05). In NTG patients, VD was lower than in controls in all regions except for inside disc, inferior temporal, and temporal inferior values (p<0.05). Peripapillary, inferior hemifield, inferior temporal, and temporal inferior VD was lower in NAION patients than in NTG patients (p=0.004, p=0.003, p=0.002, p=0.006, respectively).

Upon examination of the PERG characteristics across the groups, the P50 amplitudes in NAION and NTG patients were significantly lower than those in the control group (p=0.001, p=0.012, respectively). There was a statistically significant difference between the NAION and NTG groups only in N95 amplitude (p=0.035). Table 3 presents the PERG results between groups.

Table 1. Demographic and clinic features of patients with NAION, NTG, and healthy eyes

	NAION group (n=25)	NTG group (n=24)	Healthy group (n=30)	p value
Age (years)	59.68±11.49	60.33±8.75	59.93±8.10	0.971
Gender, female, n (%)	15 (60)	16 (66.7)	17 (56.7)	0.753
BCVA (logMAR)	0.54±0.34	0.35±0.41	0.03±0.05	p^a=0.079 p^b<0.001 p^c<0.001
CCT (µm)	534.44±31.96	495.08±25.46	550.27±22.47	p^a<0.001 p^b=0.079 p^c<0.001
VF MD (dB)	-5.70±1.97	-5.20±2.77	-0.87±2.93	p^a=0.639 p^b<0.001 p^c<0.001
IOP (mmHg)	14.88±2.18	14.58±2.02	15.50±1.77	p^a=0.861 p^b=0.485 p^c=0.218
Cup to disc ratio	0.38±0.08	0.39±0.07	0.34±0.09	p^a=0.885 p^b=0.269 p^c=0.111
RNFL thickness, average (µm)	83.84±4.78	82.41±7.66	100.03±3.99	p^a=0.646 p^b<0.001 p^c<0.001

p^a: NAION vs. NTG, p^b: NAION vs. healthy group, p^c: NTG vs. healthy group
NAION: Non-arteritic ischemic optic neuropathy, NTG: Normal tension glaucoma, BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, CCT: Central corneal thickness, VF: Visual field, MD: Mean deviation, IOP: Intraocular pressure, RNFL: Retinal nerve fiber layer

Table 4 shows the significant discriminators of NAION and NTG according to ROC analysis. The most sensitive discriminator was N95 amplitude, and the most specific discriminator was inferior temporal VD.

The correlation analysis between N35, P50, and N95 parameters (latency and amplitude) and VD is shown in Table 5. The results include the whole image, inside disc, peripapillary, upper and lower hemifields, and different nasal and temporal regions. We did not obtain any statistically significant results for N35 latency, amplitude, or N95 latency across any regions. P50 latency had significant negative correlations with multiple regions. In the superior nasal, inferior nasal, inferior temporal, inferior temporal, and superior nasal regions, P50 latency showed a statistically significant negative correlation ($p<0.050$ for all). These results indicate that increasing latency is associated with reduced values in these regions. Various regions showed a positive correlation with the P50 amplitude. The highest positive correlation was in the superior hemifield ($r=0.249$, $p=0.027$). N95 amplitude showed significant negative correlations in several regions. The peripapillary region exhibited the strongest significant negative correlation ($r=-0.309$, $p=0.006$).

Table 2. Comparison of peripapillary vascular density between groups

	NAION group (n=25)	NTG group (n=24)	Healthy group (n=30)	p value
Whole image (%)	41.90±6.51	44.80±6.16	50.97±2.39	p^a=0.132 p^b<0.001 p^c<0.001
Inside disc (%)	49.84±5.26	51.77±4.36	52.23±3.84	p^a=0.295 p^b=0.129 p^c=0.927
Peripapillary (%)	40.21±7.36	46.15±7.98	52.92±2.52	**p^a=0.004** p^b<0.001 p^c<0.001
-Superior hemi (%)	41.70±9.04	44.95±8.72	53.06±2.87	p^a=0.262 p^b<0.001 p^c<0.001
-Inferior hemi (%)	42.56±9.01	47.58±7.93	52.62±2.42	**p^a=0.003** p^b<0.001 p^c=0.024
Nasal superior (%)	40.26±11.99	44.10±7.94	50.88±3.38	p^a=0.244 p^b<0.001 p^c=0.011
Nasal inferior (%)	40.44±12.46	42.55±8.21	49.13±3.74	p^a=0.671 p^b=0.001 p^c=0.019
İnferior nasal (%)	44.76±10.08	46.73±9.76	52.53±4.58	p^a=0.684 p^b=0.003 p^c=0.034
İnferior temporal (%)	44.24±11.68	53.60±10.49	57.82±4.12	**p^a=0.002** p^b<0.001 p^c=0.216
Temporal inferior (%)	43.17±10.15	49.38±5.53	53.63±3.87	**p^a=0.006** p^b<0.001 p^c=0.069
Temporal superior (%)	43.79±8.08	47.74±11.81	56.15±3.43	p^a=0.218 p^b<0.001 p^c=0.001
Superior temporal (%)	41.87±9.83	45.69±12.01	55.07±3.94	p^a=0.301 p^b<0.001 p^c=0.001
Superior nasal (%)	39.76±13.31	41.13±10.22	51.60±5.51	p^a=0.880 p^b<0.001 p^c=0.001

p^a: NAION vs. NTG, p^b: NAION vs. healthy group, p^c: NTG vs. healthy group
NAION: Non-arteritic ischemic optic neuropathy, NTG: Normal tension glaucoma

Table 3. Comparison of pattern electroretinogram parameters between groups

	NAION group (n=25)	NTG group (n=24)	Healthy group (n=30)	p value
N35 latency (ms)	29.12±10.38	28.34±14.42	25.07±5.31	p^a=0.962 p^b=0.325 p^c=0.488
N35 amplitude (mV)	-0.13±1.11	-0.31±0.71	-0.39±0.96	p^a=0.791 p^b=0.101 p^c=0.360
P50 latency (ms)	56.84±10.83	55.65±10.03	53.99±6.34	p^a=0.892 p^b=0.483 p^c=0.783
P50 amplitude (mV)	3.56±1.22	4.05±1.39	5.63±2.67	p^a=0.652 **p^b=0.001** **p^c=0.012**
N95 latency (ms)	100.72±10.66	94.89±16.58	94.95±15.37	p^a=0.341 p^b=0.310 p^c=0.998
N95 amplitude (mV)	-2.05±3.06	-4.12±1.60	-5.19±3.41	**p^a=0.035** **p^b<0.001** p^c=0.368

p^a: NAION vs. NTG, p^b: NAION vs. healthy group, p^c: NTG vs. healthy group
NAION: Non-arteritic ischemic optic neuropathy, NTG: Normal tension glaucoma

Table 4. Differentiation of NAION and NTG according to ROC analysis

	Cut-off point	AUC	95% CI	Sensitivity (%)	Specificity (%)	p value
Peripapillary VD (%)	44.2	0.724	0.578-0.871	70.8	72	0.007
Inferior hemi VD (%)	43.6	0.668	0.516-0.819	75	56	0.044
Inferior temporal VD (%)	54.75	0.731	0.587-0.874	66	80	0.006
Temporal inferior VD (%)	47.80	0.715	0.570-0.860	66	68	0.010
N95 amplitude (mV)	-5.25	0.272	0.127-0.417	75	12	0.006

NAION: Non-arteritic ischemic optic neuropathy, NTG: Normal tension glaucoma, ROC: Receiver operating characteristic, VD: Vascular density, CI: Confidence interval

Table 5. Correlation between vascular density and pattern electroretinography parameters

	N35 latency (ms)		N35 amplitude (mV)		P50 latency (ms)		P50 amplitude (mV)		N95 latency (ms)		N95 amplitude (mV)	
	r	p	r	p	r	p	r	p	r	p	r	p
Whole image (%)	-0.175	0.123	-0.189	0.094	-0.231	**0.040**	0.226	**0.045**	-0.070	0.542	-0.259	**0.021**
Inside disc (%)	0.037	0.745	-0.114	0.319	0.138	0.237	0.175	0.124	0.074	0.517	-0.001	0.923
Peripapillary (%)	-0.089	0.436	-0.204	0.071	-0.216	0.055	0.221	**0.050**	-0.116	0.308	-0.309	**0.006**
-Superior hemi (%)	-0.164	0.148	-0.176	0.120	-0.232	**0.040**	0.249	**0.027**	-0.110	0.335	-0.212	0.061
-Inferior hemi (%)	-0.098	0.363	-0.190	0.093	-0.271	**0.016**	0.183	0.106	-0.071	0.533	-0.228	**0.043**
Nasal superior (%)	-0.141	0.214	-0.178	0.216	-0.278	**0.013**	0.223	**0.049**	-0.048	0.672	-0.293	**0.009**
Nasal inferior (%)	-0.118	0.299	-0.150	0.187	-0.255	**0.023**	0.124	0.278	-0.063	0.580	-0.229	**0.042**
Inferior nasal (%)	-0.054	0.635	-0.175	0.122	-0.186	0.101	0.092	0.420	-0.011	0.922	-0.166	0.143
Inferior temporal (%)	-0.094	0.409	-0.161	0.157	-0.263	**0.019**	0.239	**0.034**	-0.083	0.468	-0.225	**0.047**
Temporal inferior (%)	-0.119	0298	-0.183	0.107	-0.250	**0.026**	0.190	0.094	-0.20	0.863	-0.210	0.063
Temporal superior (%)	-0.175	0.122	-0.096	0.399	-0.215	0.057	0.236	**0.037**	-0.135	0.237	-0.106	0.354
Superior temporal (%)	-0.158	0.164	-0.088	0.441	-0.129	0.259	0.235	**0.037**	-0.076	0.507	-0.151	0.185
Superior nasal (%)	-0.148	0.194	-0.199	0.079	-0.225	**0.046**	0.190	0.094	-0.068	0.552	-0.133	0.241

Discussion

This study revealed that N95 amplitude decreased more significantly in the NAION group than in the NTG group. A significant reduction in VD was seen, particularly in the inferior region of the peripapillary area. Furthermore, we identified a statistically significant association among N95 amplitude, P50 amplitude, P50 latency, and VD. Our findings indicate that NAION and NTG can be differentiated by a decrease in VD.

Decreased perfusion is a well-established factor in the pathophysiology of both NTG and NAION, with several studies showing reduced perfusion in both conditions.[13,14] In line with previous research, our study confirmed a decrease in VD in both NAION and NTG when compared to the control group. In NAION, the short posterior ciliary artery, which supplies the ONH, is the primary artery affected during the acute phase. In NTG, one of the strongest hypotheses suggests that retinal ganglion cell damage occurs due to chronically decreased blood flow in the ONH. OCTA studies that compared NAION and NTG found that NAION had a bigger decrease in peripapillary VD.[5,6] Our results support this observation. A few studies, however, have claimed that the reduction in peripapillary VD is greater in NTG and primary open-angle glaucoma.[7,8] This disparity may be due to differences in RNFL thickness between groups in one study and the fact that the primary open-angle glaucoma group in the other study was receiving antiglaucoma treatment. Patients receiving beta-blocker therapy may also experience significant changes in VD and blood flow due to RNFL thickness. Kim et al.[6] compared VD in NTG and NAION and found that in NTG, VD was lower at the prelaminar tissue and lamina cribrosa levels, while in NAION, it was lower at the peripapillary level, but this difference was not statistically significant. The evidence suggests that peripapillary region involvement increases as NAION progresses into the chronic phase. The short posterior ciliary artery supplies both the prelaminar ONH and parapapillary choroid. Ischemic damage to these areas stops the transport of axons and causes retinal ganglion cell damage that worsens over time. As ischemic damage persists, the reduction in VD may spread across all quadrants. Shin et al.[5] found a significant reduction in VD in NAION patients compared to NTG patients, particularly in the temporal region. They also saw that the choroidal microvascular dropout area was bigger in NAION patients, with more involvement in the temporal area in NAION patients and less involvement in NTG patients.[5] Similarly, Liu et al.[15] reported lower peripapillary VD in NAION compared to POAG across all quadrants except the inferior quadrant. In our study, VD in the temporal quadrant was significantly lower in NAION compared to NTG.

