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BEYOGLU EYE JOURNAL

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Ethical Responsibilities and Policies

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Systematic Review

Efficacy and Safety of Topical Insulin Eye Drops for Corneal Epithelial Defects: A Systematic Review, Meta-Analysis, and Grading of Recommendations Assessment, Development, and Evaluation Assessment

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Abstract

Objectives: The aim of this study was to review and meta-analyze the efficacy and safety of topical insulin eye drops (TIED) in treating corneal epithelial defects (CED).

Methods: We registered the protocol in PROSPERO (CRD420251051879). A systematic literature search on PubMed, Cochrane, ScienceDirect, Scopus, and Google Scholar until May 2025 was done to identify controlled comparative studies. Outcomes of interest include time to complete re-epithelialization, re-epithelialization rate, treatment failure, recurrence, and adverse events. We performed meta-analysis using a random-effects model and assessed the certainty of evidence for each result using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment.

Results: Seven studies involving 238 patients were included in the analysis. TIED significantly shortened re-epithelialization time (mean difference [MD] −1.20 days [−1.71–−0.69], p<0.0001) and accelerated the healing rate (MD +0.26 mm^2/h [0.10–0.42], p=0.002). In addition, TIED significantly reduced the risk of treatment failure (risk ratio [RR] 0.30 [0.16–0.57], p=0.003) and recurrence (RR 0.25 [0.11–0.56], p=0.0007) compared to conventional treatments, with no adverse events reported. GRADE assessments indicated very low to low certainty of evidence.

Conclusion: TIED may speed corneal healing, cut failures and recurrences, and is well-tolerated and inexpensive. Robust randomized controlled trials are still needed to nail down the optimal dosing, long-term safety, and its role in CED management.

Keywords: Corneal epithelial defect, Corneal wound healing, Ocular surface disease, Topical insulin

Introduction

Corneal epithelial defects (CED) – breaks in the cornea's outermost layer – predispose patients to infection, stromal scarring, persistent epithelial defect (PED), and permanent vision loss (1). The epidemiologic burden is substantial: PED affects around 245,000 patients in 2023 across the United States, Japan, and the five largest European countries (France, Germany, Italy, Spain, and the United Kingdom) (2). In an

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Iranian population study, almost half of adults ≥60 years had some corneal abnormality, with punctate epithelial defects present in 8.8% (3). Etiologies include trauma, infection, and ocular surgery (incidence after vitrectomy up to 22.4%,(4) neurotrophic keratopathy, and systemic diseases such as diabetes mellitus) (5,6).

Conventional therapy – preservative-free lubricants, topical antibiotics, bandage contact lenses, and autologous serum – often provides incomplete or delayed healing, particularly when corneal innervation or tear stability is compromised (7,8). Consequently, more effective, regenerative treatments are needed. Topical insulin eye drops (TIEDs) have emerged as a promising option, especially for refractory or neurotrophic CED. Beyond glucose regulation, insulin acts as a growth factor that stimulates CE proliferation, migration, and survival and suppresses ocular-surface inflammation (9,10). In diabetic animal models, it shows an effect of up-regulating Ki-67, lowering inflammatory cytokines, and reducing neutrophil infiltration, while also promoting corneal-nerve regrowth and elevating neuropeptides (neuropeptides substance P [SP] and calcitonin gene-related peptide [CGRP]) that modulate inflammation and oxidative stress (11).

Clinical data corroborate experimental work, as several trials showed that TIED reliably shrinks epithelial-defect area, speeds re-epithelialization in refractory PED of varying sizes, and lowers recurrence of recurrent erosions – all with excellent tolerance and safety profiles (12,13). Yet, dosing protocols and long-term safety still need definition, and the published evidence remains fragmented across small, heterogeneous trials (14-17). To resolve these gaps, we performed a systematic review and meta-analysis comparing TIED with conventional therapy for CED, focusing on time to complete healing, overall healing rate, treatment failure, recurrence, and adverse events.

Methods

We registered the protocol for this systematic review and meta-analysis in the International Prospective Register of Systematic Reviews (PROSPERO: CRD420251051879) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18).

Eligibility Criteria

We selected studies through clearly defined inclusion and exclusion criteria. Eligible designs encompassed randomized or non-randomized controlled trials (RCTs) and prospective or retrospective comparative cohort studies. Any study enrolling patients – regardless of age – with CED (including PED, neurotrophic keratopathy, or postoperative epithelial breakdown) qualified for review. The intervention of interest was TIED, whether administered as a stand-alone therapy or as an adjunctive treatment to conventional care. Comparators had to comprise standard treatments such as artificial tears, autologous serum, bandage contact lenses, or other topical agents. To ensure consistency, when a single article contained multiple TIED formulations or control arms that fit our criteria, we combined those arms into one composite group for the primary analysis; we then tested the robustness of this decision by conducting sensitivity analyses in which the arms were re-separated and all possible pairings were analyzed independently (19).

A study needed to report at least one clinically relevant endpoint – time to complete re-epithelialization, rate of re-epithelialization, treatment failure or non-healing, recurrence of epithelial defects, or adverse events attributable to TIED – to be included. Only abstracts in English were considered, and if the full-text was in another language, we used DeepL (DeepL SE, Cologne, Germany) (20) to translate it. We excluded studies without a comparison group; case reports, case series, letters to editors, conference abstracts, expert opinions, and review articles; as well as animal or in vitro investigations. Duplicate publications or data subsets already incorporated into more comprehensive reports were likewise removed from consideration.

Literature Search and Study Selection

We performed a systematic search on PubMed, the Cochrane Central Register of Controlled Trials, ScienceDirect, Scopus, and Google Scholar from database inception to May 5, 2025 (last searched: May 5, 2025). The full search strings for each database are listed in Supplementary Table S1. Search strings combined relevant keywords and MeSH terms for "corneal epithelial defects," "topical insulin," "re-epithelialization," and "recurrence," joined with Boolean operators ("AND," "OR"). Reference lists of all included studies were handsearched, and the first author performed an additional manual search to capture records not indexed in the databases. No limits on publication year or language were applied at the search stage. All records were imported into Rayyan (Qatar Computing Research Institute, Doha, Qatar), (21) where duplicates were removed. Two reviewers (CW and AZ) independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies; disagreements were settled by discussion or, when necessary, adjudication by another reviewer (MA).

Data Extraction and Risk of Bias (RoB) Assessment

Two reviewers (CW and AZ) independently extracted study details – author, year, setting, design, sample size, demographics, defect etiology and size – and key outcomes (time and rate of re-epithelialization, treatment failure, recurrence, and adverse events). They evaluated RoB using the Cochrane

RoB 2 tool (22) for RCT, where domains of assessment include randomization, intervention deviations, missing data, outcome measurement, and selective reporting. For non-randomized studies, the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool (23) was used, which assessed bias due to confounding, participant selection, intervention classification, deviations, missing data, outcome measurement, and selective reporting. Disagreements were resolved by consensus, with a third reviewer (MA) adjudicating when required.

Data Synthesis and Analysis

We summarized study characteristics in a descriptive table that listed study design, country, CED etiology, patient groups, age, sex, number of eyes, insulin dose regimen, baseline epithelial-defect area, primary outcomes, and a brief results summary. We synthesized all remaining qualitative information narratively.

Statistical Analysis Process

We performed all meta-analyses in RStudio (v 2024.04.2, Posit Software, Boston, MA, USA). For continuous outcomes, time to complete re-epithelialization and re-epithelialization/healing rate, we expected between-study variation in definitions. Therefore, we extracted each study's measurement techniques and intervals for these two outcomes (Supplementary Table S2) and used these to guide pooling versus narrative synthesis. If the variation is large, we consider synthesizing them narratively rather than pooling. Otherwise, we pooled the data as mean differences (MD) (95% confidence interval [CI]) using inverse-variance weighting in a random-effects model. For dichotomous outcomes, treatment failure and recurrence, we calculated pooled risk ratios (RR) with the Mantel–Haenszel method and a Paule-Mandel random effect, adding a 0.5 continuity correction to zero-event cells.(24)

To quantify heterogeneity, we calculated Cochran's Q, I2, and $\tau 2$ with Q-profile confidence intervals, interpreting I2 values of 25%, 50%, and 75% as low, moderate, and high heterogeneity, respectively.(25) Where applicable, we explored heterogeneity with prespecified subgroup meta-analyses – surgical versus non-surgical etiology, dose-defined insulin concentration, and diabetes status – according to what each trial reported. We fitted random-effects models within each stratum and used a X^2 test for between-subgroup differences when both strata contained ≥2 studies; otherwise, we reported findings narratively. When a trial included multiple eligible insulin or comparator arms, we combined arms in the primary analysis to avoid double-counting and, in sensitivity analyses, re-separated the arms, and evaluated all valid pairings (19).

To assess design effects, for outcomes that mixed randomized and non-randomized evidence, we re-ran the meta-analysis using RCTs only. We did not pursue Bayesian or quality-weighted models because, with so few trials, posterior inferences would hinge on unverifiable priors for $\tau 2$ and the effect, adding assumptions without commensurate information. We, therefore, relied on the RCT-only restriction and discussed residual confounding from observational cohorts in the discussion (24). When at least ten studies are available, we explored publication bias with funnel plots and Egger's test; (26) if fewer qualify, we reviewed study characteristics qualitatively to uncover selective reporting or design-related bias. We also performed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment (27) to assess the certainty of evidence from every synthesis.

Ethical Approval

Due to the nature of this study, which uses secondary anonymous data from the published literature, the Health Research Ethics Committee of the Faculty of Medicine at Universitas Indonesia have confirmed that this study was exempted from review for ethical approval. This study also follows the Tenets of the Declaration of Helsinki (2013 version).

Results

Literature Search

We found 554 search records in total, and through the rigorous selection process, we ultimately included seven studies (13-17,28,29). Figure 1 contains the PRISMA flow chart of this study.

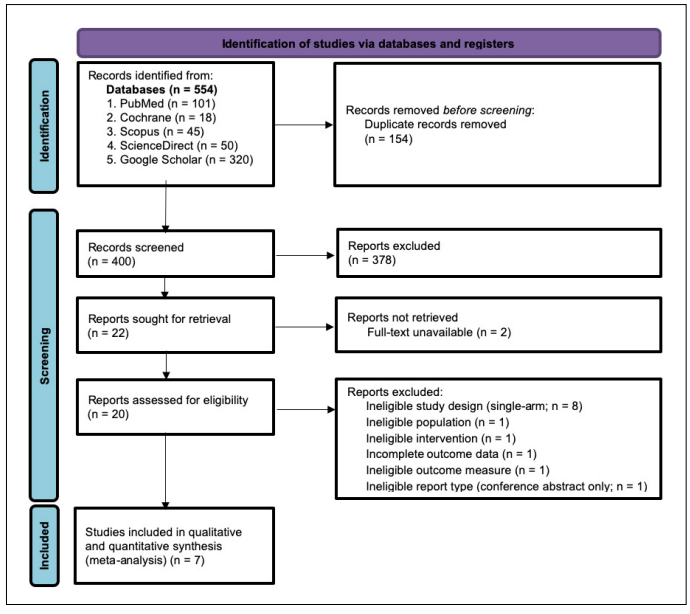

Figure 1. PRISMA flow chart of the study selection process.