Electrophysiological tests provide important insights into diseases affecting the optic nerve and retinal ganglion cells. Both glaucoma and NAION patients have reported decreases in PERG parameters, particularly P50 and N95 amplitudes.[9,10] Research indicates that PERG signals represent nerve injury and become compromised when macular ganglion cells are injured.[16,17,18] Several studies have examined the relationship between PERG and OCTA, with correlations identified between PERG and VD in the macular and peripapillary regions.[18,19,20] In our study, we identified correlations between N95 amplitude, P50 amplitude, P50 latency, and VD. The correlations between P50 and N95 amplitudes and macular VD in the normal and early NTG groups suggests that these metrics may serve as indicators of retinal ganglion cell functionality prior to significant impairment.[18] A similar interpretation may be applicable to NAION patients. Our findings suggest that differences in N95 amplitudes may aid in differentiating NAION from NTG patients. Although we matched the groups for age, IOP, global MD, and peripapillary RNFL thickness and restricted analyses to untreated NTG and chronic-phase NAION (≥6 months post-edema resolution) to minimize acute-phase effects, disease stage may still influence OCTA-derived peripapillary VD and PERG measurements. More advanced structural and functional loss, such as lower BCVA in NAION, is likely correlated with increased capillary loss and diminished PERG amplitudes. In contrast, earlier NTG may exhibit more subtle changes, potentially obscuring or amplifying intergroup differences despite matched MD.

Study Limitations

The most significant limitation of our study is the small sample size, which was required due to the need to match RNFL thickness and visual field parameters among groups. This standardization allowed for a more accurate comparison of VD changes. Another limitation was the inclusion of only patients with sufficient visual acuity to ensure optimal image quality in the imaging tests. Additionally, we were unable to include patients with advanced retinal nerve fiber damage, as we focused on newly diagnosed NTG patients before the initiation of antiglaucoma treatment. Consistent with the study's hypothesis, the matching of NAION and NTG patients based on MD, as well as the generally mixed visual field patterns of the current NAION patients, precluded an investigation into the relationship between peripapillary VD and visual field pattern. This relationship warrants investigation in a pre-specified, adequately powered study focused solely on NAION, incorporating a larger sample size and including all NAION patients. Nevertheless, the limited sample size in our matched design, certain variables (especially worse BCVA in NAION) may affect both OCTA-VD and PERG due to the basic nature of the diseases.

Conclusion

Peripapillary VD, particularly in the temporal region, provides valuable information for differentiating NAION from NTG. Changes in PERG parameters support this differentiation. There is also a significant correlation between peripapillary region VD and PERG parameters.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Helsinki Declaration after obtaining approval from the Balıkesir University Faculty of Medicine Ethics Committee (decision number: 2022/101, date: 28.09.2022).

Informed Consent: Written informed consent was obtained from all patients.

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Declarations

Authorship Contributions

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

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Original Article

Refractive Results and Complications of Lensectomy in Simple Extreme Microphthalmos Cases

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Abstract

Objectives: To evaluate the refractive outcomes, changes in intraocular pressure (IOP) and anterior chamber depth (ACD), and postoperative complications following lensectomy for angle-closure in cases of simple extreme microphthalmos.

Materials and Methods: This retrospective study analyzed eyes with simple extreme microphthalmos (axial length <18 mm) that underwent lensectomy between January 2015 and July 2024. Data collection included demographic details, preoperative and postoperative best corrected visual acuity (BCVA), IOP, number of antiglaucoma medications, ACD, the diopter (D) of the implanted intraocular lens (IOL) according to the Hoffer-Q formula, postoperative refractive error, and surgical complications.

Results: A total of 20 eyes from 12 patients were analyzed, with a mean patient age of 55.4±8.7 years and an average axial length of 16.48±0.8 mm. The average power of the implanted IOL was 53.32±6.2 D, ranging from 44 to 64 D. The mean preoperative spherical refractive equivalent (SE) was +12.4±2.8 D, while the mean postoperative SE was -6.67±5.2 D ($p<0.05$). Postoperative spherical refractive error exceeding -1.00 D was detected in 15 eyes (75%). Postoperatively, significant decreases were observed in IOP and the need for antiglaucoma medication ($p=0.02$ for both). The mean ACD increased significantly after surgery compared to the preoperative ACD ($p=0.01$). The difference between the intended refractive outcome and the postoperative spherical refractive error was statistically significant ($p<0.05$). Postoperatively, 8 eyes (40%) had a BCVA of ≤0.7 logarithm of the minimum angle of resolution (logMAR), 10 (50%) had a BCVA between >0.7 and <1.4 logMAR and 2 eyes (10%) had a BCVA of ≥1.4 logMAR.

Conclusion: Lensectomy in cases of extreme microphthalmos effectively reduces IOP and reliance on antiglaucoma medications and increases the ACD. However, a notable incidence of postoperative myopic refractive error remains a concern.

Keywords: Axial length, lensectomy, nanophthalmos

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Introduction

Microphthalmos is defined as an eye with an axial length (AL) that is at least 2 standard deviations (SDs) below the average for individuals in the same age group. This condition may involve developmental abnormalities in both the anterior and posterior segments.[1,2] Simple microphthalmos is described as an anterior chamber depth (ACD) of ≤2.2 mm and AL of ≤20.0 mm without other congenital ocular anomalies.[3,4] Nanophthalmos is a type of simple microphthalmos marked by a thickened sclera and the absence of notable systemic or ocular abnormalities.[2] Eyes with an AL shorter than 18.0 mm are described as extreme microphthalmos.[5]

With age, the lens thickens and tends to protrude into the anterior chamber, increasing the risk of angle-closure glaucoma, especially in eyes with a short AL.[6] In such cases, a lensectomy should be performed to prevent damage to the optic nerve. Eyes with microphthalmos usually require very high dioptric intraocular lenses (IOLs).[1] Performing lensectomy in these cases presents a significant challenge in ophthalmic surgery. The restricted operating area, shallow anterior chamber, and small corneal diameter can result in more complex surgical procedures and an increased risk of complications.[4,7]

Precise preoperative IOL calculations before lensectomy are crucial for achieving good visual outcomes. Advancements have been made in IOL calculation formulas, with Hoffer Q, Haigis, and Holladay II commonly used for eyes with moderately short AL, including those with nanophthalmos.[7,8] Despite advancements in IOL calculations, the effective lens position (ELP) can influence refractive outcomes, and patients with short AL often experience significant refractive deviations from emmetropia.[7] Therefore, this study aimed to assess the refractive outcomes, intraocular pressure (IOP) and ACD changes, and complications associated with lensectomy in eyes with simple extreme microphthalmos.

Materials and Methods

This retrospective study included eyes with simple extreme microphthalmos that underwent lensectomy for angle-closure at our clinic between January 1, 2015, and July 1, 2024 and had at least 6 months of follow-up. Written informed consent to use their data was obtained from all patients in accordance with the tenets of the Declaration of Helsinki. Ethical approval was received from a Hamidiye Scientific Research Ethics Committee of the University of Health Sciences, Türkiye (meeting number: 2024/8, decision number: 8/9, dated: 01.08.2024).

Inclusion criteria were lens surgery due to angle closure, age over 18 years, no history of previous intraocular surgery, and AL <18 mm. Patients with AL >18 mm, those under the age of 18, and those who had undergone previous intraocular surgery were excluded.

Data collected for each patient included sex, age, presence of glaucoma before lensectomy, preoperative best corrected visual acuity (BCVA), IOP, number of preoperative antiglaucoma medications, preoperative cup/disc ratio, preoperative keratometry values, preoperative corneal thickness, preoperative ACD and white-to-white (WTW) distance, follow-up time, implanted lens diopter (D), target refractive error according to the chosen IOL, resulting spherical refractive error, intraoperative and postoperative complications, and need for further surgery after lensectomy. Lens power was calculated preoperatively via the Hoffer Q formula, with the goal of achieving emmetropia. IOP was measured with a Goldmann applanation tonometer (AT 900, Haag Streit, Bern, Switzerland). Spherical equivalent (SE) was calculated as half of the cylindrical value added to the spherical value.

ACD was assessed using the Visante OCT, an anterior segment optical coherence tomography device (Carl Zeiss Meditec, Dublin, CA, USA). Keratometric values (K1 and K2), corneal thickness, and WTW corneal diameter were evaluated using the Sirius corneal topography and aberrometry system (Costruzioni Strumenti Oftalmici, Florence, Italy). Optical biometry was performed using a Nidek AL-Scan instrument (Nidek, Aichi, Japan).

Surgical Technique

One hour before surgery, all patients received an intravenous administration of 20% mannitol at a dose of 1 mg/kg to reduce vitreous pressure. All surgeries were performed under general anesthesia. After conducting an anterior chamber paracentesis, viscoelastic was injected, followed by a 2.6-mm clear corneal temporal incision. A pars plana core vitrectomy was performed to deepen the anterior chamber before lens removal in some cases in which the anterior chamber was too shallow. Phacoemulsification was performed using a Centurion system (Alcon Laboratories Inc, USA). IOL implantation was performed after the main incision was enlarged to allow IOL implantation. Anterior vitrectomy, synechiolysis, and capsular tension ring implantation were performed intraoperatively as indicated based on the surgical findings.

Postoperative Follow-up

Postoperative medications included topical prednisolone acetate 1% eye drops (Pred Forte; Allergan, Irvine, CA, USA) and moxifloxacin 0.5% eye drops (Moxai; Abdi İbrahim İlaç Sanayi ve Ticaret A.Ş., İstanbul, Türkiye) administered four times a day, as well as nepafenac 0.1% ophthalmic suspension (Apfecto; World Medicine İlaç Sanayi ve Ticaret A.Ş., İstanbul, Türkiye) three times a day. Antiglaucoma eye drops or oral medication were administered as needed.

Statistical Analysis

SPSS software (version 20.0®, IBM Corp., Armonk, NY) for Windows was used for all statistical computations. The distribution of variables was measured using the Shapiro-Wilk test. Descriptive statistics included the mean ± standard deviation (SD) and range or frequency and percentage values for each variable. Postoperative changes were analyzed using the dependent-samples t-test or Wilcoxon signed-rank test, depending on the distribution. $p<0.05$ was considered statistically significant.

Results

The study included 20 eyes of 12 patients (7 women [58.3%]; 5 men [41.7%]). Lensectomy was performed in 16 eyes (80%), whereas 4 eyes (20%) underwent a combined procedure consisting of lensectomy and a 23-gauge pars plana core vitrectomy to deepen the anterior chamber before lens removal. The mean age of the patients was 55.4±8.7 (35-69) years, and the mean follow-up duration was 47.25±30.71 (6-96) months. The mean AL was 16.48±0.8 (15.26-17.87) mm (Table 1).

Table 1. Baseline characteristics of the eyes

	Mean ± SD (range)
Patient age (years)	55.4±8.7 (35-69)
AL (mm)	16.48±0.8 (15.26-17.87)
CCT (µ)	567.6±30.8 (509-633)
K1 (D)	48.62±1.69 (45.85-51.66)
K2 (D)	50.08±1.98 (46.36-54.43)
WTW (mm)	10.73±0.53 (9.42-11.5)

SD: Standard deviation, K: Keratometry, AL: Axial length, CCT: Central corneal thickness, D: Diopter, WTW: White-to-white distance

Preoperative glaucoma was present in 19 out of 20 eyes (95%), the mean IOP was 19.2±6.6 mmHg, and the mean number of antiglaucoma medications used was 2.5±1.4. Postoperatively, the mean IOP was 14.2±7.7 mmHg and the mean number of medications fell to 1.4±1.4 (p<0.02 for both). The mean preoperative SE was +12.4±2.8 (+8.25 to +20.50) D. The mean power of the implanted IOL was 53.32±6.2 (44-64) D, and the mean target refractive error according to biometry was -0.42±0.3 (-0.87 to +0.12) D in all eyes. The mean postoperative SE was -6.67±5.2 (-15.00 to +0.75) D (p<0.05). A postoperative refractive error greater than -1.00 D was observed in 15 eyes (75%). Postoperative refractive error was within ±1 D in 3 eyes (15%), within ±2 D in 3 eyes (15%), within ±3 D in 2 eyes (10%), and exceeded ±4 D in 12 eyes (60%). The postoperative differences in spherical refractive error and SE were also significant (p<0.05 for both) (Table 2).

The mean preoperative BCVA was 1.16±0.50 logarithm of the minimum angle of resolution (logMAR), while the mean postoperative BCVA was 0.94±0.68 logMAR (p=0.26). Following surgery, BCVA improved in 13 eyes (65%), remained unchanged in 1 eye (5%), and declined in 6 eyes (30%). Eight eyes (40%) achieved a BCVA of ≤0.7 logMAR, 10 eyes (50%) had a BCVA between >0.7 and <1.4 logMAR, and 2 eyes (10%) demonstrated a BCVA of ≥1.4 logMAR.

IOL implantation was successfully performed in all eyes, and no posterior capsular ruptures occurred in any case. In 1 eye (5 %), iris retractors were used to maintain pupil dilation before phacoemulsification. A capsular tension ring was inserted in 3 eyes (15%) to reinforce inadequate capsular support, and posterior synechiolysis was performed in 1 eye (5%). Three eyes (15%) had postoperative choroidal effusion, 1 eye (5%) had malignant glaucoma postoperatively, and 4 eyes (20%) received diode laser cyclophotocoagulation due to IOP elevation unresponsive to medical treatment.

Discussion

Microphthalmos is a congenital ocular abnormality defined by a markedly smaller globe size and is frequently linked to early-onset cataract and angle-closure glaucoma.[4] Cataract surgery in microphthalmic eyes presents significant challenges due to the heightened risk of complications during and after the surgery. Moreover, the condition is associated with a poor visual prognosis and decreased accuracy in IOL calculations.[4]

There is no universally accepted formula for accurately calculating IOL in microphthalmos cases. The Royal School of Ophthalmologists recommends the Hoffer Q formula as the preferred method for eyes with AL shorter than 22 mm.[9] Different clinical studies have shown that the Haigis and Holladay II formulas are also acceptable for eyes with short AL.[7,1011,12,13] Newer IOL formulas such as the Kane and Olsen formulas have been developed, with some studies showing that the Kane formula is particularly suitable for microphthalmic eyes.[4,12,14] However, a meta-analysis of 15 studies comprising 2,395 eyes with short AL (≤22 mm) found no significant differences in accuracy between the Barrett Universal II, Olsen, and conventional IOL formulas such as Haigis, Hoffer Q, and SRK/T.[15] A large-scale study also showed that the Hoffer Q formula yielded the highest accuracy in eyes with an AL ≤21.50 mm, outperforming both the Holladay I and SRK/T formulas.[16] Another study evaluating the accuracy of various IOL calculation formulas—including Haigis, Hoffer Q, Holladay I, SRK/T, Barrett Universal II, and Hoffer QST—in eyes with nanophthalmos (AL <20 mm) found that the overall prediction errors tended to shift toward myopia.[17]

When the Hoffer Q formula was applied to eyes with AL shorter than 22 mm, a mean of 0.22 D myopic refractive error was observed.[18] Zheng et al.[5] evaluated the outcomes of lensectomy in both simple (n=11) and complex (n=6) extreme microphthalmos cases (AL <18 mm) and used the Hoffer-Q formula for IOL power calculation. They observed postoperative refractive errors of 5.6 D and 4.2 D in simple microphthalmos and complex microphthalmos, respectively. However, they did not mention how many of the cases had a myopic refractive error after surgery.[5] We also used the Hoffer-Q formula in our cases and observed a postoperative myopic refractive error greater than -1.00 D in 75% of cases. The mean postoperative SE was -6.67±5.2 D, with a range of -15.00 to +0.75 D.

As a third-generation formula, the Hoffer Q formula relies on the relationship between AL and corneal curvature, estimating postoperative ELP using AL and K values, based on a dataset

Table 2. Preoperative and postoperative measurements

	Preoperative Mean ± SD (range)	Postoperative Mean ± SD (range)	p value
BCVA (logMAR)	1.15±0.49 (0.3-2.3)	0.95±0.68 (0.16-3.10)	0.1
IOP (mmHg)	19.2±6.6 (11-34)	14.15±7.7 (7-41)	**0.02**
Antiglaucoma medications (n)	2.5±1.4 (0-4)	1.4±1.4 (0-4)	**0.02**
Spherical refractive error (D)	+12.63±2.9 (+8.25 to +20.50)	-5.55±5.05 (-13.00 to +1.25)	**<0.05**
Spherical equivalent (D)	+12.39±2.8 (+8.25 to +20.50)	-6.67±5.3 (-15.00 to +0.75)	**<0.05**
ACD (mm)	1.59±0.21 (1.24-1.86)	2.72±0.55 (1.68-3.62)	**0.01**

SD: Standard deviation, BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, IOP: Intraocular pressure, D: Diopter, ACD: Anterior chamber depth

from cases with posterior chamber lenses.[19] Fourth-generation formulas like Haigis and Holladay II incorporate additional biometric variables such as ACD, lens thickness, and WTW distance to refine the estimation of postoperative ELP and improve IOL power calculations.[20] As preoperative expectations regarding ELP often do not align with postoperative ELP, significant refractive deviations are frequently observed in microphthalmos cases.

In eyes with microphthalmos, the lens tends to be relatively larger and thicker, and angle closure may occur earlier compared to eyes with normal AL.[7,9] Lensectomy can alleviate lens-induced anterior chamber narrowing and help deepen the anterior chamber to avoid angle closure glaucoma.[4,7] ACD, AL, and the degree of angle closure before surgery are reported to be closely associated with the likelihood of postoperative glaucoma.[5] In our study, we observed a significant reduction in IOP and number of antiglaucoma medications after surgery. However, no significant difference was observed in postoperative BCVA. Zheng et al.[4] reported that 75% of eyes exhibited persistent low vision postoperatively, with visual acuity of 20/60 or worse, while 25% remained legally blind. The authors attributed these suboptimal visual outcomes predominantly to the high incidence of postoperative complications (16.7%) associated with cataract surgery. In our study, 60% of eyes had a BCVA greater than 0.7 logMAR. There was an improvement in BCVA, but it was not statistically significant. Postoperative complications included choroidal effusion in 15% of eyes, malignant glaucoma in 5% of eyes, and various other complications in 20% of eyes. Additionally, preoperative glaucoma was present in 95% of cases, which may account for the relatively low postoperative BCVA values.

Intra- and postoperative complications during lensectomy include damage to the corneal endothelium, temporary severe swelling of the cornea, cystoid macular edema, inflammation of the anterior uvea, uveal effusion, and malignant glaucoma.[1,7,21] Uveal effusions may develop either before or after surgery due to impaired venous outflow.[1,6] Zheng et al.[5] reported rates of 18% for choroidal effusion, 13% for malignant glaucoma, and 33% for postoperative IOP elevation. In our study, we observed choroidal effusion in 3 eyes (15%), malignant glaucoma in 1 eye (5%), and postoperative IOP elevation in 5 eyes (25%), which is consistent with previous studies.

Study Limitations

Limitations of this study include a limited sample size, the lack of a control group, and the unavailability of ultrasound biomicroscopy for postoperative assessment of effusion and lens position.

Conclusion

Our findings demonstrated that lensectomy was associated with a significant reduction in IOP and the number of antiglaucoma medications, along with a notable increase in ACD. However, postoperative myopic refractive error may occur, and improvement in BCVA may be limited due to intraoperative and postoperative complications. The Hoffer Q formula shows variability in eyes with nanophthalmos, where inaccurate prediction of the ELP can result in considerable postoperative refractive error. Patients should be informed that a myopic refractive outcome may occur following surgery.

Ethics

Ethics Committee Approval: Ethical approval was received from a Hamidiye Scientific Research Ethics Committee of the University of Health Sciences, Türkiye (meeting number: 2024/8, decision number: 8/9, dated: 01.08.2024).

Informed Consent: Written informed consent to use their data was obtained from all patients in accordance with the tenets of the Declaration of Helsinki.

Declarations

Authorship Contributions

Surgical and Medical Practices: G.G.A., N.A., N.K.B., A.K., İ.Ç., Ç.A., Concept: G.G.A., N.A., T.Y., Design: G.G.A., N.A., T.Y., Data Collection or Processing: E.D., N.K.B., A.K., E.E., Analysis or Interpretation: G.G.A., E.E., İ.Ç., Ç.A., T.Y., Literature Search: G.G.A., E.D., E.E., Writing: G.G.A., N.A.

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Review

Decision-Making in Keratoprosthesis: Navigating Device Selection in Complex Ocular Scenarios

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Abstract

Keratoprosthesis (KPro) implantation serves as a last resort for visual rehabilitation in patients with end-stage bilateral corneal blindness, particularly when conventional corneal transplantation is no longer viable. Advances in biomaterials and refinements in prosthetic design have significantly enhanced anatomical retention and visual outcomes. Among the various types available, the Boston type 1 and 2 devices and the modified osteo-odonto-KPro remain the most widely utilized globally. This review aims to support comprehensive clinical decision-making by providing an in-depth overview of the design characteristics, surgical considerations, and postoperative care protocols associated with the most widely used KPro devices. In addition, we discuss a broad range of influencing factors, including the status of the ocular surface, eyelid anatomy, tear film adequacy, underlying systemic or autoimmune diseases, and patient-related logistical and socioeconomic concerns. Special emphasis is placed on the importance of preoperative evaluation and counselling and the role of a multidisciplinary approach in achieving successful long-term outcomes. Drawing on current evidence and clinical experience, we propose a practical decision-making algorithm to aid ophthalmologists in selecting the most appropriate KPro tailored to individual patient profiles.

Keywords: Keratoprosthesis, Boston type 1, modified osteo-odonto-keratoprosthesis, MOOKP, Boston type 2, tibial keratoprosthesis

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Introduction

Keratoprosthesis (KPro) is considered as a last resort for visual rehabilitation in end-stage ocular surface disorders with bilateral corneal blindness, particularly when the risk of failure with conventional penetrating keratoplasty is high. Pellier de Quengsy first introduced the concept of a KPro using a convex glass plate with a silver rim. Although early outcomes were poor and interest declined, the discovery of polymethyl methacrylate (PMMA) as a biocompatible material reignited advancements in KPro development.[1,2]

Broadly based on the indication for use, KPros are categorized as type 1 or 2, with the choice dependent on the underlying etiology, adequacy of the preocular tear film, eyelid function, overall health of the recipient, specific expertise of the surgeon, and also the availability of the KPro. Decision-making in KPro is a critical factor in determining the final outcome. The prognosis of type 1 KPro in autoimmune disorders is generally less favorable compared to type 2, and therefore it is not typically recommended.[3,4] Selecting the appropriate type of KPro is essential for achieving the best possible prognosis and clinical outcome.

This article aims to support clinical decision-making across diverse scenarios by outlining key design features of commonly used and available KPros, assessment of ocular and systemic conditions, and consideration of other relevant factors.

Keratoprosthesis Devices and Surgical Technique

KPro devices vary in design, material, and indication. Commonly used types include the Boston type 1 and 2, modified osteo-odonto-KPro (MOOKP) and the osteo/tibial bone KPro (TBK) (Figure 1). Each device requires a tailored surgical approach depending on the ocular surface condition (Table 1).

Type 1 Keratoprosthesis

The Boston type 1 KPro (Massachusetts Eye and Ear, Boston, MA, USA) consists of two main components: a front plate (5 mm) with central optic (3.5-3.7 mm) made of PMMA, and a fenestrated back plate made of PMMA or titanium which keeps the device in place and allows aqueous humor to reach the corneal graft. A corneal graft is sandwiched between the front and back plate and enables implantation of the device into the host. Both aphakic and pseudophakic versions are available. The aphakic version is selected based on the axial length of the eye, whereas the pseudophakic comes in a standard configuration.[5,6]

The Auro and Lucia type 1 KPros are modified versions of the Boston type 1 KPro. The Aurolab KPro (AuroKPro; Aurolab, Madurai, India) closely replicates the design of the Boston KPro, comprising a PMMA optic and back plate, secured with a titanium locking ring. Like the Boston KPro, it is also available in both aphakic and pseudophakic versions.[7] The Lucia KPro (Massachusetts Eye and Ear, Boston, MA, USA) features a titanium back plate with a PMMA optic and front plate and is designed as a single-axial-length device to reduce manufacturing costs and improve affordability (Figure 2).[8]

Once assembled around the corneal donor graft, the surgical steps are the same for all these Boston KPro modifications, and require suturing of the assembled device and corneal graft as in a full-thickness penetrating keratoplasty (Figure 3). A bandage contact lens is placed over the KPro at the end of the surgery to avoid desiccation and replaced on a schedule determined by the type of contact lens and the quality of the recipient's tear film (usually every 2-3 months).