Study Characteristics

Seven studies (266 eyes) got included in this systematic review and meta-analysis. The studies were conducted across diverse geographical regions, including Malaysia, Egypt, Spain, Mexico, and the United States, and encompassed a range of study designs: three RCTs, (14,15,28) two retrospective case–control studies, (16,29) one retrospective cohort study, (17) and one prospective non-RCT (13). The most common etiology for CED was post-operative complications following vitreoretinal surgery, reported in five studies. Other etiologies included neurotrophic keratopathy, immune-mediated ocular surface disease, and post-traumatic PED. Patient ages ranged from 25 to 72 years across studies, with varying gender distributions.

All studies administered TIED at concentrations between 0.5 U and 2 U per drop, applied 2–4 times daily. Control arms included routine steroid–antibiotic packs, preservative-free lubricants such as sodium hyaluronate (SH) or cornetears gel, autologous serum, and normal saline. Baseline epithelial areas, when reported, spanned roughly 4.7 mm^2 in post-traumatic defects to beyond 60 mm^2 in large post-vitrectomy lesions. Two trials (15,28) have more than two arms design. Fai et al. (15) tested 0.5, 1, and 2 IU/drop; we combined these three arms into one arm in for the meta-analysis. Meanwhile, Quiroz-Mendoza et al. (28) tested 0.5 IU/drop, SH, and the combination of the previous two; we combined all arms who received 0.5 IU/drop for the meta-analysis.

RoB in Included Studies

All three RCTs (14,15,28) were rated as having a low RoB across all RoB two domains. These trials demonstrated appropriate randomization procedures, minimal deviations from intended interventions, low levels of missing outcome data, and objective outcome measurements. In addition, there was no evidence of selective outcome reporting.

Among the four non-randomized studies, one study (29) was rated as low RoB based on the ROBINS-I tool, having clearly defined participant selection and balanced intervention groups, with no major concerns across domains. The remaining three studies (13,16,17) carried a moderate overall RoB, chiefly because they did not adjust for key confounders such as defect duration or etiology, systemic disease, or prior therapy; none employed matching or multivariable adjustment. Figure 2a and b details the domain-specific ratings.

Overview of Study Results

Across every study, TIED accelerated healing, increased closure rates, and reduced recurrences. Eleiwa et al. (16) halved the median healing time to 10.9 days, whereas Diaz-Valle et al. (17) achieved an 84% epithelialization rate versus 48% in controls and cut recurrences to 11% from 43%. Esmail et al. (13) observed no recurrences with insulin compared with 21.4% in the comparator group, and four studies (14,15,28,29) consistently reported faster re-epithelialization or superior healing rates without compromising safety. Fai et al. (15) also observed 0.5 IU/drop as the dose with the fastest result. A summary of study characteristics is presented in Table 1.

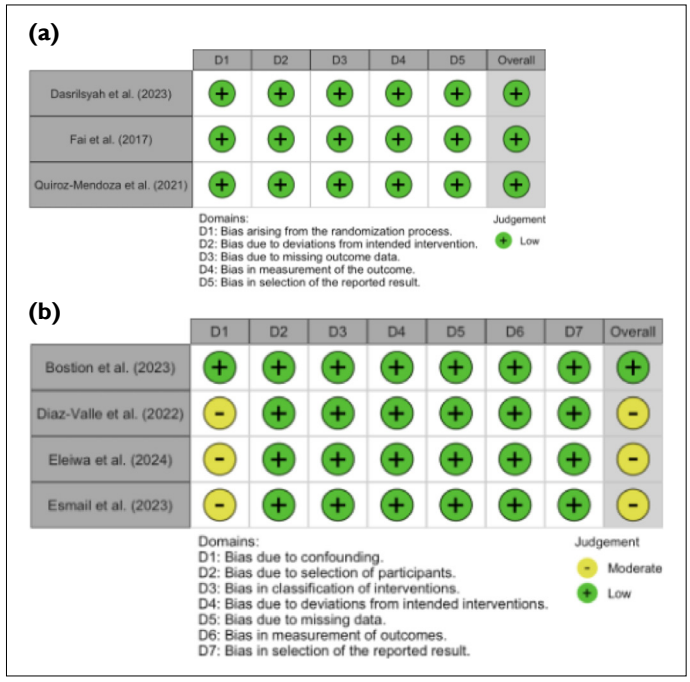

Figure 2. (a) Risk of bias assessment using the Cochrane Risk of Bias (RoB) 2 tool. **(b)** RoB assessment using the Risk of Bias in Non-randomized Studies – of Interventions tool.

Time to Complete Re-epithelialization (Days)

Four studies (16,17,28,29) reported data on the duration required to achieve full corneal re-epithelialization in days. Because their outcome definitions were sufficiently comparable (Supplementary Table S2), we decided to pool them. The results showed that TIED significantly reduced healing time compared to conventional therapies. The MD was −1.08 days (95% CI: −1.53–−0.62; $P < 0.01$), indicating both statistically and clinically meaningful acceleration of corneal healing (Fig. 3a). High heterogeneity was detected ($I2=84.3\%$, $\tau2=0$, $p<0.01$), likely attributable to variations in baseline defect size, underlying pathology, and insulin dosing protocols. Nonetheless, all included studies consistently favored TIED. No adverse effects were reported. Sensitivity analysis using all possible pairings from the original and combined arms shows similar results (Supplementary Appendix 1). We stratified by etiology (surgical vs. non-surgical; Supplementary Appendix 2) to explore heterogeneity. In the surgical subgroup, heterogeneity persisted, indicating that etiology alone did not account for the dispersion. The non-surgical subgroup contained a single study, so meta-analysis was not feasible, and the subgroup-difference test was not interpretable. Overall, etiology stratification did not resolve

Table 1. Characteristics of included studies comparing topical insulin eye drops vs. standard treatment

Study	Type	Country	Etiology of cornea epithelial defects	Group	Age (Mean, standard deviation)	Male (%)	*n* (eyes)	Insulin concentration and frequency	Topical non-insulin treatments (agents and frequency)		Baseline epithelial defect area (mm^2)	Outcomes	Result summary
									Non-SOC	SOC			
Bastion, 2013 (29)	RCCS	Malaysia	Surgery (vitrectomy)	Topical insulin+SOC	49.00±11.57	60.0	5	50 IU/mL (1 IU/drop; 20 µL/drop) – QID	-	• Dexamethasone 0.1% – q2h; • Ciprofloxacin HCl 0.3% – q2h in the first week after surgery, then tapered	63.92±12.63	Time to re-epithelialization, healing rate, recurrence, adverse events	Significantly shorter healing time in insulin group; no adverse events reported
				SOC	56.40±9.99	40.0	5	-	-		63.14±12.40		
Dasrilsyah, 2023 (14)	RCT	Malaysia	Surgery (vitrectomy)	Topical insulin+SOC	57.05±12.33	42.1	19	25 IU/mL (0.5 IU/drop; 20 µL/drop) – QID	-	• Dexamethasone 0.1% – q2h; • Ciprofloxacin HCl 0.3% – q2h in the first week after surgery, then tapered; • Neomycin sulfate 3500 IU/g+Polymyxin B sulfate 6000 IU/g+Dexamethasone 0.1% gel administered after all other drops and once/night	NR	Healing rate (mm^2/h), complete re-epithelialization time, safety	Insulin group had significantly higher healing rate, no adverse events
				Topical SH+SOC	58.63±9.24	63.2	19	-	SH 0.18% – QID		NR		
Diaz-Valle, 2022 (17)	RCS	Spain	Infectious, neurotrophic, immunomediated	Topical insulin	71.50±19.30	42.6	61	1 IU/mL (NR IU/drop; NR µL/drop) – QID	-	NR	14.8 ± 16.2	Epithelialization rate, time to healing, AMT need, recurrence	Higher epithelization (84% vs. 48%), lower recurrence (11% vs. 43%) in insulin group
				Topical autologous serum	72.30±17.90	34.7	23	-	Autologous serum 20% – QID		18.6 ± 15.0		
Eleiwa, 2024 (16)	RCCS	Egypt	Surgery (vitrectomy)	Topical insulin+SOC	49.30±8.60	57.9	19	50 IU/mL (1 IU/drop; 20 µL/drop) – QID	-	• PF-L (SH 1 mg+Carboxymethyl cellulose 5 mg+Glycerin 9 mg; single dose unit) – 6x/day • Moxifoxacin 0.5% +prednisolone acetate 1% – tapered (starting frequency NR)	NR	Time to healing, AMT requirement, safety	Mean healing 10.9 vs. 23.1 days; fewer AMTs and failures in insulin group
				SOC	52.50±10.70	55.5	18	-	-		NR		
Esmail, 2023 (13)	NRCT	Egypt	Post traumatic PED	Topical insulin+SOC	29.00±8.72	40.0	15	1 IU/mL (NR IU/drop; NR µL/drop) – QID	-	• Cornetears gel – QID; • Gatifloxacin 0.5% – QID	4.93±1.75	Area improvement, recurrence rate	0% recurrence in insulin vs. 21.4% in control; significant area improvement
				SOC	25.00±7.58	35.7	14		-		4.71±1.86		
Fai, 2017 (15)	RCT	Malaysia	Surgery (vitrectomy)	Topical insulin+SOC	62.62±5.99	87.5	8	25 IU/mL (0.5 IU/drop; 20 µL/drop) – QID	-	• Dexamethasone 0.1% – q2h; • Ciprofloxacin HCl 0.3% – q2h in the first week after surgery, then tapered	62.52±57.16	Healing rate (mm^2/h), complete healing	0.5 U/d best efficacy (100% healed in 72h); safe
					56.12±7.77	75.0	8	50 IU/mL (1 IU/drop; 20 µL/drop) – QID	-		57.16±26.43		
					55.75±6.64	62.5	8	100 IU/mL (2 IU/drop; 20 µL/drop) – QID	-		59.50±10.04		
				Normal saline+SOC	60.00±10.98	37.5	8	-	0.9% normal saline – QID		60.32±12.92		
Quiroz-Mendoza, 2021 (28)	RCT	Mexico	Surgery (vitrectomy)	Topical insulin+SOC	51.5 (47-55)	41.7	12	25 IU/mL (0.5 IU/drop; 20 µL/drop) – QID	-	• Prednisolone acetate 1% – q4h; • Gatifloxacin 0.3% – q4h in the first week after surgery, then tapered	56.4±9.5	Time to complete healing, defect area	Faster healing in insulin group; combo not superior; no adverse events
				SH+SOC	56 (53.5-60)	41.7	12	-	SH 0.15% – 6x/day		58.1±8.9		
				Topical insulin+SH+SOC	55 (50.5-64)	58.3	12	25 IU/mL (0.5 IU/drop; 20 µL/drop) – QID	SH 0.15% – 6x/day		57.2±8.9		

RCT: Randomized controlled trial, RCCS: Retrospective case–control study, RCS: Retrospective cohort study, NRCT: Non-randomized controlled trial, SH: Sodium hyaluronate, SOC: Standard of care, QID: Quater in die (4 times daily), q2h: Quaque 2 hora (every 2 h), q4h: Quaque 4 hora (every 4 h), NR: Not reported, PF-L: Preservative-free lubricants, IU: International unit, AMT: Amniotic membrane transplantation, PED: Persistent epithelial defects

the between-study variability and should be viewed as exploratory.