The surgical steps are as demonstrated in recent surgical videos on ocular surface surgeries.[9]

Type 2 Keratoprosthesis

The Boston type 2 KPro (Massachusetts Eye and Ear, Boston, MA, USA) shares a similar design with the type 1 Boston KPro, with the key difference being a 2-mm-longer optical stem that extends anteriorly through surgically fused eyelids or an oral mucosal graft.[10] It is implanted in a single surgery with complete removal of all ocular surface epithelium and is usually combined with a complete vitrectomy and glaucoma valve implant. If the eyelids are retracted due to scarring or lost due to trauma, it can be implanted through an oral mucosal graft, in which case implantation requires an intact and healthy mucosa before the KPro is implanted. In a first stage, buccal mucosa is harvested and draped over a surgically deepithelialized ocular surface followed by implantation of the KPro months later, once the mucosa is confirmed to be intact and well-vascularized. For KPro implantation, the mucosa is reflected and after securing the KPro, the mucosa is sutured back with the optic protruding through an opening created by the surgeon (Figure 4).[11]

The surgical steps are as demonstrated in recent surgical videos on ocular surface surgeries.[9]

Modified Osteo-Odonto-Keratoprosthesis

The osteo-odonto-KPro was first designed by Strampelli and later modified by Falcinelli (MOOKP).[12] In MOOKP, the anterior segment is reconstructed with an epicorneal tooth root alveolar complex, a mucosal graft, and a central PMMA optic

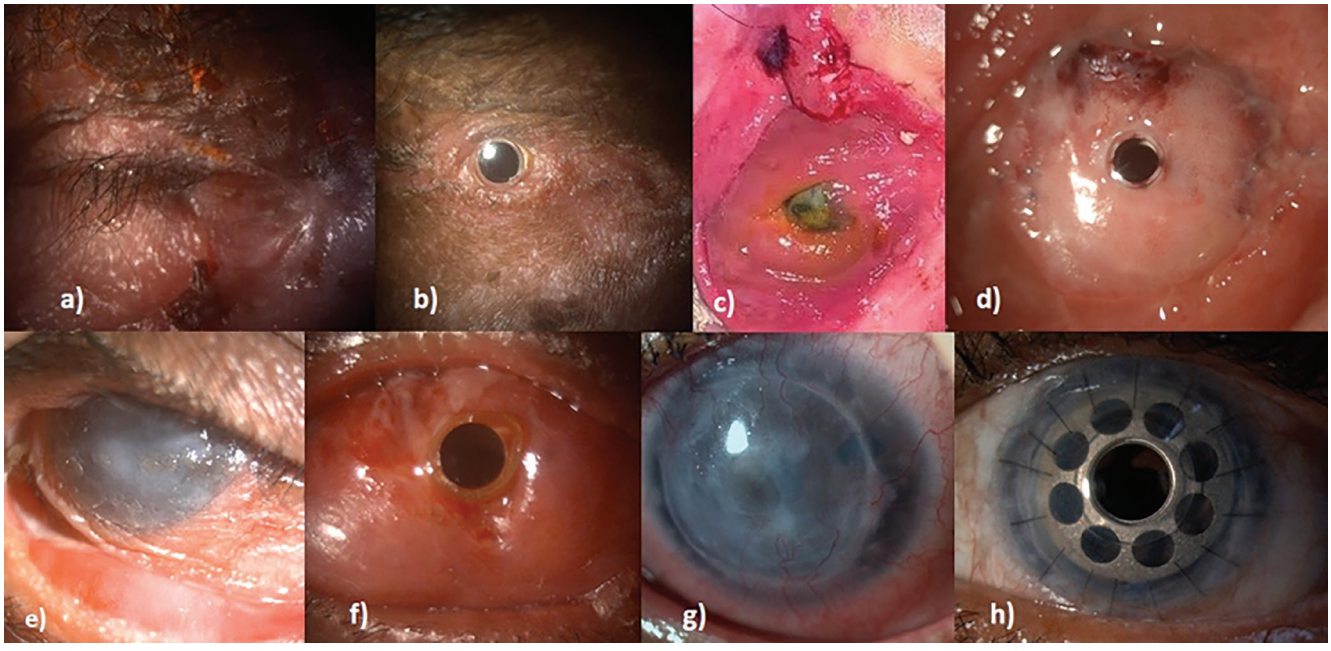

Figure 1. Representative clinical images demonstrating the use of various keratoprosthesis devices customized to underlying ocular surface and adnexal conditions. a, b) Boston type 2 keratoprosthesis done through the lid for a patient with total ankyloblepharon following chemical burns. c, d) Boston type 2 keratoprosthesis done through the mucosa for a patient with absent lids and significant facial burns following thermal burns. e, f) Osteo-odonto-keratoprosthesis done in a patient with Stevens-Johnson syndrome with dry keratinized ocular surface. g, h) Lucia type 1 keratoprosthesis in a patient with multiple failed grafts

Table 1. Overview of commonly used keratoprostheses: design features, indications, and surgical techniques

Keratoprosthesis reference	Composition	Indications	Wet/dry eye*	Surgical Technique
Boston type 1[6]	Solid PMMA front plate and optical stem, donor corneal button, and titanium or PMMA back plate with holes. Aphakic and pseudophakic versions available	- Multiple failed grafts - Herpetic keratitis - Silicon oil filled eyes - Post chemical/thermal injury - Aniridia	Wet	Single stage surgery similar to PK
Aurolab type 1[7]	Same as Boston 1 (only PMMA back plate) and has a locking ring	Same as Boston 1	Wet	Single stage surgery similar to PK
Lucia type 1[8]	Same as Boston 1 with titanium back plate. Available as single axial length aphakic device	Same as Boston 1	Wet	Single stage surgery similar to PK
Boston type 2[9]	Same as Boston 1 with longer optical stem	- Autoimmune disorders (SJS, OCP) - Severe chemical/thermal burns	Dry	Single-stage surgery similar to PK, with complete removal of conjunctival epithelium and tarsorrhaphy with central opening for the optic
MOOKP[11]	Osteo-odonto-acrylic lamina with central PMMA optic	- Autoimmune disorders (SJS, OCP) - Severe chemical/thermal burns	Dry	2/3-stage surgery Stage 1A: iris removal + lens cryoextraction + anterior vitrectomy +/- tectonic PK Stage 1B+C: Buccal mucosa anchored over the eye and OOAL complex prepared and placed in subcutaneous pouch Stage 2: OOAL placed in the eye
TBK[14]	Tibial bone haptic with central PMMA optic	- Autoimmune disorders (SJS, OCP) - Severe chemical/thermal burns	Dry	Similar to MOOKP but using tibial bone instead of canine tooth

*Wet eye defined as Schirmer's >5 mm. PMMA: Polymethyl methacrylate, SJS: Stevens-Johnson Syndrome, OCP: Ocular cicatricial pemphigoid, PK: Penetrating keratoplasty, OOAL: Osteo-odonto acrylic lamina, MOOKP: Modified osteo-odonto-keratoprosthesis, TBK: Tibial bone keratoprosthesis

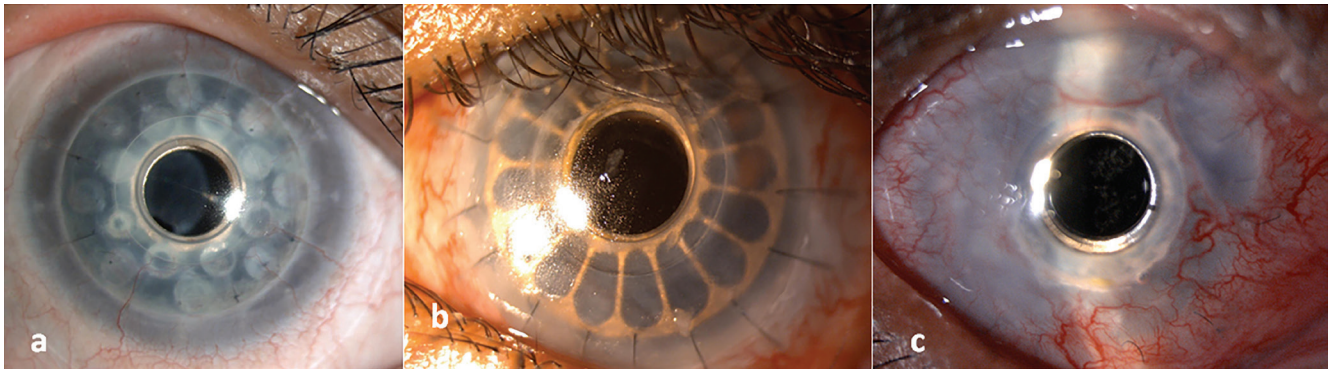

Figure 2. Slit-lamp pictures demonstrating the 3 different versions of type 1 keratoprosthesis. a) Boston, b) Lucia, c) Auro

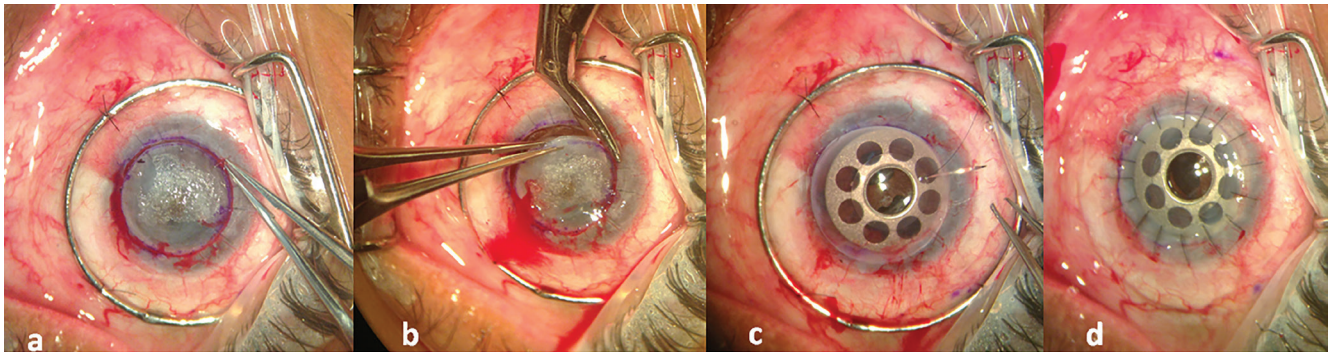

Figure 3. Surgical steps in type 1 keratoprosthesis (KPro) in an aphakic eye with total limbal stem cell deficiency following chemical injury. a) Fleringa ring is anchored and host bed is marked with 8/8.5-mm trephine. b) After KPro assembly, the host cornea is excised carefully. c) The assembled KPro is anchored using 16 interrupted 9-0 nylon sutures. d) The sutures are then buried and a 16-mm bandage contact lens is placed

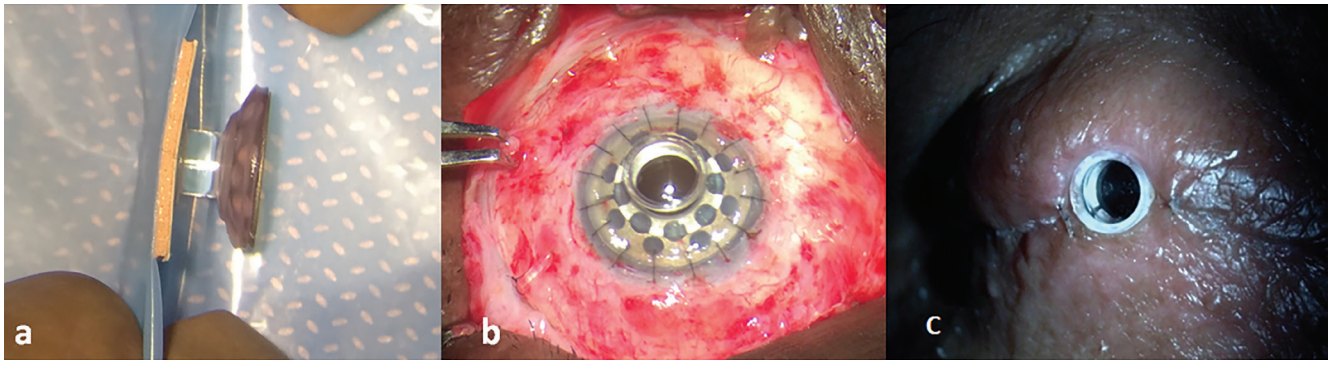

Figure 4. Surgical steps in Boston type 2 keratoprosthesis (KPro) in an eye with total limbal stem cell deficiency following Stevens-Johnson syndrome. a) The assembled Boston type 2 KPro. b) The KPro is secured with 16 interrupted 9-0 nylon sutures; Ahmed glaucoma valve is placed superotemporally with pars plana tube after complete vitrectomy; conjunctiva is excised from bulbar, palpebral, and tarsal surfaces. c) The lids are then sutured in 2 layers with the optic protruding centrally

cylinder cemented through a drilled hole in the tooth. A single rooted tooth (preferably the canine) is harvested, fashioned into a lamina, and drilled centrally, and the PMMA optic is then glued in the center. MOOKP is typically performed in 2 or 3 stages, following the Rome-Vienna protocol.[12,13] In Stage 1A, the eye is prepared by iris removal, lens cryoextraction, and limited anterior vitrectomy. A tectonic penetrating keratoplasty is added only if significant corneal thinning is present. Approximately one month later, Stages 1B and C involve harvesting a maxillary canine tooth, shaping it into a lamina, and embedding the optical cylinder within it. This complex is stored in a subcutaneous cheek pouch to allow fibrovascular ingrowth. Simultaneously, buccal mucosa (~3 cm) is harvested and grafted onto the ocular surface, anchored to the four recti muscles. After 2-3 months, Stage 2 is performed: the lamina is retrieved, the cornea is trephined to accommodate the optical cylinder, and the lamina is secured in place by suturing to the episclera. The oral mucosa is repositioned over the implant with a central opening to expose the optical cylinder (Figure 5).[13,14] The detailed surgical steps for each stage are as demonstrated in recent surgical videos on ocular surface surgeries.[9]

Tibial/Osteo-Keratoprosthesis

In 1987, Temprano introduced the use of a tibial bone-derived osteo-lamina for KPro in edentulous patients. Instead of the canine tooth–bone complex, this technique harvests a round lamina from the upper inner third of the tibia. The PMMA optical cylinder is affixed to a drilled hole in the lamina and implanted into a subcutaneous pocket in the inferior orbit for approximately three months to allow for biointegration (Figure 6). In the second stage, the integrated complex is retrieved, buccal mucosa is lifted, and following central corneal trephination and removal of the iris and lens (if not done in stage 1A), the lamina is implanted onto the corneal surface with the optic through the cornea. The buccal mucosa is then repositioned over the optic as in MOOKP.[15]

Moscow Eye Microsurgery Complex

The Moscow Eye Microsurgery Complex (MICOF KPro) involves a two-stage implantation. In the first stage, a titanium frame with a central ring is embedded in a lamellar pocket created within the corneal stroma. After three months, the cornea within the ring is trephined, and the PMMA optic is inserted

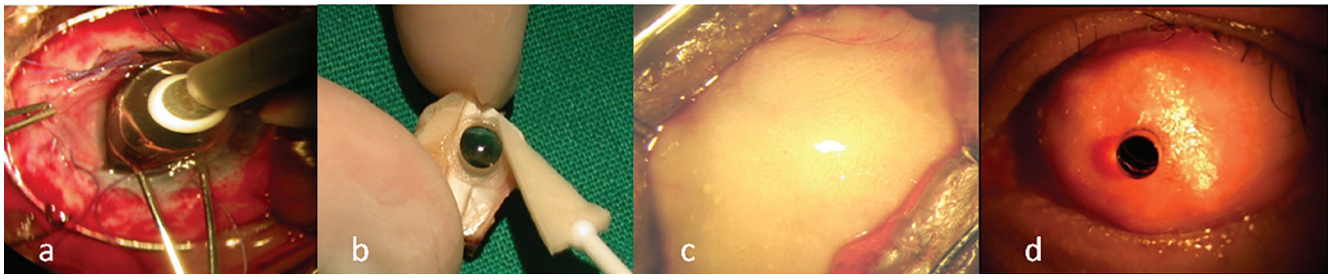

Figure 5. Surgical steps of modified osteo-odonto-keratoprosthesis in a patient following Stevens-Johnson syndrome. a) Stage 1A: intracapsular cataract extraction, complete iridectomy, and limited anterior vitrectomy are performed, along with tectonic keratoplasty if required. Intraoperative posterior segment evaluation is performed to assess the optic nerve and macula. b, c) Stage 1B (after ~2 months): the canine tooth is harvested, fashioned into a lamina, and implanted in the cheek for fibrovascular cover. Simultaneously, the ocular surface is covered with oral mucosa harvested from the cheek. d) Stage 2 (after ~3 months): the buccal mucosa is reflected, corneal trephination is performed, and the osteo-odonto-lamina is anchored into the eye, followed by resuturing the mucosa and making a central opening for optic exposure

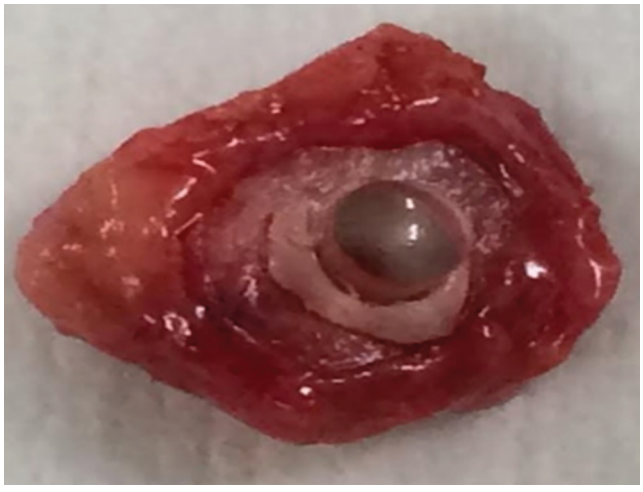

Figure 6. Lamina of the tibial bone keratoprosthesis with fibrovascular cover and central optic following stage 1C, ready to be implanted in the eye during stage 2

to extend into the anterior chamber. A pars plana vitrectomy is performed to remove the iris and lens.[16]

The Fyodorov-Zuev KPro, an early Russian design very similar to the MICOF, features a titanium frame with ear-shaped flanges and a threaded PMMA optic that can be implanted in one or two stages. The device is embedded within a donor corneal lamella and implanted like a penetrating keratoplasty. Lens, iris, and anterior vitreous removal is performed, and the construct is covered with conjunctiva or oral mucosa.[16] For the most part, both devices are available only in Russia and China.

Complications

KPro surgery carries a distinct set of complications that demand meticulous and lifelong follow up. These have been primarily grouped as KPro-related or ocular. KPro-related events include retroprosthetic membrane, perioptic graft melts, and lamina resorption or extrusion, whereas the ocular complications primarily encompass glaucoma, retinal detachment, and endophthalmitis. Their occurrence is most often influenced by the underlying etiology, the condition of the ocular surface, and patient compliance.

In a recently published systematic review and meta-analysis of the Boston type 1 KPro, retroprosthetic membrane (36.6%) and glaucoma (39.3%) were reported to be the most common long-term complications.[17] In a 15-year follow-up of 157 eyes (136 patients) undergoing Boston type 1 KPro, Bernstein et al.[18] reported de novo glaucoma as the most common complication (63.6%), followed by retroprosthetic membrane formation (46.5%). The most common indication was aniridia (26.1%) and 54% of their patients had at least one failed graft prior to KPro, possibly explaining the higher incidence of glaucoma in their study. The timing of glaucoma intervention is crucial in such cases. In their retrospective study of 100 eyes, Geoffrion et al.[19] noted that glaucoma progression was significantly higher when glaucoma surgery was performed post-KPro compared with pre-KPro surgery or medical management alone, thus recommending surgical intervention prior to or simultaneous to KPro implantation.

Long-term outcome data provide valuable guidance in selecting the appropriate type of KPro. In a cohort with follow-up of 5 years or more, the probabilities of maintaining or improving visual acuity were 75.0% and 66.7% at 5 and 10 years, respectively, with device retention remaining stable at 89.2%. Notably, the incidence of complications continued to rise beyond 5 years, with corneal melt, surgical glaucoma interventions, and endophthalmitis showing a tendency for late onset (Figure 7a, b).[20] While there are few studies comparing the three different versions of type 1 KPro, Shanbhag et al.[21] reported that the outcomes of the Auro KPro were comparable to those achieved with the Boston type 1 KPro in eyes with limbal stem cell deficiency.

Over an average follow-up of approximately 4 years, the most frequently reported postoperative complications among 56 eyes that underwent Boston type 2 KPro were new-onset or progressive glaucoma (41.1%), choroidal effusion (30.3%), retinal detachment (25.0%), and end-stage glaucoma (25.0%). Univariate analysis revealed that patients who suffered

irreversible visual decline (≥20/200 loss) were significantly less likely to have received concurrent glaucoma drainage device implantation compared to those who maintained visual acuity of ≥20/200.[10] Perioptic skin gape requiring skin resuturing is another common complication in the early postoperative period (Figure 7c, d).

MOOKP complications vary across surgical stages, as multiple procedures are performed in the same eye and require lifelong monitoring. In a comprehensive review of 37 case series (28 analyzed for complications) involving 958 patients, autoimmune disorders (39.1%) and chemical injuries (38.8%) were the leading indications. Intraoperative complications (21.7%) commonly included maxillofacial issues, vitreous hemorrhage or vitritis, and mucosal breakdown. The predominant postoperative complications were lamina-related (16.1%), oral mucosa-associated (14.8%), secondary glaucoma (11.5%), and choroidal or retinal detachment (10%), while retroprosthetic membrane formation occurred in 6.2% (Figure 7e, f). The follow-up duration ranged from 1 to 364 months (median: 36.7 months). Overall, 78% of eyes achieved a visual acuity of ≥20/400, with a mean anatomic retention rate of 88.3% (range: 50-100%).[22]

Charoenrook et al.[23] compared long-term outcomes of MOOKP and TBK. Anatomical survival at 10 years was similar between groups (MOOKP 67%, TBK 54%), whereas functional survival favored MOOKP (49% vs. 25%). Postoperative complications were more frequent in TBK (65%) than MOOKP (40%), with mucous membrane necrosis and retroprosthetic membrane formation occurring predominantly in the TBK group.[23]

In a series of 90 eyes with MICOF KPro and a mean follow-up of 58.2±36.3 months, the most common complications were glaucoma (60%) and corneal melt (40%). One eye experienced KPro extrusion, and two eyes had implant site leakage. Among 7 eyes with endophthalmitis, final visual acuity was limited to light perception.[16] Ghaffariyeh et al.[24] evaluated 10 eyes implanted with the Fyodorov-Zuev KPro over a mean follow-up of 52 months and reported a retention rate of 70%. The main postoperative complications included retroprosthetic membrane formation (40%), glaucoma (20%), retinal detachment (10%), and endophthalmitis (10%).

While outcomes and complication profiles vary across KPro types, glaucoma, retroprosthetic membrane formation, and corneal melt remain the most frequent long-term challenges influencing visual prognosis and device retention.

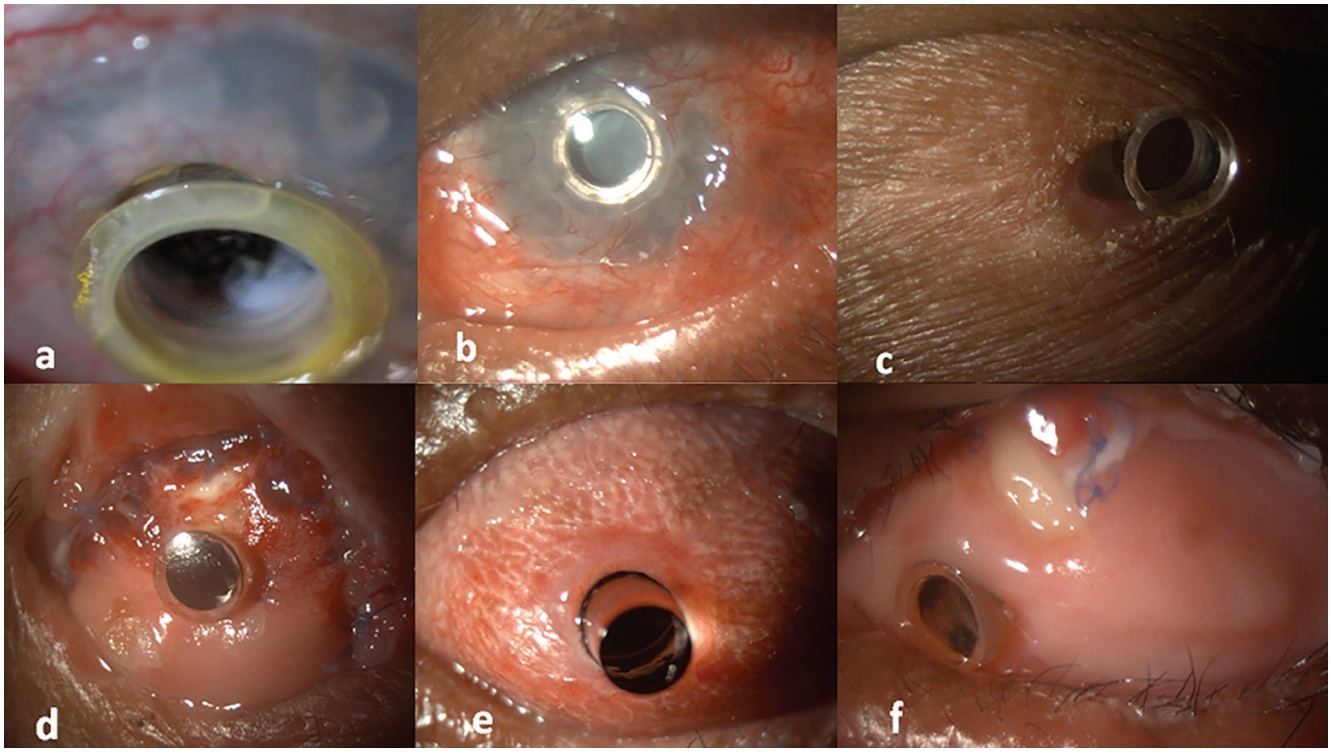

Figure 7. Representative complications across different keratoprosthesis (KPro). a) Perioptic melt in Boston type 1 KPro managed with lamellar patch graft. b) Dense retroprosthetic membrane in Boston type 1 KPro requiring surgical membranectomy. c) Perioptic skin gape in Boston type 2 KPro necessitating resuturing. d) Mucosal necrosis over Boston type 2 KPro managed with mucous membrane revision. e) Optic protrusion with perioptic leak eight years after modified osteo-odonto-KPro, indicating laminar resorption. f) Early postoperative lamina exposure after modified osteo-odonto-KPro, managed by mucous membrane revision

Key Factors in Keratoprosthesis Selection

Choosing the appropriate KPro is a complex decision that requires careful evaluation of multiple interrelated factors. Each KPro has unique design features, surgical demands, and postoperative requirements. Key factors include careful consideration of the ocular surface, the status of which is directly related to the etiology of the corneal blindness, as well as the overall health of the patient. It is also important to consider implementation-related factors such as the patient's capacity to understand and comply with medication and eye care instructions, attend scheduled follow-up visits, and seek care in a timely fashion should concerning symptoms arise. Compliance is typically dependent to a great degree on the support of family members. If living distant to the surgeon, the patient must have proximity to transportation and the resources to access it.