Re-epithelialization Rate (mm²/hour)

Five studies (14,15,17,28,29) assessed the rate of CE regeneration represented as area of re-epithelialization/hours (mm²/h). Because their outcome definitions were sufficiently comparable (Supplementary Table S2), we decided to pool them. We performed the meta-analysis where the data from Fai et al.(15) and Quiroz-Mendoza et al.(28) are from the combined arms and found that TIED significantly enhanced re-epithelialization rate, with a pooled MD of +0.27 mm²/h (95% CI: 0.10 to 0.44; p<0.01) (Fig. 3b). Substantial heterogeneity was noted (I^2 = 94%, τ2 = 0.03, p<0.01), likely due to variations in methodological design, insulin concentration, and wound measurement techniques. Despite this, all studies demonstrated a positive effect favoring TIED. Sensitivity analysis using all possible pairings from the original and combined arms shows similar results (Supplementary Appendix 3). We also performed the subgroup analysis to break down the heterogeneity using studies surgical etiology versus non-surgical etiology (Supplementary Appendix 2), and it turned out that the amount of heterogeneity in the pooling result using all studies with surgical etiology is still large. Using another subgroup comparison (studies with insulin concentration of 25 IU/mL [0.5 IU/drop] vs. non-25 IU/mL [non-0.5 IU/drop]), the heterogeneity slightly decreased in the group of studies with insulin concentration of 25 IU/mL (0.5 IU/drop), where the I^2 = 55%. Although a fixed-effect comparison suggested a difference between subgroups (X^2 = 43.6, p<0.01), the random-effects test, which accounts for substantial within-subgroup heterogeneity (I^2 = 95%), showed no signifi-

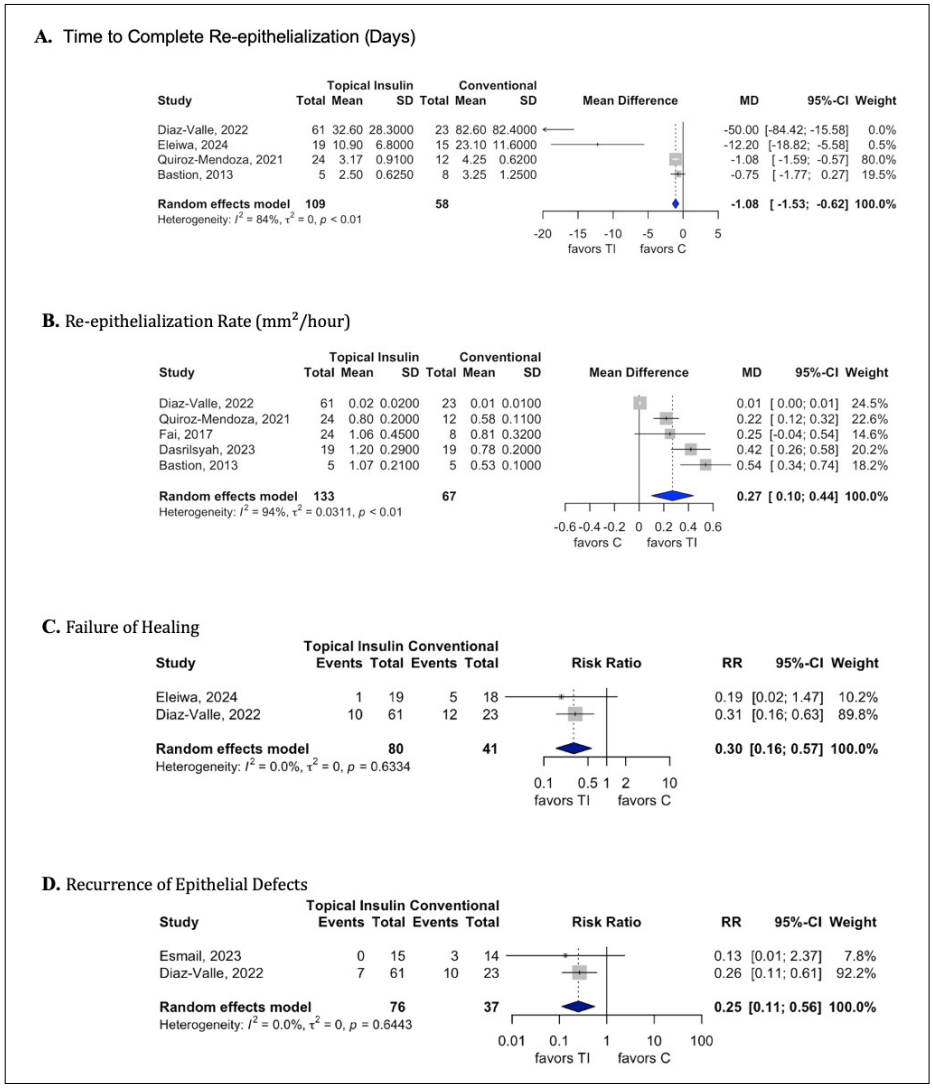

Figure 3. (a-d) Forest plots of meta-analyses comparing topical insulin eye drops versus conventional therapies for corneal epithelial defects.

All outcomes were analyzed using random-effects models. Horizontal lines represent 95% confidence intervals; diamonds represent pooled effect estimates. TI = topical insulin; C = conventional treatment.

cant difference (X^2 = 0.03, p=0.87). We, therefore, found no convincing evidence that the treatment effect varies between the subgroups. Meanwhile, in the RCT-only sensitivity analysis (Supplementary Appendix 3), the re-epithelialization rate remained higher with TIED (MD 0.30 mm^2/h, 95% CI 0.15–0.44). Heterogeneity was moderate (I^2 54%), while Cochran's Q was non-significant (p=0.11), a common discordance with only three trials, because Q has low power; we, therefore, interpret heterogeneity mainly from I^2/τ^2.

Failure of Healing

Two studies (16,17) contributed data on failure of epithelial healing, defined as the persistence of epithelial defects despite intervention. A random-effects model revealed that TIED significantly reduced the treatment failure risk, with a pooled RR of 0.30 (95% CI: 0.16 to 0.57; p=0.0003) (Fig. 3c). We found no heterogeneity (I^2 = 0%, τ^2 = 0, p=0.6334), suggesting consistency across studies.

Recurrence of Epithelial Defects

Recurrence rates were reported in two studies (13,17). Pooled analysis indicated that TIED significantly decreased recurrence, with an RR of 0.25 (95% CI: 0.11–0.56; p=0.0007), representing a 75% reduction in recurrence compared to controls (Fig. 3d). There was no detected (I^2= 0%, τ^2 = 0, p=0.6443), further reinforcing the consistency of findings.

Adverse Events

There were no major adverse effects reported in any of the included studies. Across all trials, TIED was well tolerated with no systemic or local safety concerns documented. This seemingly clean profile is reassuring but not definitive. All studies were small and short, leaving them underpowered to detect rare or delayed toxicities such as late corneal neovascularization or epithelial hyperplasia. Sparse follow-up after epithelial closure further limits confidence. Future RCTs should predefine and grade ocular and systemic adverse events, maintain active surveillance for at least 6–12 months, and use masked adjudication so that a robust safety margin for TIED can be established.

Publication Bias

Due to the limited number of studies per comparison (n<10), we did not perform publication bias analysis, as small-study effects tests such as Egger's test lack statistical power in this context. However, study characteristics were systematically reviewed to identify potential sources of bias.

GRADE Assessment

Using the GRADE framework, we rated the certainty of every pooled estimate in this review as low to very low. We downgraded the evidence chiefly for four reasons. First, several studies carried an appreciable RoB. Second, most analyses rested on small sample sizes, which heightens the chance of undetected publication bias and widens confidence intervals, generating imprecision. Third, high between-study heterogeneity in several outcomes signaled inconsistency. Finally, because only a handful of trials contributed data to each comparison, the results remain fragile and could shift with the addition of new evidence. Table 2 presents the summary-of-findings matrix and the corresponding GRADE ratings for every meta-analytic outcome.

Table 2. Summary of findings and GRADE assessments.

Topical insulin eye drops versus conventional treatments for corneal epithelial defects

Outcomes	Effect (95%CI)	No. of eyes (studies)	Certainty of the evidence (GRADE)
Time to complete re-epithelialization (days)	MD=−1.08, 95% CI: −1.53—0.62, I^2=84.3%	167 (4 studies)	⊕⊖⊖⊖ Very low[1,2,3] Due to risk of bias among included studies (principally from the residual confounding in retrospective cohorts), the small sample size, and inconsistency
Re-epithelialization rate (mm^2/hour)	MD=0.27, 95% CI: 0.10–0.44, I^2=94%	200 (5 studies)	⊕⊖⊖⊖ Very low[1,2,3] Due to risk of bias among included studies (principally from the residual confounding in retrospective cohorts), the small sample size, and inconsistency
Failure of healing	RR=0.30, 95% CI: 0.16–0.57, I^2=0%	121 (2 studies)	⊕⊕⊖⊖ Low[1,2] Due to risk of bias among included studies (principally from the residual confounding in retrospective cohorts) and the small sample size
Recurrence of epithelial defects	RR=0.25, 95% CI: 0.11–0.56, I^2=0%	117 (2 studies)	⊕⊕⊖⊖ Low[1,2] Due to risk of bias among included studies (principally from the residual confounding in retrospective cohorts) and the small sample size

GRADE Working Group grades of evidence. High: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. 1We decided to downgrade for 1 point due to risk of bias (principally from the residual confounding in retrospective cohorts) among included studies. 2We decided to downgrade for another 1 point due to the small sample size used in the synthesis of the meta-analysis result. 3We decided to downgrade for another 1 point due to inconsistency as shown by high heterogeneity found in the meta-analysis result. GRADE: Grading of recommendations assessment, development and evaluation, RR: Risk ratios, CI: Confidence interval.

Discussion

This comprehensive meta-analysis and systematic review demonstrates that TIED represents a transformative therapeutic intervention that has superior effects in treating CED compared to conventional treatments (12,15,30). Our finding is consistent with individual clinical trials reporting complete corneal re-epithelialization within 3–25 days depending on defect size and patient characteristics (12,17,28). Several systematic reviews without meta-analysis (10,30,31) also conclude the same, revealing superior healing outcomes of TIED.

Pathomechanistic Foundations and Molecular Rationale

The clinical efficacy of TIED derives from its multifaceted molecular mechanisms that address fundamental deficiencies in diabetic corneal wound healing (32,33). Insulin activates the PI3K-Akt signaling pathway in corneal epithelial and stromal cells, promoting cellular proliferation, migration, and survival through receptor-mediated mechanisms involving both insulin receptors and insulin-like growth factor receptors (34). This pathway activation correlates directly with enhanced DNA synthesis in basal epithelial cells within 48 h post-injury, explaining the accelerated healing observed clinically (33). In addition, insulin stimulates epidermal growth factor receptor phosphorylation and extracellular signal-regulated kinase activation, creating synergistic signaling cascades that optimize cellular migration and wound closure (32,34).

The therapeutic mechanism extends to neurotropic regeneration, with TIED promoting corneal nerve recovery and neuropeptide release, including SP and CGRP (16,35). This neurotropic action addresses the fundamental pathophysiology of diabetic keratopathy, where hyperglycemia-induced basement membrane damage and advanced glycation end-product accumulation compromise epithelial-stromal interactions (36). The anti-inflammatory properties of insulin, demonstrated through reduced interleukin-1 beta expression and neutrophil infiltration, create an optimal microenvironment for sustained tissue repair (16).

Heterogeneity Sources and their Impact

The wide dispersion in healing times and rates most likely stems from differences in baseline defect size, underlying pathology, insulin dose, and measurement technique. Subgroup exploration based on etiology included an insufficient number of studies; therefore, it remains uncertain whether etiology truly modifies the effect. Yet, it was certain that etiology was not the source of heterogeneity in the two outcomes: Time to re-epithelialization and re-epithelialization. Healing rates were likewise similar in trials that used approximately 25 IU/mL (0.5 IU/drop) insulin and those that used higher concentrations, but the number of studies were too small to establish a dose-response gradient. A planned comparison of diabetic versus non-diabetic eyes could not be carried out because the individual-patient data needed for that stratification were unavailable. Despite this variability, all studies consistently favored TIED, underscoring its robust therapeutic potential. Notably, TIED was effective in all patients regardless of the diabetic status, addressing a critical need given the impaired corneal healing often seen in diabetes (12,33). To reduce the residual heterogeneity presumably from unreported variation in defect chronicity, concomitant therapy, and wound-measurement methods; larger, well-reported trials that capture these covariates prospectively are required to determine definitively whether etiology, insulin concentration, or diabetes status modifies the treatment effect.

Population-specific Efficacy in the Vitreoretinal Surgery Context

The clinical relevance of TIED becomes particularly pronounced in post-vitrectomy populations, as they represent the majority of subjects included in the meta-analysis, where corneal complications affect 22.4% of patients, with 4.6% developing PED (4,37). Diabetic patients represent a uniquely vulnerable cohort, with diabetes mellitus, perfluoropropane tamponade, and surgical complexity serving as independent risk factors for PED after vitrectomy. In this high-risk population, TIED at 0.5 units/drop administered 4 times daily achieved 100% healing within 72 h, substantially outperforming placebo (62.5%) and higher concentrations (15,16). It might be due to receptor saturation kinetics that favor physiological rather than pharmacological dosing (31). This finding has profound implications for clinical implementation, as lower concentrations reduce preparation costs while maximizing therapeutic efficacy. The consistency of benefits across diabetic and non-diabetic populations, regardless of age, gender, or hypertensive status, underscores the universal applicability of insulin's regenerative mechanisms (35).

Adherence Profile and Clinical Implementation Advantages

TIED demonstrates exceptional adherence characteristics that address traditional barriers to PED management (35). The formulation's isotonic properties (280–300 mOsm/L), neutral pH (7–8), and low viscosity ensure optimal tolerability without ocular irritation, factors critical for sustained patient compliance in chronic conditions (38). The 4-times-daily dosing regimen aligns with standard ophthalmic medication schedules, facilitating integration into existing therapeutic routines without additional complexity (15,16).

A microbiological stability study confirms 28-day refrigerated storage capability with maintained insulin potency in the 90–110% range when formulated in normal saline, providing practical advantages for both compounding pharmacies

and patient use (38). The absence of systemic absorption or glycemic effects eliminates concerns regarding diabetes management interference, a significant advantage over systemic interventions (15,33). Several previous reviews also demonstrate consistent safety profiles with no specific or major adverse events (10,31,35).

Economic Considerations and Healthcare Resource Optimization

The cost-effectiveness profile of TIED presents compelling healthcare economic advantages, particularly when considered against alternative interventions such as amniotic membrane transplantation or complex surgical procedures (35). Insulin's widespread availability as a generic medication enables cost-effective compounding, with formulations prepared from commercially available subcutaneous insulin through simple dilution procedures (38). The accelerated healing timeline directly translates to reduced healthcare utilization, with mean healing times of 16.6±10.8 days for compounded preparations compared to conventional therapy timelines exceeding 40 days (4,38).

The prevention of surgical interventions represents substantial cost savings, as evidenced by the elimination of amniotic membrane transplantation requirements in insulin-treated groups compared to 11% (2/18) in control populations (16). Long-term economic benefits extend beyond direct treatment costs to encompass reduced complication management, with 77% of patients achieving complete improvement and significant visual acuity gains, minimizing long-term disability costs (35).

Practical Implications: Integration into Existing Treatment Algorithms and Compounding Logistics

Practical implications from the comparative studies are modest but clear. TIED were used as an adjunct to standard care for difficult or postoperative epithelial defects, rather than as monotherapy (14,15,17). The most common regimen was ~0.5 U/drop 4 times daily, prepared by diluting U-100 regular insulin to ~25 IU/mL; higher concentrations were also studied, but available trials do not establish a dose–response advantage over 0.5 U/drop (14,15,28). Patients were typically reviewed within 24–72 h with fluorescein photography to document the defect area, then followed at least weekly until closure; rescue measures (bandage lens or surgery) were considered when improvement failed over about a week (15,28,29). Compounding in these studies was aseptic and pharmacy-led, using regular insulin in 0.9% saline, dispensed in sterile ophthalmic droppers, refrigerated, and in some protocols replaced every ~3 days – practical details that hospitals or licensed compounders can reproduce while applying local beyond-use dating (15,28). Safety reporting was reassuring but short-term: Across controlled studies, no systemic hypoglycemia or vision-threatening events were attributed to TIED, yet small samples and limited follow-up mean uncommon or delayed harms cannot be excluded (14,15,17). Stability data from compounding research support refrigerated saline formulations, but real-world sterility and potency monitoring remain advisable (38).

Taken together, current evidence supports considering TIED as an early adjunct when post-operative or PED are not responding with standard measures, coupled with early reassessment, pharmacy-standard compounding, and prompt escalation if the epithelial area fails to decrease (14,15,17).

Strengths and Limitations of this Study and Future Research Recommendations

This appears to be the first meta-analysis synthesizing controlled human data on TIED for CED. Evidence is still thin: Only seven studies qualified, and few reported dichotomous outcomes such as recurrence or treatment failure. Several pooled estimates showed substantial heterogeneity, likely driven by variations in insulin formulation, dosing, defect etiology, and follow-up duration. Most trials provided only short-term data, and long-term efficacy and safety remain uncertain. Three studies were non-randomized, leaving residual confounding despite ROBINS-I assessment.

Future research should adopt standardized outcome definitions and uniform insulin preparations, recruit larger cohorts, extend follow-up, and incorporate patient-centered endpoints (visual acuity and quality of life). Well-designed RCTs comparing dose regimens and exploring combination therapies (e.g., insulin plus hyaluronic acid or autologous serum) could also clarify optimal strategies and mechanisms, including effects on corneal nerve regeneration. Concretely, future trials should be multicenter, parallel-group RCTs with concealed allocation and blinding (participants, clinicians, and image graders) using identical vehicles/labels. Use multi-arm or factorial designs for dose or add-on questions, with stratified randomization by etiology (post-surgical vs. neurotrophic/other) and diabetes status. Standardize and report compounding procedures, cold-chain handling, and bottle-replacement schedules. Employ centrally read, image-based outcomes: Time to complete re-epithelialization (no fluorescein staining on two exams ≥24 h apart) and re-epithelialization rate (mm^2/h) from calibrated planimetry on a fixed schedule; also report proportion healed by certain timepoints (e.g. day 7/14 or further), need for rescue, recurrence at 1/3 months or further, Ocular Surface Disease Index (OSDI) score, and visual acuity, with ≥6–12 months' follow-up. Predefine and report adverse-event categories with masked adjudication. Analyze by intention-to-treat, specify handling of two eyes per patient, adjust for baseline area/etiology/diabetes, and power for a clinically meaningful difference. For transparent reporting, register a protocol and publish a prespecified statistical analysis plan.

Conclusion

TIED emerges from this review as a promising, well-tolerated therapy that speeds corneal re-epithelialization, boosts overall healing, and lowers both treatment failures and recurrences across varied patient groups and defect etiologies. Readily available, inexpensive, and mechanistically compelling, TIED may serve as an adjunct – or even an alternative – to current CED treatment. Nonetheless, larger, rigorously designed trials are still needed to clarify the optimal dose and schedule, document long-term safety and durability, and anchor TIED within evidence-based guidelines for managing CED.

Supplementary: *https://jag.journalagent.com/beyoglu/abs_files/BEJ-00821/BEJ-00821_(2)_Supplementary_Tables.pdf*

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Original Article

Compatibility Between the Intraocular Lens Master and Pentacam Devices in White-to-White Measurements Used in Phakic Intraocular Lens Calculations

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Abstract

Objectives: Measurement of white-to-white (WtW) distance is essential in the pre-operative evaluation of candidates for cataract or refractive surgery, and in determining the appropriate haptic size of newly developed phakic intraocular lenses (IOLs). This distance can be measured quickly and easily using various methods. However, inconsistencies among reported results raise concerns about whether these measurements can be used interchangeably. Although previous studies have analyzed the agreement between different devices, there has been no such study conducted at the national level. Based on this, our study aimed to analyze the agreement between WtW measurements obtained by the IOLMaster 500 and Pentacam devices for use in phakic IOL (pIOL) calculations.

Methods: A total of 66 eyes from 66 candidates for cataract or refractive surgery were included in the study. WtW distance measurements obtained from both devices were recorded and analyzed. A one-sample t-test was used to compare the mean WtW values. Bland-Altman analysis was performed to assess the agreement between the two devices.

Results: The mean age of the participants was 63.42±18.27 years, and 20 (60.6%) were male. The mean WtW distances measured by the IOLMaster 500 and Pentacam were 11.80±0.48 mm and 11.50±0.56 mm, respectively ($p<0.001$) (limits of agreement: Lower limit 0.19, upper limit 0.41; 95% confidence interval).

Conclusion: Our study showed that the IOLMaster 500 measured significantly higher WtW distances compared to the Pentacam. Therefore, these two devices should not be used interchangeably for WtW measurements. We recommend using the devices endorsed by the chosen pIOL manufacturer.

Keywords: Biometric measurement, IOLMaster, Pentacam, Phakic intraocular lens, White-to-white

Introduction

Measurement of the white-to-white (WtW) (limbus-to-limbus horizontal diameter) is an essential parameter in contemporary cataract and refractive surgery, involving procedures such as anterior chamber lens implantation, phakic intraocular lens (IOLs) implantation, foldable collamer lens implantation, and others (1,2). Accurate measurements play a crucial role in preventing complications such as cataract

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formation, endothelial loss, angle closure, malignant glaucoma, pigment dispersion, and more during the post-operative period. Various methods are employed for WtW measurements in current practice (3,4). These can range from manual measurements using calipers to imaging techniques such as ultrasound biomicroscopy, anterior segment optical coherence tomography (OCT), IOLMaster 500, and Pentacam devices (5).

The IOLMaster 500 (Carl Zeiss Meditec, Jena, Germany) is a device that utilizes a light-emitting diode light source tailored to the iris's structure. It determines the WtW distance with a swept-source OCT technology laser, calculating ocular biometric parameters (5). On the other hand, the Pentacam (Oculus, Irvine, California) is a device that generates a three-dimensional image of the anterior segment. It consists of a Scheimpflug camera rotating 180° around the optical axis of the eye, with a monochromatic light source (emitting blue light at 470 nm from a diode). The device measures the WtW distance using an iris camera optic capable of recognizing iris landmarks and determining pupil shape (6).