Presurgical Evaluation

A thorough assessment of ophthalmic and general medical history, visual acuity, the ocular surface, intraocular pressure (IOP), and intraocular structures is essential before deciding if KPro implantation is appropriate, and then in selection of the optimal device and surgical procedure. The visual potential must be weighed in light of pre-existing limitations such as amblyopia, glaucoma, and retinal disorders.

Ocular Factors

The status of the ocular surface, including eyelid position, blink, tear film, and fornices, is critical in determining the appropriate KPro. A moist ocular surface with a complete blink and intact fornices is essential for successful outcomes with type 1 KPros. In contrast, type 2 KPros are indicated for eyes with a compromised ocular surface, for example those with absent or non-functional eyelids, incomplete blink, marked dryness, keratinization, or ankyloblepharon, in which conventional surface reconstruction is not feasible or is likely to fail.

The underlying etiology remains a key determinant in the selection of the appropriate type of KPro. Eyes with multiple failed grafts, silicone oil tamponade, herpetic keratitis, or aniridia typically exhibit a relatively favorable prognosis with type 1 KPro implantation.[25,26,27] In contrast, chemical and thermal burns are associated with a more guarded outcome when managed with type 1 devices, and at minimum implantation of a KPro in such cases requires careful consideration.

Patients with autoimmune disorders such as ocular cicatricial pemphigoid and Stevens-Johnson syndrome, as well as other causes of severe cicatricial surface disease with ocular surface keratinization and significantly foreshortened fornices, are generally poor candidates for type 1 KPros because of a much higher incidence of persistent graft defect, corneal melts, and infection. In such cases, type 2 KPros are preferred due to their design tailored for severely compromised ocular surfaces.[3,10,13,22]

Glaucoma remains a major vision-threatening complication following KPro implantation. It is often also pre-existing—either primary or secondary to the underlying pathology or prior ocular surgeries—or may develop de novo postoperatively. Diagnosing glaucoma preoperatively can be difficult because severe corneal opacity makes preoperative assessment of the pupillary responses and optic disc impossible.[28] IOP assessment can be compromised by corneal calcification, thinning, and a flat anterior chamber. Imaging the anterior segment with ultrasound biomicroscopy may be hindered by severe symblepharon or ankyloblepharon.[29] After KPro implantation, IOP measurements are at best estimations based on palpation of the globe, although disc and regular visual fields can be assessed and are recommended for monitoring. Topical antiglaucoma medications can be used after type 1 KPro but their efficacy after a type 2 KPro is limited because of poor penetration through mucosa and essentially non-existent with fused eyelids, leaving only systemic carbonic anhydrase inhibitors as non-surgical alternatives when treatment or prophylaxis is indicated. The timing of glaucoma surgery is very crucial. For patients with preexisting glaucoma receiving a type 1 KPro, glaucoma surgery is recommended prior to or simultaneously with KPro implantation.[19] In eyes with uncontrolled pre-existing glaucoma undergoing MOOKP or TBK, glaucoma valve implantation is best performed before the mucosal graft, when the surface anatomy is least altered. This approach also helps prevent an IOP spike after the mucosal graft, which can further obstruct episcleral outflow.[30] In monocular patients being considered for a type 2 KPro, particularly those with advanced glaucomatous damage and a guarded visual prognosis, a single-stage Boston type 2 KPro may be a more practical option compared to the more complex, multi-stage procedures such as MOOKP or TBK.

Determining the status of the posterior segment of the eye is essential before embarking on KPro implantation. B-scan ultrasonography is essential to evaluate retinal attachment and optic nerve cupping. The presence of posterior segment pathology such as retinal detachment or posterior staphyloma may significantly limit visual outcomes, thereby influencing both the choice of KPro and the nature of preoperative counselling. If cupping is evident on B-scan, it can be assumed to be significant and likely greater than or at least equal to a 0.8 cup-to-disc ratio.

Systemic Factors

In addition to local ocular factors, comorbidities such as poorly controlled diabetes, other autoimmune disorders, or severe cardiopulmonary disease may preclude surgical eligibility or influence the choice of prosthesis, as systemic fitness for general anesthesia is mandatory in all type 2 KPro surgeries,

given the multi-stage and/or prolonged surgical procedures involved.[10,11,12,15] Additionally, patients considered for MOOKP must undergo detailed preoperative dental and oral mucosal assessment, including a spiral computed tomography scan to evaluate the canine teeth. In contrast, candidates for TBK utilizing tibial bone should ideally undergo a bone mineral density scan to exclude underlying osteoporosis, which may compromise the long-term viability of the osteo-lamina.[11,15] In patients with immunosuppressive states, poor oral hygiene, or edentulism, a Boston type 2 may be preferable over osteo-based KPros.

Implementation-Related Factors

Patient-related factors, including psychological resilience and the ability to adhere to long-term care and rehabilitation, play a critical role in selecting the appropriate type of KPro. Socioeconomic and logistical considerations—such as access to specialized care, the capacity to attend regular follow-ups, and compliance with lifelong topical therapy—can significantly impact the long-term outcome of surgery. The need for bandage contact lens replacement once every 3 months and continued monitoring for onset or worsening of glaucoma mandates close follow-up. Cosmetic considerations need to be addressed appropriately by counselling of the patient and family, especially with the type 2 KPros, as they dramatically alter the patient's appearance. Counselling regarding the lifelong possibility of complications, the potential need for repeat or multiple surgeries, the real risk of implant failure and irreversible blindness, and even KPro extrusion, is crucial to ensure that patient expectations are aligned with reality.

Finally, the success of KPro surgery, particularly the more complex procedures like MOOKP, is heavily dependent on the experience of the surgical team and the capabilities of the center. A multidisciplinary team including cornea, glaucoma, and retinal surgeons, oral and maxillofacial surgeons, and anesthesiologists is mandatory. The steep learning curve for the surgical team, especially for osteo-based KPros, underscores the need for adequate training, surgical backup, and long-term patient management infrastructure. In addition to surgical expertise, comprehensive postoperative care to identify complications early and manage them goes a long way in improving outcomes. The availability of specific KPro types may vary by region or center, influencing the choice of implant. Regulatory approvals and cost can also impact surgical planning and timing.

Based on the above factors, we propose a structured algorithm to guide the appropriate selection of KPro (Figure 8). The algorithm does not include MICOF and Fyodorov-Zuev KPros due to their limited availability.

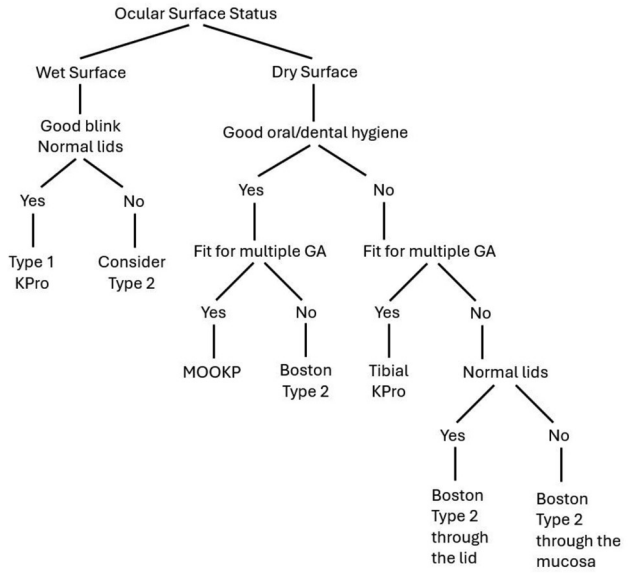

Figure 8. Algorithm to guide keratoprosthesis device selection based on ocular surface and systemic status

GA: General anesthesia, MOOKP: Modified osteo-odonto-keratoprosthesis

Conclusion

Recent progress in material science and a better understanding of the drawbacks of earlier KPro designs have led to the development of several new models, as well as improvements in existing ones, with the goal of achieving better outcomes. Among the currently available options, the Boston type 1 KPro is the most commonly used worldwide. Over the years, changes in the design and material of the backplate have helped to reduce complications such as retroprosthetic membrane formation and perioptic melts. Among the type 2 devices, the MOOKP is often considered the gold standard due to its superior long-term visual and anatomical results. However, its complex surgical steps and less favorable cosmetic appearance have limited wider use. The Boston type 2 and tibial KPro serve as good alternatives in suitable cases. Given an expanding array of KPro options—each with distinct advantages, indications, and limitations—it is increasingly important to adopt a structured, individualized approach to device selection. A comprehensive algorithmic framework, informed by ocular surface status, systemic factors, and surgical feasibility, is essential to optimize patient outcomes and guide clinical decision-making in this complex and evolving field.

Declarations

Authorship Contributions

Concept: S.A., J.C., Design: S.A., J.C., Data Collection or Processing: S.A., V.B., M.R., J.C., Analysis or Interpretation: S.A., V.B., M.R., J.C., Literature Search: S.A., V.B., M.R., J.C., Writing: S.A., V.B., M.R., J.C.

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Pharmacological Pinhole in Presbyopia Treatment: A Brief History from Pilocarpine to Aceclidine

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Dear Editor,

In recent years, the pharmacological treatment of presbyopia has gained attention as a safe, reversible, and non-invasive alternative to glasses and surgery. The recent U.S. Food and Drug Administration (FDA) approval of VIZZ™, the first aceclidine-based eye drop, is an important milestone in this area and is expected to impact daily practice.[1]

The use of eye drops for the treatment of presbyopia has mainly been based on efforts to manipulate pupillary physiology. The approach is to improve near visual acuity by increasing focal depth, because studies to address the pathophysiology of presbyopia by increasing the elasticity of the crystalline lens have not yet yielded the desired effect.[2]

When examined historically, the first eye drops used in the treatment of presbyopia were myotic agents that increase the depth of focus by inducing myosis, thereby creating the pinhole effect. Pilocarpine stimulates the ciliary muscle and iris sphincter, causing both accommodative spasm and myosis. Initially used to treat glaucoma, pilocarpine was also observed to temporarily improve near vision.[3] However, pilocarpine has often been associated with side effects such as headache, poor low-light vision, and myopic shift. These adverse effects occur as a result of pilocarpine stimulating the ciliary muscle as well as the iris sphincter. Therefore, it did not offer an acceptable solution for daily use in the treatment of presbyopia.

From the mid-20th century, lower-concentration formulas or combinations with other agents that promote the myotic effect and reduce the adverse effects of pilocarpine have been investigated. Although these approaches have managed to slightly improve the side effect profile, a fully "pupil-selective" effect has not been achieved. In the literature, frequent emphasis has been placed on the search for an ideal molecule that targets only pupillary myosis while minimizing the effect on the ciliary muscle.[4]

In the early 21st century, advances in pharmaceutical technology enabled the development of a new generation of eye drops. The new formulations aimed to provide a longer-lasting effect and reduce side effects. The most important development of this revival period in terms of pharmacological treatment of presbyopia was the FDA's approval of the first presbyopia eye drop containing 1.25% pilocarpine HCl (Vuity™, Allergan) in 2021.[5] Vuity™ was able to achieve the desired effect with a lower concentration of pilocarpine by using an optimized pH and formulation, thereby minimizing side effects. As a result of low-dose efficacy studies, Qlosi™ (Orasi), an unpreserved eye drop containing pilocarpine 0.4%, is another formulation approved by the FDA in 2023. Although there are studies in the literature involving the use of pilocarpine in different doses or in combination, these formulations have not received FDA approval.

Most recently, the FDA approved eye drops containing 1.44% aceclidine (VIZZ™, LENZ) for the treatment of presbyopia.[5] Aceclidine (in the VIZZ™ formulation) differs mechanistically from pilocarpine. It has a more pupil-selective effect, providing a stable pupil constricting to below 2 mm, thus increasing the

Keywords: Aceclidine, pilocarpine, presbyopia

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depth of field without causing myopic shift. Efficacy lasting up to 10 hours and a good safety profile have been reported in phase 3 studies.[5]

Pharmacological treatment of presbyopia is of great interest for both presbyopic individuals and the pharmaceutical industry. As a result, pharmacological treatments for presbyopia are evolving from experimental approaches to clinically validated options. The approval of aceclidine and the accumulated evidence on pilocarpine indicate that these treatments will have an important place in the management of presbyopia. However, it is important that the pharmacological treatment used is effective, reliable, and reversible and that its long-term side effect profile is known.

Declarations

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Retinal Sensitivity Loss and Beyond in *KCNV2*-Related Retinopathy: The First Genetically Confirmed Case in Türkiye

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Dear Editor,

Hereditary retinal dystrophies pose significant challenges in diagnosis and monitoring because of their phenotype-genotype variability and low incidence. *KCNV2*-associated retinopathy, also known as cone dystrophy with supernormal rod response (CDSRR), was first described in the literature in 1983 as a clinical entity characterized by electroretinography (ERG) findings of attenuated and delayed cone and rod responses to low-intensity stimuli and paradoxically elevated b-wave amplitudes with high-intensity flash stimuli.[1] The genetic basis of *KCNV2*-associated retinopathy is biallelic pathogenic mutations in the *KCNV2* gene. The Kv8.2 protein encoded by this gene is a modulatory subunit of the voltage-gated potassium channel in photoreceptors.[2] The disease typically emerges in childhood or adolescence, presenting with symptoms of decreased central vision, photophobia, impaired color vision, and nyctalopia. The diagnosis can be made by evaluating specific clinical findings and ERG results, but genetic analysis is required for definitive confirmation.[1,2]

A review published in 2020 reported that a total of 114 cases of *KCNV2*-associated retinopathy had been described in the literature.[3] However, no genetically confirmed case of *KCNV2*-associated retinopathy has been reported from Türkiye to date. In this letter, we report on a female patient with a homozygous c.782C>A (p.Ala261Asp) variant in the *KCNV2* gene, presenting her detailed electrophysiological, multimodal imaging, and microperimetry findings.

A 35-year-old female patient presented to our clinic with a history of decreased vision, photophobia, and difficulty seeing at night (nyctalopia) since childhood. There was no family history of retinal disease or consanguinity between the parents. She was born at term with no perinatal complications.

Her best corrected visual acuity was 0.1 (decimal) in the right eye with a refractive error of -0.25 diopters spherical and -2.50 diopters cylindrical at 110° axis, and 0.16 (decimal) in the left eye with a refractive error of -1.25 diopters cylindrical at 65° axis. She scored 1/21 bilaterally in the Ishihara color vision test. Anterior segment examination and intraocular pressures were within normal limits.

Fundus examination revealed symmetrical, well-circumscribed circular areas of foveal retinal pigment epithelium (RPE) atrophy in both eyes. Congenital RPE hypertrophy was present in the temporal periphery of the right eye (Figure 1a, d). Autofluorescence imaging revealed hypoautofluorescence in the foveal region (Figure 1b, e). Spectral-domain optical coherence tomography (SD-OCT) demonstrated ellipsoid zone and RPE loss in the central fovea, resulting in a more prominent appearance of the choroidal capillaries (Figure 1c, f). OCT angiography showed filling defects in the foveal area in both eyes, especially in choriocapillaris sections (Figure 2).

In full-field ERG performed in accordance with the International Society for Clinical Electrophysiology of Vision

Keywords: *KCNV2* retinopathy, cone dystrophy with supernormal rod response, electroretinogram, microperimetry, genetic

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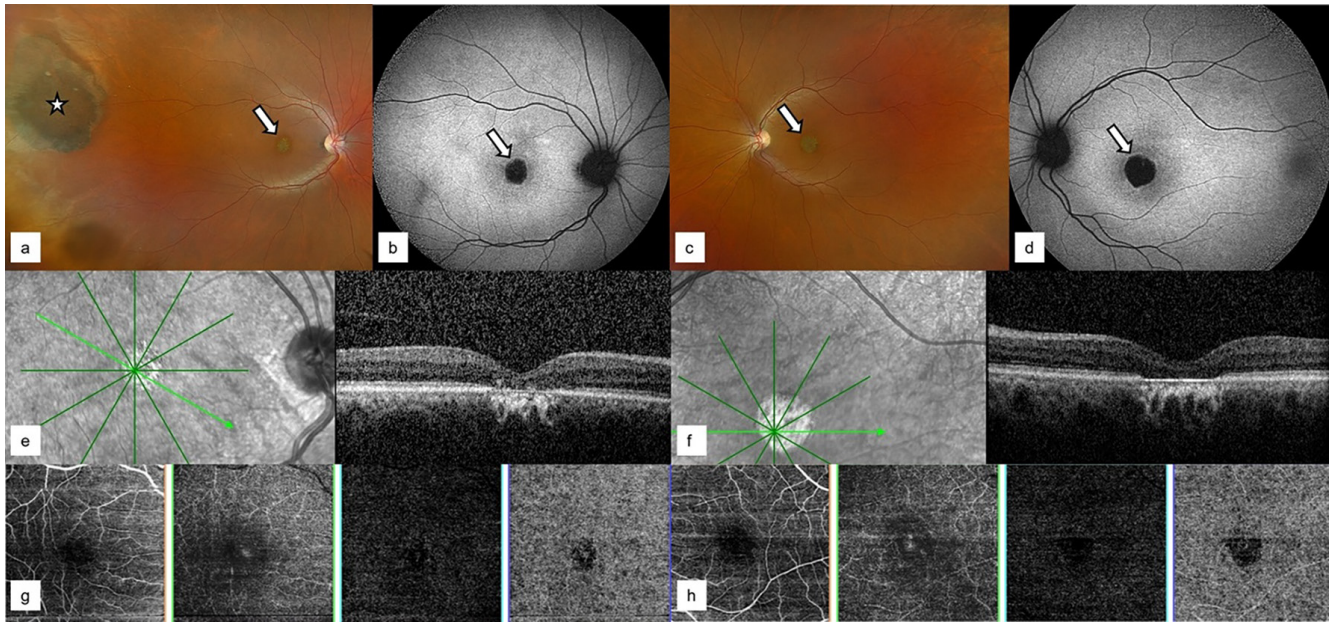

Figure 1. Right eye: a) Well-circumscribed circular foveal retinal pigment epithelium (RPE) atrophy (arrow) and prominent congenital RPE hypertrophy area (star) are observed in the temporal peripheral retina on the colored fundus image; b) Fundus autofluorescence (FAF) image shows central hypoautofluorescence (arrow); e) Spectral domain optical coherence tomography (SD-OCT) reveals increased visibility of choroidal capillaries with loss of ellipsoid zone and RPE in the central foveal region; g) Optical coherence tomography angiography (OCTA) shows filling defect in the foveal area, especially in choriocapillaris sections. Left eye: c) Circular central foveal RPE atrophy (arrow) is observed in the colored fundus image, similar to the right eye; d) FAF image shows symmetrical changes with central hypoautofluorescence (arrow); f) SD-OCT reveals loss of ellipsoid zone and RPE in the central foveal region and associated increased choroidal capillary visibility; h) OCTA shows filling defect in the foveal area, especially in choriocapillaris sections, as in the fellow eye

standards, the dark-adapted 0.01 (DA 0.01) response was delayed and subnormal (Figure 2). Increasing flash intensity (DA 3.0 and combined panel) elicited a supernormal b-wave amplitude. Light-adapted responses (LA 3.0, single flash, and 30 Hz flicker) were delayed and attenuated. On multifocal ERG, reduced amplitudes and prolonged implicit times were recorded in all rings, particularly the central ring of the right eye. These findings supported the diagnosis of CDSRR. Molecular genetic analysis revealed a homozygous c.782C>A (p.Ala261Asp) variant in the patient. One of the parents was a heterozygous carrier but had no visual complaints.

Microperimetry (MAIA, CenterVue, Padova, Italy) confirmed central vision loss and a significant reduction in retinal sensitivity (Figure 3). Mean sensitivity values were between 10 and 15 dB, with pronounced areas of central scotoma. P1 and P2 were 7% and 27% in the right eye and 13% and 49% in the left eye, respectively. According to bivariate contour ellipse area (BCEA) analysis, fixation points were more dispersed in the right eye (63% BCEA: 46.9°², 95% BCEA: 140.5°²) and more stable in the left eye (63% BCEA: 19°², 95% BCEA: 56.8°²). Fixation was in the superonasal region in the right eye and the superotemporal region in the left eye. Eccentric fixation was located 7.6° from the fovea in the right eye and 1.73° from the fovea in the left eye. Sensitivity ≥20 dB was partially preserved in the parafoveal regions.

This case reflects the characteristic clinical, electrophysiological, and genetic spectrum of *KCNV2*-associated retinopathy. The homozygous c.782C>A (p.Ala261Asp) *KCNV2* variant identified in our patient has been previously reported in the literature in patients diagnosed with *KCNV2*-associated retinopathy.[4,5] However, to the best of our knowledge, this is the first genetically confirmed case in Türkiye. Interestingly, the same variant was previously described in a consanguineous Turkish family living in Austria.[4] Two different hereditary retinal dystrophies were detected in the family, with a homozygous p.Ala261Asp variant causing *KCNV2*-associated retinopathy in the mother and a homozygous frameshift mutation in the *MFRP* gene in the son.[4]

The *KCNV2* Retinopathy Study Group identified 75 different variants in 117 patients in their multicenter retrospective series.[2] The disease was shown to have an early onset and a typically stable electrophysiological course, but is characterized structurally by progressive macular atrophy.[2] The OCT findings in our case were consistent with ellipsoid zone loss and RPE defects and corresponded to the advanced stage described in the literature. *KCNV2* Study Group reports 1 and 2 focused on electrophysiological and structural characteristics, respectively, whereas report 3 provided a detailed analysis of genotype-phenotype correlations.[2,6,7] Report 3 also demonstrated the prognostic importance of genetic diagnosis by revealing that best corrected visual acuity and retinal structure are better preserved in patients with missense variants.[7]

Our microperimetry findings showed that central function loss occurs and eccentric fixation strategies are developed in *KCNV2*-associated retinopathy. In this respect, microperimetry offers both functional and topographic information

complementary to ERG and has the potential to be a sensitive biomarker in therapeutic studies.[8]

KCNV2-associated retinopathy is considered a promising candidate for gene therapy because it is a monogenic disorder, the small gene is suitable for therapeutic delivery, and preclinical data indicate that cone cells can be preserved in the early stages of the disease.[3] Furthermore, the fact that the structural changes observed with OCT become pronounced in the later stages of the disease suggests a broad therapeutic window for treatment.[3] In addition, pharmacological approaches such as potassium channel modulators appear theoretically feasible, depending on the effect of the genetic variant on channel function.[3] However, despite these favorable biological and technical conditions, no genetic or pharmacological treatment studies for *KCNV2*-associated retinopathy have been registered in large databases such as ClinicalTrials.gov. This clearly demonstrates the need to develop translational research and clinical trials for this rare disease.

This first genetically confirmed case of *KCNV2*-associated retinopathy in Türkiye was consistent with the phenotype-genotype characteristics described in the literature. Multimodal imaging and microperimetry findings revealed both the structural and functional spectrum of the disease in detail. This case is important as it confirms the presence of *KCNV2*-associated retinopathy in our country, demonstrates the contribution of microperimetry in functional assessment, and may guide future therapeutic studies.