While various studies have analyzed the compatibility of different devices in measurements, there is currently no national study addressing this issue. Therefore, in this study, we aimed to analyze the inter-device compatibility of WtW measurements calculated using IOLMaster 500 and Pentacam devices in the context of phakic IOL (pIOL) calculations in the Turkish population.

Methods

This study was conducted in compliance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Kayseri City Hospital before its initiation (Decision No: 414, dated April 15, 2025). Between the years 2021 and 2022, a retrospective evaluation was carried out on 66 eyes of 66 patients who underwent cataract surgery at Kayseri City Training and Research Hospital.

Patients with systemic diseases (such as diabetes mellitus, hypertension, thyroid-related diseases, rheumatoid arthritis, and scleroderma), those with pterygium or similar conjunctival, limbal, or corneal diseases, individuals who had previously undergone ocular surgery, and those using systemic and ocular medications were excluded from the study.

Before surgery, all included patients underwent a detailed pre-operative examination, including measurement of pre-operative refractive values, best-corrected visual acuity, and intraocular pressure with Goldmann applanation tonometry. A comprehensive biomicroscopic examination was performed, and fundus evaluation was conducted after dilation. The WtW measurements of all patients before surgery were obtained using IOLMaster 500 and Pentacam devices.

All measurements were taken in a dark room without the use of any eye drops. Participants were instructed to place their chins on the chin rest and focus on the target light. They were asked to blink to ensure an adequate tear film on the corneal surface before each measurement. Subsequently, participants were instructed to open their eyes and minimize blinking to reduce interference with the limbus during the scan.

WtW measurements were first obtained using the IOLMaster 500, followed by the Pentacam. For each device, three consecutive measurements were taken, and the average value was used for statistical analysis. To avoid inter-eye correlation, only the right eye of each patient was included in the study.

After each capture, the quality of the scan was assessed, and only scans of acceptable quality were included. The criteria for determining "acceptable quality" were established based on the specific device used and the criteria provided by each device's manufacturer.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Values were presented as numbers (%), and mean±standard deviation. $P<0.05$ was considered statistically significant. One-sample t-test was employed to compare the mean values of the WtW distances. To assess the agreement between measurements obtained from both devices, Bland-Altman analysis was utilized.

Results

A total of 66 patients (20 males and 46 females) with a mean age of 63.42±18.27 were included in the study. Using the IOLMaster device, the K1 value was measured as 43.5961, K2 value as 45.299, and K-mean value as 44.4485. On the other hand, with the Pentacam, the K1 value was 43.3515, K2 value was 44.8242, and K-mean value was 44.0697. The WtW value was recorded as 11.8485 with IOLMaster 500 and 11.5303 with Pentacam (compatibility limits; 0.19 lower limit, 0.41 upper limit; 95% confidence interval), with a significant difference ($p<0.01$). Table 1 demonstrates that the WtW value measured with IOLMaster was statistically higher than the value obtained with Pentacam. The anterior chamber depth (ACD) values were recorded as 3.2345 with IOLMaster and 3.5518 with Pentacam.

No statistically significant difference was found between IOL Master and Pentacam measurements for K1, K2, K-mean, and ACD values. However, a statistically significant difference was observed in WtW measurements ($p<0.05$) (Table 2).

Figure 1 shows the Bland-Altman plot illustrating the agreement between the IOLMaster 500 and Pentacam devices for WtW measurements.

Table 1. Measurements of K1, K2, K-mean, ACD, and WtW with IOLMaster and Pentacam

	K1	K2	K-mean	ACD	WtW
IOLMaster 500					
Mean	43.5961	45.2991	44.4485	3.2345	11.8485
Standard deviation	1.83436	2.36556	1.75569	0.73162	0.50998
Pentacam					
Mean	43.3515	44.8242	44.0697	3.5518	11.5303
Standard deviation	1.81093	2.25763	1.78702	0.93293	0.57905
Mean	43.4738	45.0617	44.2591	3.3932	11.6894
Total					
Standard deviation	1.81280	2.30681	1.76807	0.84709	0.56463

IOL: Intraocular lens; ACD: Anterior chamber depth; WtW: White-to-white.

Table 2. Statistical differences in inter-device agreement of K1, K2, K-mean, ACD, and WtW measurements

	t	df	Sig. (2-tailed)	Ort. Dif	Standard deviation	95% Confidence interval of the difference	
						Lower	Upper
K1	0.545	64	0.588	0.24455	0.44871	-0.65186	1.14095
	0.545	63.989	0.588	0.24455	0.44871	-0.65186	1.14095
K2	0.834	64	0.407	0.47485	0.56923	-0.66232	1.61202
	0.834	63.861	0.407	0.47485	0.56923	-0.66237	1.61207
K-mean	0.869	64	0.388	0.37879	0.43609	-0.49241	1.24999
	0.869	63.980	0.388	0.37879	0.43609	-0.49242	1.24999
ACD	-1.537	64	0.129	-0.31727	0.20639	-0.72958	0.09503
	-1.537	60.558	0.129	-0.31727	0.20639	-0.73003	0.09548
WtW	2.369	64	0.021	0.31818	0.13432	0.04985	0.58652
	2.369	62.994	0.021	0.31818	0.13432	0.04976	0.58660

IOL: Intraocular lens; ACD: Anterior chamber depth; WtW: White-to-white.

Discussion

Precise measurements are crucial for minimizing refractive errors and preventing post-operative complications after cataract and refractive surgery. Accurate determination of the WtW distance, in particular, plays a critical role in pIOL selection. This study examined the agreement between WtW measurements obtained with the IOLMaster 500 and Pentacam devices.

In our study, significant WtW measurement differences were identified between the IOLMaster 500 and Pentacam. The IOLMaster 500 yielded significantly higher WtW values compared to the Pentacam. In the literature, a study by Ramin et al. (7) reported that the IOLMaster measurements were longer when comparing WtW measurements between the IOLMaster 700 and Pentacam devices. Similarly, Sayed et al. (8) identified a 0.05 mm difference between the IOLMaster and Pentacam and attributed this difference to differences in the measurement methodologies and limbus identification methods of the two devices. Another study compared the Pentacam HR, IOLMaster 700, Anterion, and Cassini devices, reporting statistically significant differences in WtW measurements. Specifically, the Pentacam HR measurements were noted to be approximately 0.50 mm higher than those of the IOLMaster 700. These differences stem from the devices' measurement principles and the methods used to define the limbus borders. Given that pIOL sizes vary in increments of approximately 0.50 mm, a difference of this magnitude is clinically significant (3).

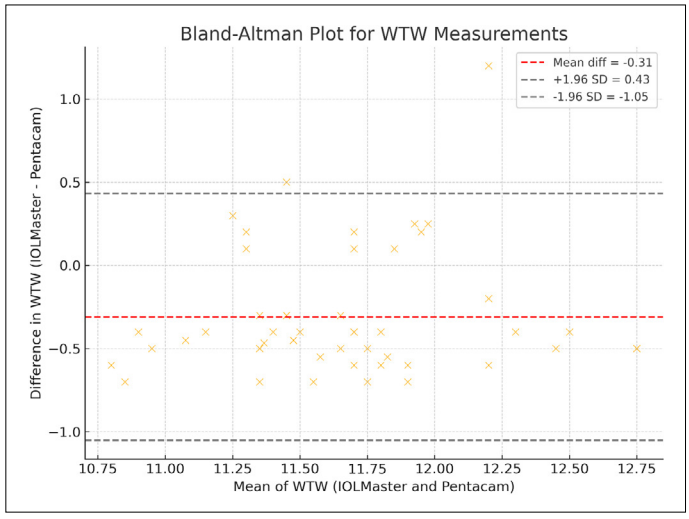

Figure 1. Bland-Altman plot showing the agreement between WTW measurements obtained by IOLMaster 500 and Pentacam devices. The solid line indicates the mean difference (bias), and the dashed lines represent the 95% limits of agreement (±1.96 SD).
The mean difference was calculated as +0.32 mm (IOLMaster 500 measured higher than Pentacam), with 95% limits of agreement ranging from +0.15 mm to +0.49 mm. This figure visually supports the results of the statistical Bland-Altman analysis described in the Results section of the manuscript.

A comprehensive review analyzing the results of nine different devices measuring WtW revealed a wide range of measurement results, with mean differences ranging from 0.05 to 0.86 mm (9). Similar heterogeneity was observed in our study.

However, Shajari et al. (4) compared WtW measurements in 40 healthy eyes using four different devices (Pentacam HR, IOLMaster 500, Lenstar 900, and Visante OCT) and found no significant difference between them. Salouti et al., (3) in their study using the Pentacam HR and Orbscan IIz devices, reported statistically significant differences in mean WtW values ($p<0.001$). They concluded that these differences were not clinically significant and suggested that the devices could be used interchangeably.

These conflicting findings in the literature indicate that WtW measurements may vary depending on the device used, which may lead to errors in pIOL calculations. The absence of such a study in our country's population increases the importance of this study.

Measurement differences can be influenced not only by the operating principles of the devices but also by light sources, optical systems, limbus identification software, light intensities, and patient-related factors (such as head tilt and changes in blink duration due to discomfort from light sources). Given that pIOL dimensions typically vary in increments of 0.5 mm, even a discrepancy of 0.2–0.3 mm between devices can lead to clinically significant errors. This can trigger complications such as improper dome structure, risk of endothelial cell loss, pigment dispersion, or lens rotation (10,11).

Therefore, in pre-operative planning, it is crucial to use devices recommended by pIOL manufacturers and consistent with the device specifications. It is important to note that manufacturers' calculation programs are often optimized for specific devices (e.g., the IOLMaster).

Limitations of our study include the inability to analyze post-operative surgical outcomes (e.g., dome shape, refractive stability, and IOL displacement) due to the retrospective design. Furthermore, the IOLMaster 500 is an older-generation device compared to the IOLMaster 700, which may limit the generalizability of our findings to current devices. Future prospective studies incorporating the IOLMaster 700 and post-operative follow-up data will likely provide more definitive clinical guidance.

Disclosures

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Original Article

Comparison of Two Techniques in Phacoemulsification: Hydroimplantation and Viscoimplantation

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Abstract

Objectives: The aim of this study was to compare hydroimplantation and viscoimplantation techniques in phacoemulsification surgery by analyzing corneal tomography parameters and changes in intraocular pressure (IOP).

Methods: This retrospective study included 74 eyes of 74 consecutive patients who underwent phacoemulsification surgery and implantation of a foldable intraocular lens (IOL). Each eye was assigned to either the viscoelastic material (VEM) group (VEM(+); (n=39) or the VEM (–) group (n=35). Accordingly, IOL implantation was performed with VEM (1.4% sodium hyaluronate; Protectalon, VSY, Turkey) in the VEM(+) group, whereas hydroimplantation without VEM was used in the VEM (–) group. Post-operative examinations were performed on post-operative days 1, 3, and 7, and at 1 month.