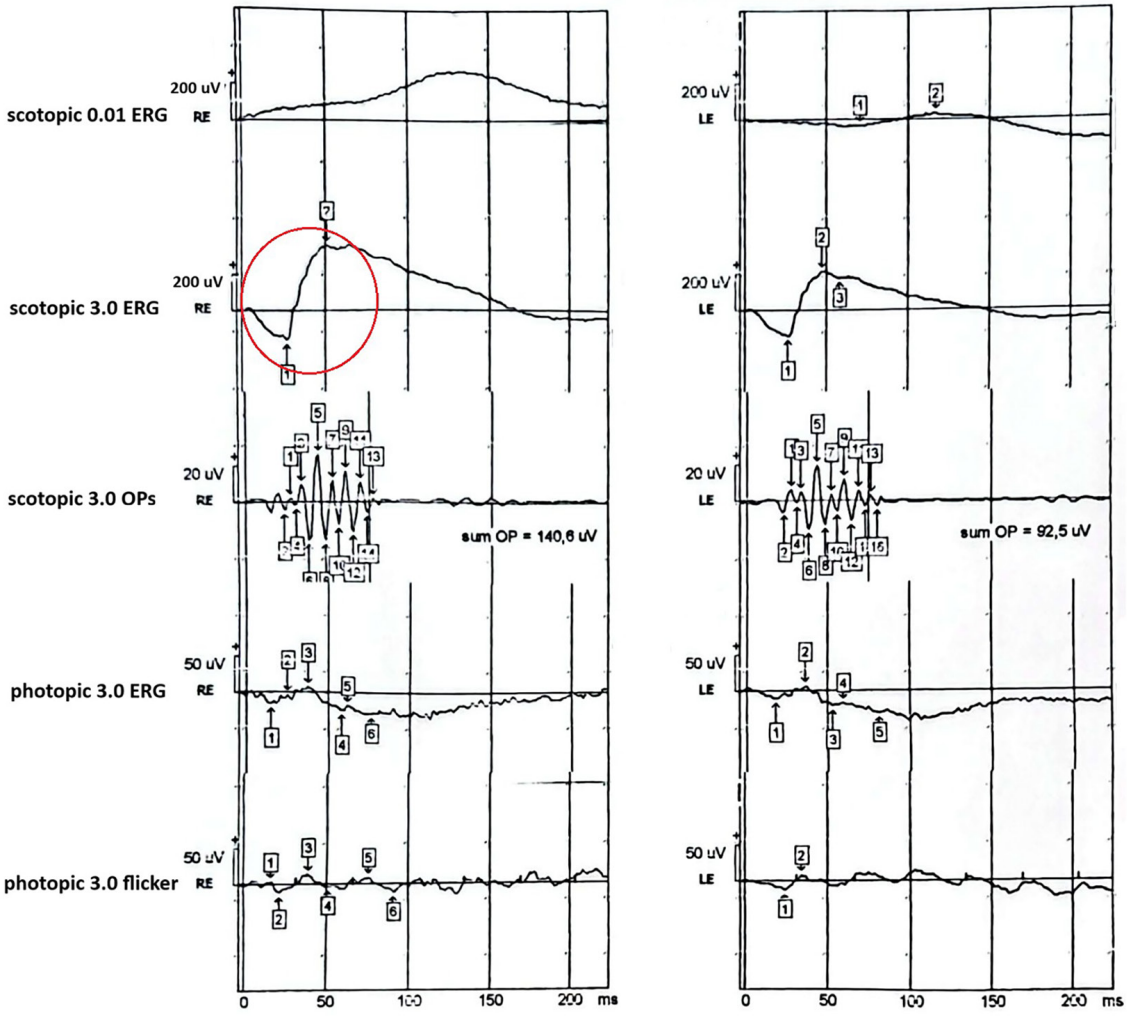

Figure 2. Full-field electroretinography (ERG) of the patient. On scotopic ERG, low intensity flash (dark-adjusted [DA] 0.01) shows delayed b-wave while DA 3.0 ERG shows a large positive b-wave followed by an enlarged negative a-wave (red circle). Photopic ERG showed marked attenuation in both single-flash and 30 Hz flicker conditions
OPs: Oscillatory potentials

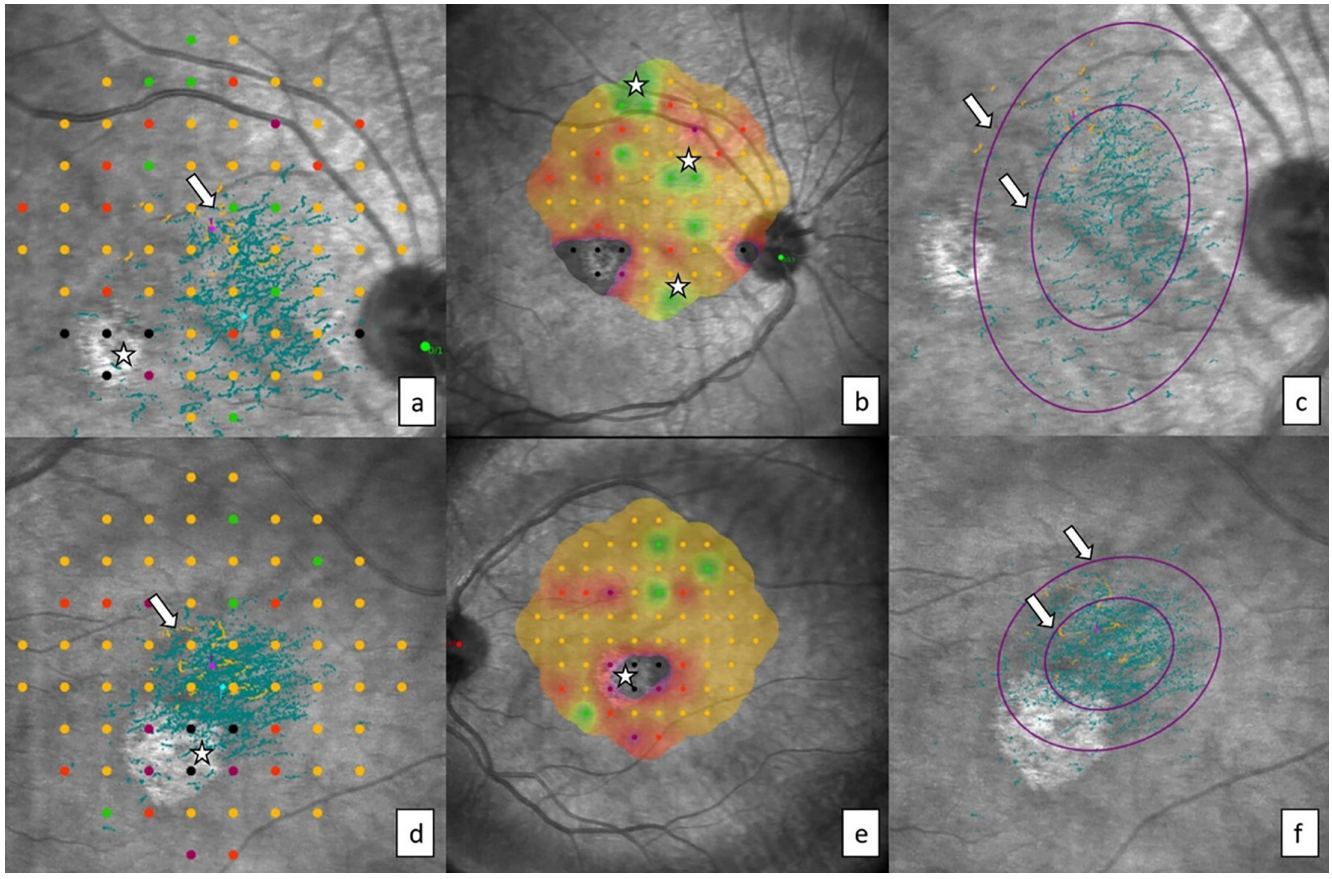

Figure 3. a) Color sensitivity values in the zoomed scanning laser ophthalmoscopy (SLO) image of the right eye show an area of absolute scotoma (star) with black dots in the central region and scattered fixation points (arrow) in the nasal region; b) Retinal sensitivity map of the right eye shows green colored retinal areas measuring ≥25 dB (stars) in the central and parafoveal regions; c) The bivariate contour ellipse area (BCEA) view of the right eye shows a large area (arrow) of scattered fixation points; d) Color retinal sensitivity values in the zoomed SLO image of the left eye show an area of absolute scotoma (star) in the central region and scattered fixation points (arrow) in the superotemporal region; e) In the color sensitivity map of the left eye, the absolute scotoma area (star) is seen in black; f) The BCEA view of the left eye shows a smaller, more limited area (arrow) compared to the right eye

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of the clinical findings and visual materials included in this study for scientific purposes.

Declarations

Authorship Contributions

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

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Letter to the Editor Re: "Bilateral Asynchronous Infraorbital Masses in a Patient Denying Dermal Filler Injection"

Bülent Yazıcı

Private Practice, Bursa, Türkiye

Dear Editor,

I read with interest the case report by Arıcı et al.[1] and would like to share my thoughts about the lesion description and surgical approach.

The authors report en bloc excision of a lesion within the orbital fat at the infraorbital nerve and extraocular muscle level, following subperiosteal dissection in the inferior orbit. However, both magnetic resonance images show the lesions anterior to the inferior orbital rim, in a pre-periosteal position. There is no evidence of intraorbital extension or a mass suitable for en bloc excision. Also, the authors also reported palpation of a firm mass in the tear trough region, and the patient's external photograph shows subcutaneous fullness. Therefore, the clinical and radiographic findings are inconsistent with the surgical description and do not support the migration of a filler material into the orbit.

The article title emphasizes that the patient denied a history of dermal filler injection. However, the patient later on admitted having undergone such a procedure. Highlighting the denial in the title may be misleading for readers.

Keywords: Dermal filler, tear trough, intraorbital migration, treatment, surgical technique, case description

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Declarations

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Reference

1. Arıcı C, Aksoy B, Mangan MS. Bilateral asynchronous infraorbital masses in a patient denying dermal filler injection. Turk J Ophthalmol. 2025;55:234-236.

Reply

We gratefully acknowledge the opportunity to address the concerns raised in the letter and to clarify specific aspects of our study.[1] We also extend our sincere thanks to the authors for their interest in our work and for taking the time to provide their thoughtful observations.

The lesion was located in the medial part of the tear trough region and demonstrated a firm consistency on palpation. During surgical excision, a subciliary incision was made, and dissection was carried out between the orbicularis oculi muscle and the orbital septum to expose the inferior orbital rim. The mass was found to be attached to the periosteum; therefore, a periosteal incision was performed. The lesion was not entirely located anterior to the inferior orbital rim surgically, as it extended into the inferior orbital region. The mass was removed as a single piece (en bloc). Evidence of intraorbital extension was observed in the right orbit on the coronal section of the magnetic resonance imaging of the same patient (Figure 1).

Despite repeated inquiries during the initial ophthalmic examination, the patient consistently denied any history of filler injection; this denial was not due to forgetfulness. Therefore, we

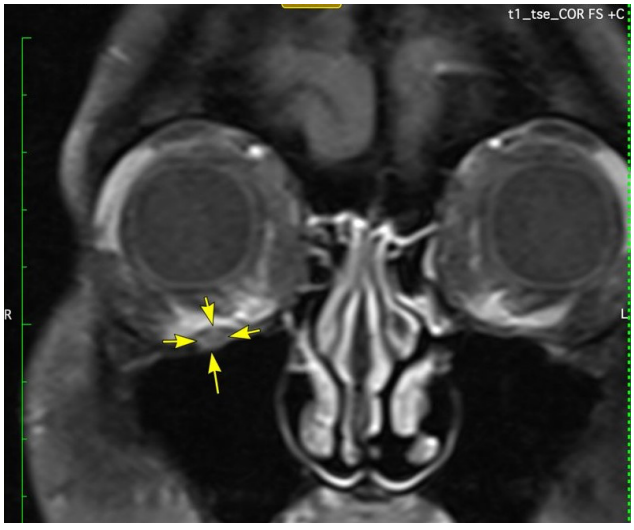

Figure 1. Coronal section on magnetic resonance imaging showed evidence of intraorbital extension in the right orbit

highlighted the patient's denial in the title. It is important to clarify that the patient's denial does not imply the absence of filler but rather a refusal to acknowledge previous filler injection. Upon further discussion, the patient admitted to having received bilateral hyaluronic acid filler injections in the lower eyelids approximately 10 years prior but chose not to disclose this information initially because the procedure was performed without family consent.

In summary, we sincerely appreciate the considerable interest shown in our article.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Declarations

Authorship Contributions

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

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Reference

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