Results: There was no statistically significant difference in IOP between the VEM(+) and VEM(–) groups before surgery or at any post-operative time point except at 24 h. At 24 h postoperatively, the VEM(+) group had a significantly higher IOP compared to the VEM(–) group (p=0.010). In addition, the central corneal thickness at 1 month was significantly higher in the VEM(+) group than in the VEM(–) group (p=0.027). No statistically significant differences were found between the groups in best corrected visual acuity, anterior chamber depth, and axial length. There was no posterior capsule rupture or zonular dialysis in either group.

Conclusion: Phacoemulsification using the hydroimplantation technique appears to be a safe and feasible approach that may help mitigate early post-operative IOP elevation; however, assessing corneal endothelial cell function by specular microscopy would be important for a more comprehensive safety comparison between techniques.

Keywords: Hydroimplantation, Intraocular pressure, Phacoemulsification, Viscoimplantation

Introduction

Cataract surgery is the most common operative procedure performed by ophthalmologists. This operation is predominantly performed using the modern technique of phacoemulsification combined with intraocular lens (IOL) implantation (1). During the IOL implantation stage of phacoemulsification, viscoelastic material (VEM) is routinely employed. However, several reports have indicated that VEM remaining in the anterior chamber (AC) cannot be completely removed using the irrigation-aspiration system following the application of VEM during IOL implantation (2,3).

Recent studies have described a hydroimplantation technique for IOL implantation that eliminates the need for VEM (4,5). In this approach, the irrigation cannula is introduced into the AC through the lateral port, while the injector is maneuvered through the main incision (6,7). As no VEM is used during the procedure, there is no risk of residual sub-

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stance remaining in the capsular bag. Furthermore, this technique is regarded as both simple and safe, particularly as the irrigation cannula provides additional ocular stability when introduced through the lateral port.

Previous studies have compared pre- and post-operative central corneal thickness (CCT) and intraocular pressure (IOP) values between the viscoimplantation and hydroimplantation groups; however, differences in AC depth (ACD) on days 1, 3 and 7, as well as at 1 month, were not compared between the two groups (8,9).

In this study, we investigated the effects of IOL implantation performed with or without VEM on post-operative measurements, including IOP, corneal curvature (K1: flat meridian, K2: steep meridian), ACD, and CCT.

Methods

Study Design and Ethics

This retrospective study included 74 eyes of 74 patients who underwent standard phacoemulsification with foldable IOL implantation at the Department of Ophthalmology, Akdeniz University, Antalya, Türkiye, between November 2016 and January 2017. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee of Akdeniz University (KAEK 20 No:77). Written informed consent was obtained from all participants before surgery.

Participants

Eligible participants were patients with nuclear age-related cataract up to Grade 2 according to the Lens Opacity Classification System III, without additional ocular diseases (10). Exclusion criteria included a history of ocular trauma or surgery, lens subluxation, zonular weakness, complicated cataract, degenerative myopia, uveitis, corneal endothelial pathologies such as Fuchs' endothelial dystrophy, and clinically evident pseudoexfoliation syndrome.

Pre-operative Evaluation

All patients underwent a comprehensive ophthalmological examination, including assessment of best corrected visual acuity (BCVA) with a Snellen chart (converted to LogMAR), assessment of the anterior and posterior segment of the eye, and measurement of IOP with non-contact tonometry (CT-80, Topcon, Japan). Corneal curvature (K1, K2), ACD and CCT were measured with a corneal topography system (Pentacam HR, Oculus, Germany). The axial length (AL) and the corneal curvature for the calculation of the IOL power were determined with the IOLMaster 500 (Carl Zeiss Meditec, Germany).

Randomization and Surgical Technique

The patients were randomly divided into two groups: The viscoimplantation group (VEM+) and the hydroimplantation group (VEM–). Group allocation was determined using a computer-generated table of random numbers to ensure unbiased distribution. All surgical procedures were performed by two experienced surgeons (M.Ü. and H.D.İ.) under topical anaesthesia with proparacaine hydrochloride (Alcon, Switzerland), utilizing the same phacoemulsification platform (Infinity Vision System, Alcon, USA). To minimize variability between surgeons, each surgeon performed the same number of procedures in both groups.

Standard main and secondary corneal incisions were performed using 20 G MVR knives, and the AC was filled with dispersive (Viscoat, Alcon, USA) and cohesive (Protectalon, VSY, Turkey) VEM. A continuous curvilinear capsulorhexis approximately 0.5 mm smaller than the IOL optic diameter was performed, followed by hydrodissection and hydrodelineation. The nucleus was removed using the stop-and-chop technique, and the residual cortical material was aspirated with bimanual irrigation/aspiration.

In the VEM(+) group, the capsular bag was filled with viscoelastic before IOL implantation, whereas in the VEM(–) group, IOL implantation was performed under continuous irrigation without the use of VEM. When VEM was employed, it was thoroughly aspirated at the end of the procedure. The wounds were sealed by stromal hydration, and 0.1 cc of intracameral moxifloxacin was administered; no sutures were required. Postoperatively, all patients received topical antibiotic drops 4 times daily for 1 week and topical corticosteroids 4 times daily for 1 week, which were subsequently tapered over a 4 weeks period.

Post-operative Follow-up and Measurements

Post-operative evaluations included IOP, ACD, AL, CCT, corneal curvature (K1, K2), refraction, and BCVA (LogMAR). Measurements were obtained on post-operative days 1, 3, and 7, and at 1 month. The ACD, CCT, and corneal curvature were measured using the Scheimpflug imaging system (Pentacam HR, Oculus, Germany). These follow-up intervals were specifically selected to reflect our routine post-operative schedule for patients undergoing phacoemulsification and are optimal for detecting early alterations in the anterior segment. Similar intervals have been reported in previous studies, e.g. by Cho (11), Sallam and Zaky and Zhu et al., (12) who investigated early post-operative AC dynamics, IOP fluctuations and endothelial outcomes after cataract surgery.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA) and Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC, USA). Normality was assessed with the Shapiro–Wilk test. Continuous variables are summarized as mean±standard deviation when approximately normal and

as median when non-normal. Between-group comparisons used the independent-samples t test or the Mann–Whitney U test, respectively. For repeated measurements over time, repeated-measures Analysis of Variance was applied when assumptions were met (sphericity assessed by Mauchly's test with Greenhouse–Geisser correction when violated); otherwise, the Friedman test (with Wilcoxon signed-rank tests for post hoc comparisons) was used. Categorical variables were compared using Fisher's exact test. Effect sizes were reported as Hedges' g (or Cohen's d) for parametric contrasts and as the Hodges–Lehmann median difference with 95% confidence intervals for non-parametric contrasts. The primary endpoint was post-operative day-1 IOP. In addition, the proportion of eyes with IOP >30 mmHg on day 1 was analyzed as a clinically relevant binary outcome (risk ratio with 95% confidence interval; Fisher's exact p value). No formal multiplicity correction was applied to secondary or exploratory analyses; the primary endpoint was prespecified a priori. Two-sided $p<0.05$ was considered statistically significant.

Results

A total of 74 eyes of 74 patients were included in the study, of which 39 patients were in the viscoimplantation group (VEM+) and 35 in the hydroimplantation group (VEM–). The demographic characteristics and cataract grading of the groups are summarized in Table 1. There were no statistically significant differences between the groups in terms of age, gender distribution or cataract grade. No intraoperative complications were observed in either group.

Table 2 shows BCVA, IOP, CCT, corneal curvature values (K1, K2), ACD, AL, IOL power, and P-values of patients before and after surgery (Figs. 1-3). There was no difference between the groups in terms of BCVA before and after surgery (p=0.241 and p=0.426, respectively). Distributional checks indicated that day-1 IOP in the VEM(+) group deviated from normality; therefore, non-parametric testing was used for this endpoint. There were no between-group differences in IOP at baseline or at post-operative day 3, day 7, or month 1 (p=0.097, 0.147, 0.106, and 0.781, respectively)

Table 1. Comparison of demographic and clinical characteristics between the VEM(+) and VEM(–) groups

	VEM				All		X^2	P
	VEM(+)		VEM(-)					
	n	% (mean)	n	% (mean)	n	% (mean)		
Age (years)	39	52.70 (66.38)	35	47.30 (68.31)	75	(67.54)	0.231	0.821
Eye							0.043	0.835
Right eye	18	46.15	17	48.57	35	47.30		
Left eye	21	53.85	18	51.43	39	52.70		
Sex							0.711	0.399
Female	13	33.33	15	42.68	28	37.84		
Male	26	66.67	20	57.14	46	62.16		
PAMC							6.728	0.081
0	29	74.36	33	94.29	62	83.78		
1	4	10.26	2	5.71	6	8.11		
2	4	10.26			4	5.41		
3	2	5.13			2	2.70		
LOS (NO2)					5.572	0.233		
2	5	12.82	4	11.43	9	12.16		
3	6	15.38	1	2.86	7	9.46		
4	16	41.03	13	37.14	29	39.19		
5	8	20.51	14	40.00	22	29.73		
6	4	10.26	3	8.57	7	9.46		

Categorical variables were compared using the Chi-square (X^2) test. Data are presented as number (n) and percentage (%), and $P<0.05$ were considered statistically significant. PAMC: Post-operation antiglaucoma medication count, LOS: Lens opacification system, VEM: Viscoelastic material, VEM(+): Group of viscoimplantation, VEM(–): Group of hydroimplantation.

Table 2. Comparison of ocular parameters, including BCVA, IOP, corneal, and anterior chamber measurements, between the VEM(+) and VEM(–) groups

	VEM(+) group (n=39)	VEM(–) group (n=35)	P
VA (pre-operative, LogMAR)	0.90±0.54	0.75±0.49	0.241
VA (post-operative 1M, LogMAR)	0.08±0.13	0.12±0.27	0.426
IOP (pre-operative, mmHg)	18.13±3.13 (10–24)	19.26±2.59 (14–24)	0.097
IOP (post-operative 1d, mmHg)	22.05±5.92 (13–33)	18.74±4.68 (13–35)	0.003
IOP (post-operative 3d, mmHg)	16.87±2.52 (9–20)	16.06±2.24 (11–20)	0.147
IOP (post-operative 7d, mmHg)	17.10±2.14 (13–21)	16.26±2.31 (11–20)	0.106
IOP (post-operative 1M, mmHg)	16.82±2.44 (12–23)	16.97±2.19 (12–20)	0.781
IOL Power (D)	20.95±3.71	21.09±2.14	0.848
AL (pre-operative, mm)	23.57±1.70	23.42±0.89	0.643
K1 (pre-operative, D)	43.39±1.57	43.31±1.47	0.826
K1 (post-operative 1M, D)	43.10±1.69	43.14±1.64	0.942
K2 (pre-operative, D)	44.18±1.61	44.20±1.62	0.969
K2 (post-operative 1M, D)	44.14±1.59	44.07±1.57	0.853
ACD (pre-operative, mm)	3.13±0.47	3.22±0.36	0.334
ACD (post-operative1d, mm)	3.54±0.56	3.58±0.46	0.788
ACD (post-operative 3d, mm)	3.76±0.42	3.72±0.35	0.677
ACD (post-operative 7d, mm)	3.76±0.35	3.84±0.25	0.293
ACD (postop 1M, mmHg)	3.82±0.32	3.87±0.26	0.480
CCT (pre-operative, µm)	542.26±35.30	534.29±41.84	0.377
CCT (post-operative 1M, µm)	549.49±30.33	531.20±39.34	0.027

Statistically significant P-values are shown in bold. Values are presented as mean±SD (min–max). VEM: Viscoelastic material, VEM(+): Group of viscoimplantation, VEM(–): Group of hydroimplantation, VA: Visual acuity, logMAR: Logarithm of the minimum angle of resolution, pre-operative: Pre-operative, IOP: Intraocular pressure, mmHg: Millimeters of mercury, post-operative 1d: Post-operative day 1, post-operative 3d: Post-operative day 3, post-operative 7d: Post-operative day 7, post-operative 1M: Post-operative month 1, IOL: Intraocular lens, D: Diopter, AL: Axial length, mm: Millimeter, K1: Flat keratometry, K2: Steep keratometry, ACD: Anterior chamber depth, CCT: Central corneal thickness, µm: Micrometer, SD: Standard deviation, min: Minimum, max: Maximum.

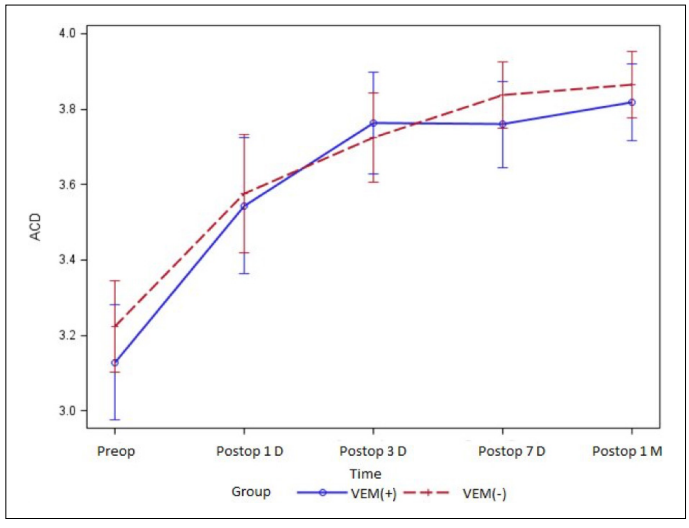

Figure 1. Anterior chamber depth-time changes.

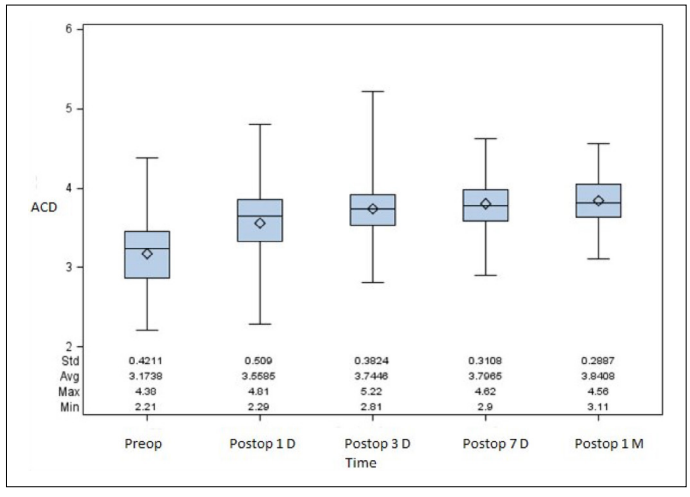

Figure 2. Anterior chamber depth-time changes.

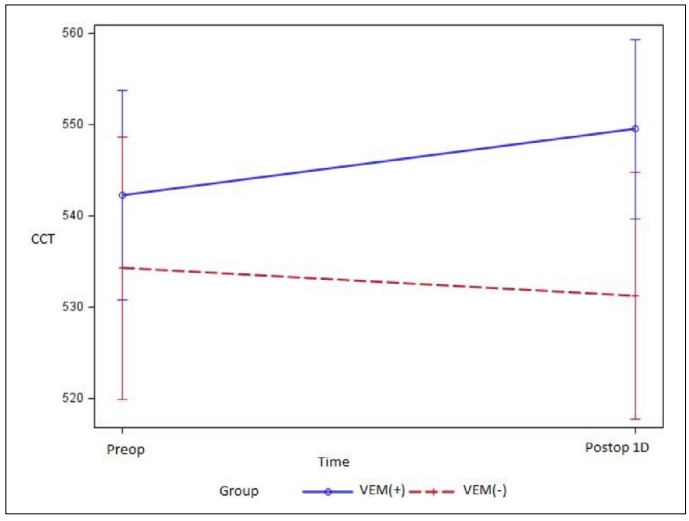

Figure 3. Central corneal thickness-time changes.

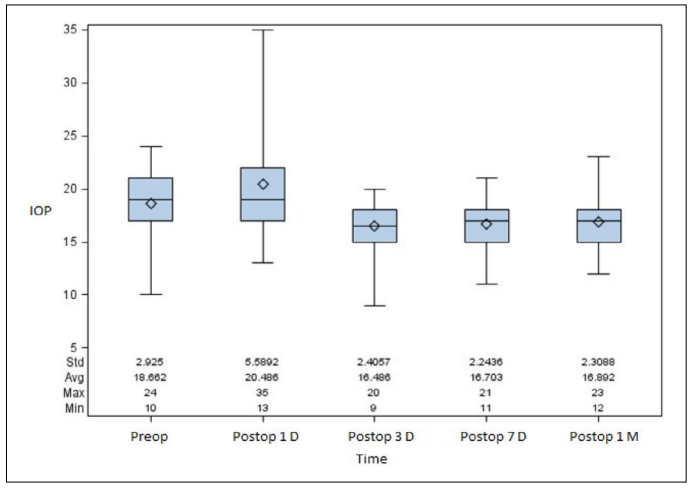

Figure 4. Intraocular pressure-time changes.

(Fig. 4). On day 1, IOP was higher in the VEM(+) than in the VEM(–) group (Mann–Whitney U, two-sided p=0.003). The proportion of eyes with IOP >30 mmHg on day 1 was 13/39 (33.3%) in VEM(+) versus 2/35 (5.7%) in VEM(–), risk ratio 5.83 (95% CI 1.41–24.06); Fisher's exact p = 0.003. All spikes were managed with systemic acetazolamide. There was no significant difference in pre-operative CCT between the two groups (p=0.377); however, CCT was significantly higher in the VEM(+) group than in the VEM(–) group 1 month post-operatively (p=0.027).

Discussion

VEM are used in cataract surgery to preserve the AC, protect intraocular tissues from ultrasound energy, maintain intraoperative ocular tone, and facilitate IOL implantation (1,2). An optimal VEM should be readily removable from the AC at the end of surgery, as any residual material may elevate IOP, induce intraocular inflammation, and potentially damage the corneal endothelium (3). Although the VEM is removed during the irrigation/aspiration phase after IOL implantation, it may remain slightly behind the IOL. Complications such as posterior capsule rupture may also occur while the VEM remains behind the IOL (13). In addition, the VEM between the IOL and the posterior capsule may lead to capsular block syndrome after surgery, and myopic shift may develop due to the displacement of the IOL in the capsular bag (14).

In 2010, Tak et al. (4) described the hydroimplantation method for IOL implantation in response to the potential adverse effects of viscoelastic agents. Hydroimplantation offers several advantages, including reduced surgical time and facilitated IOL implantation by stabilizing the eyeball with the irrigation cannula. Moreover, the improved adhesion between the IOL and the posterior capsule may help prevent posterior capsule opacification by limiting the migration of equatorial epithelial cells towards the central capsule. Although several studies have reported on this technique, no study has compared post-operative ACD and corneal curvature values with the Pentacam system.

In our study, the patients were divided into two groups: VEM(+) and VEM(–), and the post-operative values of ACD, IOP, CCT and corneal curvature (K1, K2) were compared. The post-operative IOP on day 1 was significantly higher in the VEM(+) group than in the VEM(–) group. Elevated IOP in the post-operative period is clinically important, particularly in individuals who are vulnerable to optic nerve injury (15,16). In our study, there were no cases with glaucoma or pseudoexfoliation. The most common cause of an early increase in IOP after cataract surgery is blockage of viscoelastic-induced trabecular flow in the AC (17-20). When comparing the VEM(+) and VEM(–) groups, IOP was significantly higher in the VEM(+) group only on the 1st post-operative day. Although the difference was not statistically significant, patients in the VEM(+) group were more likely to require post-operative antiglaucoma medication (Table 1). Overall, the higher incidence of IOP spikes on post-operative day 1 in the VEM(+) group likely reflects a multifactorial process rather than a single mechanism. A plausible contributor is residual VEM despite careful aspiration. Small amounts may remain in the AC angle and transiently impede aqueous humor outflow. This mechanism is well documented, particularly with dispersive ophthalmic viscosurgical devices such as Viscoat and with soft shell techniques (21). In addition, the VEM(+) group had a slightly longer mean AL. Although this difference was not statistically significant, prior studies suggest that greater AL may predispose eyes to transient IOP elevation (22). Post-operative inflammation may also contribute. We did not measure inflammatory markers in

this study, which we acknowledge as a limitation. Finally, interindividual variation in steroid responsiveness could have played a role (23). In addition, it is possible that some patients in the VEM(+) group did not strictly adhere to their post-operative medication regimen, which may have contributed to higher IOP levels; the lack of objective verification of patient compliance is another limitation of our study. A less likely explanation is that this finding was incidental in this group or that some patients squeezed their eyes during tonometry, resulting in artifactually elevated measurements. Given the relatively small cohort size, such confounding may occur, and larger prospective studies with longer follow-up are needed to confirm these findings. No difference in IOP measurements was observed at post-operative day 3 follow-up.

While previous studies generally reported no significant difference in pre- and post-operative CCT between the groups, we observed a significantly thicker CCT in the VEM(+) group at 1 month. This may be explained by several mechanisms. First, the endothelial cells in the VEM(+) group may have been better preserved during surgery due to viscoelastic protection, resulting in slightly prolonged hydration of the corneal stroma and delayed resolution of the seroma. Second, although the clinical corneal edema was not overt, the minimal inflammatory response may have led to an increase in CCT in the millimeter range. Third, the transiently higher IOP on the 1st post-operative day in the VEM(+) group may have temporarily impaired endothelial pump function, thereby delaying the normalization of stromal fluid content and CCT. Studies such as Bamdad et al. (24) and Tang et al. (25) have documented similar patterns showing an early post-operative CCT increase that gradually regresses to baseline, especially when endothelial stress is present (26). Finally, the small sample size of our study could result in a few outlier values disproportionately affecting the mean, emphasizing the need for larger cohorts to validate these observations.

Although ACD can also be assessed with conventional A-mode ultrasound, the contact of this method with the corneal surface carries risks such as corneal abrasion and infection (27). CCT can also be measured with ultrasound pachymetry. Several studies comparing Pentacam and ultrasound pachymetry have shown that although the measurements are comparable, Pentacam tends to yield slightly thinner CCT thickness values (28). In view of these findings and to minimise the risks associated with contact-based methods, we used CCT measurements with Pentacam in our study. It is important to note that CCT is influenced by the degree of hydration of the cornea, which in turn depends on the proper function of the endothelial pump and barrier mechanisms.

The limitations of our study include its relatively short follow-up period, the small sample size, and the absence of post-operative endothelial cell count (ECC) measurements, as no specular microscopy was performed. This limitation restricts our ability to comprehensively evaluate corneal endothelial cell function and the long-term safety of the hydroimplantation technique for the corneal endothelium. Furthermore, the post-operative inflammatory response was neither assessed nor compared between groups, which may have contributed to IOP fluctuations. Patient adherence to post-operative medication was also not objectively verified. In addition, it is possible that certain patients predisposed to post-operative IOP spikes, such as steroid responders or patients with undiagnosed normotensive glaucoma, were inadvertently included in the study, which may have influenced the observed results. These factors represent additional limitations that should be taken into consideration in larger prospective studies in the future.

Conclusion

To summarize, hydroimplantation appears to be a safe and effective alternative to viscoelastic-supported IOL implantation in routine phacoemulsification surgery, particularly in appropriately selected patient groups. When performed by experienced surgeons, this technique may help minimise early post-operative IOP peaks while maintaining surgical safety. Moreover, hydroimplantation offers potential advantages in terms of surgical efficiency and cost-effectiveness. Nevertheless, larger prospective studies with extended follow-up and ECC evaluations are needed to confirm these findings and to further elucidate the long-term effects of hydroimplantation on corneal health and visual outcomes.

Disclosures

Ethics Committee Approval: This study was approved by the Akdeniz University Ethics Committee (Date: 08.02.2017Number: KAEK 20 No:77).

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

Conflict of Interest: None declared.

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Original Article

Long-term Outcomes of Trabeculectomy Versus Ahmed Glaucoma Valve Implantation in Vitrectomized Eyes

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Abstract

Objectives: This study compares the long-term outcomes and success rates of trabeculectomy and Ahmed glaucoma valve (AGV) implantation in vitrectomized eyes.

Methods: This study included 58 eyes of 58 patients who had undergone pars plana vitrectomy and subsequently received either trabeculectomy (25 eyes) or AGV implantation (33 eyes) at our hospital between March 01, 2017 and April 01, 2023 and had at least 1-year follow-up. Complete success was defined as maintaining an intraocular pressure (IOP) between 5 and 21 mmHg without medication, whereas overall success was defined as achieving the same IOP range with or without medication. Failure was defined as an IOP exceeding 21 mmHg or falling below 5 mmHg, visual deterioration to light perception due to glaucoma progression or complications from glaucoma surgery, or the need for further glaucoma surgery.

Results: The complete success was higher in the trabeculectomy group. Whereas both groups' overall success rates were similar at the last follow-up (p=0.04). Both groups demonstrated a comparable failure rate (p=0.44). The probability of success in the trabeculectomy group was 92.0% at 12 months, 88.0% at 24 months, and 84.0% at 36 months, whereas in the AGV group, it was 87.8% at 12 months, 81.8% at 24 months, and 75.7% at 36 months. There was no difference in terms of post-operative complication rate in both groups. (p=0.36).

Conclusion: Both AGV implantation and trabeculectomy yield comparable outcomes in vitrectomized eyes. However, trabeculectomy reduced the requirement for antiglaucoma medications postoperatively. Consequently, trabeculectomy may be a viable option in carefully selected vitrectomized eyes.

Keywords: Ahmed glaucoma valve, trabeculectomy, vitrectomized eyes

Introduction

Vitrectomy is a commonly performed surgical procedure for the treatment of numerous vitreoretinal diseases. A variety of factors can elevate intraocular pressure (IOP) after vitrectomy, including pupillary block, inflammatory response, infiltration of the trabecular meshwork by silicone oil (SO) particles, and angle closure caused by Synechia (1,2). Secondary glaucoma is a common complication in eyes that have undergone vitrectomy, with an increase in IOP observed in 19–28% of cases following pars plana vitrectomy (PPV) (3,4). In eyes where SO is used as an endotamponade, the risk of glaucoma ranges from 2.2% to 56%, with risk increasing with the prolonged presence of SO in the eye (5).

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Treatment options range from the use of topical antiglaucoma medications to surgery or cyclodestructive procedures. When IOP elevation persists, glaucoma surgery is often necessary. Trabeculectomy with mitomycin C and glaucoma drainage device (GDD) implantation, such as the Ahmed glaucoma valve (AGV), are two widely used surgical options for managing glaucoma that is unresponsive to medical treatment. However, glaucoma surgery has a less favorable prognosis and a higher likelihood of complications in vitrectomized eyes (6). Conjunctival scarring from previous surgery is a significant cause of trabeculectomy failure, and the success rate after vitrectomy may be reduced (7). Therefore, GDDs are generally preferred for refractory glaucoma in vitrectomized eyes (8-10). However, challenges of GDD implantation include prolonged surgical duration, technical difficulties due to conjunctival scarring, and the cost of the devices, particularly in low- and middle-income countries.

Previous studies have reported on the success rates of various glaucoma surgeries in vitrectomized eyes (11-13). This study compares the long-term outcomes and success rates of trabeculectomy and AGV implantation in eyes that have undergone vitrectomy. This is the first study to compare AGV implantation and trabeculectomy in vitrectomized eyes.

Methods

This retrospective study included previously vitrectomized eyes that underwent either trabeculectomy or AGV implantation at our hospital between March 01, 2017, and April 01, 2023. Written informed consent for the use of patient data was obtained from all participants in accordance with the Declaration of Helsinki, and the study received approval from the local ethics committee (Approval number: 3/37, date: March 14, 2024).

Patients with a history of PPV before receiving either trabeculectomy or AGV implantation who had at least 1-year follow-up were included in the study. Patients were splitted into two groups according to which intervention they received. Cases with missing data or follow-up of <12 months, and those under the age of 18, were excluded from the study. Data collected for each patient included gender, age, indication for PPV, type of tamponade used during PPV, lens status, pre-existing glaucoma before PPV, type of glaucoma surgery performed, pre-operative best corrected visual acuity (BCVA), pre-operative IOP, pre-operative antiglaucoma medication use, pre-operative cup-to-disk ratio, pre-operative retinal nerve fiber layer thickness, follow-up time, number of cyclodestructive laser treatments after glaucoma surgery, post-operative complications, and the number of bleb needling and cyst excisions. BCVA was measured with a Snellen chart and was converted into logMAR for statistical analysis. IOP was measured using a Goldman applanation tonometer (AT 900, Haag Streit, Bern, Switzerland). BCVA, IOP, antiglaucoma medication use, and follow-up data were recorded at 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, and at the final follow-up.

Complete success was defined as the maintenance of IOP between 5 and 21 mmHg with a minimum 20% reduction from the baseline IOP, without requiring any glaucoma medication or surgical intervention for high IOP other than bleb needling and AGV cyst excision. Qualified success was defined as IOP maintained between 5 and 21 mmHg with the additional use of antiglaucoma medications. Overall success was defined as the sum of complete and qualified successes. Surgical failure was defined as an IOP >21 mmHg or <5 mmHg, a decline in vision to light perception attributable to glaucoma progression or surgical complications, or the need for additional glaucoma interventions, including trabeculectomy, AGV implantation, or cyclodestructive procedures (14).

The primary outcome measure of the study was the success rate in both groups, while secondary outcomes included IOP, BCVA, the number of antiglaucoma medications, complications, and the need for further glaucoma surgery.

Surgical Technique

All procedures were performed by three glaucoma consultants using uniform techniques, which are detailed below.

Trabeculectomy

A fornix-based conjunctival flap was created. Mitomycin-C (0.2 mg/mL) was administered to the scleral surface for 2–3 min. A rectangular-shaped 1/2–2/3 thick scleral flap (4 mm × 3 mm) was created, and a trabecular block (1 × 2 mm) was excised. A peripheral iridectomy was then performed, and both the scleral flap and conjunctiva were sutured using 10-0 nylon sutures.

AGV Implantation

A superior fornix-based peritomy was made and extended towards the superotemporal region. The end plate was placed 10 mm from the limbus using two 8/0 Vicryl sutures placed 7 mm from the limbus. The silicone tube was shortened, maintaining a bevel-up position, 1.5 mm in front of the limbus. A scleral tunnel was then created 4 mm behind the limbus using a 23-G needle, through which the tube was inserted into the anterior chamber, positioning with the iris plane. The posterior part of the silicone tube was covered with a pericardium. The procedure concluded by closing the conjunctiva with 8/0 Vicryl sutures.

Post-operative Follow-up

Following surgery, topical antibiotics were administered 5 times daily for 2 weeks as part of the standard post-oper-

ative regimen for all patients. Topical prednisolone acetate was used 6 times daily for the initial 2 weeks before being tapered over 6 weeks. Following trabeculectomy, all cases received cyclopentolate hydrochloride eye drops thrice daily for 2 weeks.

Statistical Analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences 20.0® for Windows (IBM Corporation, Armonk, NY). Independent t-tests were utilized to compare variables between groups, and categorical data were analyzed using a Chi-square test (two-sided). The cumulative probability of success was determined using Kaplan–Meier survival analysis, and the log-rank test was performed to compare success rates. A $p<0.05$ was considered statistically significant.

Results

From a total of 58 patients, 25 eyes of 25 patients (18 Male/7 Female) were included in the trabeculectomy group, and 33 eyes of 33 patients (27 Male/6 Female) were included in the AGV group. Pre-operative characteristics of the patients are summarized in Table 1. The mean age was significantly higher in the trabeculectomy group (59.4 years vs. 46.3 years, p=0.001). There was no significant difference in the indications for PPV between the groups (p=0.89). Hence, it was used as the endotamponade during PPV for 7 eyes (28.0%) in the trabeculectomy group and 22 eyes (66.7%) in the AGV group, with a significantly higher rate of SO use in the AGV group (P = 0.008). All patients underwent glaucoma surgery after the removal of SO. Pre-operative BCVA, IOP, and the number of antiglaucoma medications were similar in both groups (p>0.05 for all).

Table 1. Demographics and baseline characteristics of the subjects

	Trabeculectomy (n=25) (%)	AGV (n=33) (%)	p
Age (mean±SD)	59.4±14.3	46.30±14.19	0.001
Lens (n)			
Phakic	4 (16.0)	1 (3.1)	0.21
Pseudophakic	19 (76.0)	28 (84.8)	
Aphakic	2 (8.0)	4 (12.1)	
Presence of glaucoma before PPV (n)	10 (40.0)	8 (24.2)	0,20
Indication for PPV (n)			
PDR and complications	5 (20.0)	6 (18.2)	0.89
Vitreomacular interface disorders	8 (32.0)	2 (6.1)	
Retinal detachment	7 (28.0)	16 (48.5)	
IOL-nucleus drop	5 (20.0)	7 (21.2)	
Endophthalmitis	0	2 (6.1)	
Tamponad used during PPV			
Silicon oil	7 (28.0)	22 (66.7	0.008
Gas	5 (20.0	2 (6.1	
No tamponade	13 (52.0	9 (27.3)	
The time of SO removal (month) (median)	4 (IQR=2, 10)	7 (IQR=3, 13.5)	0.37
BCVA	1.23±0.66 (0.3–2.7)	1.43±0.71 (0.3–3.1)	0.27
IOP	30.76±8.4 (19–47)	32.13±7.81 (16–52)	0.51
Medication	3.5±0.65 (2–4)	3.28±0.51 (2–4)	0.15
Cup/disk ratio	0.74±0.24 (0.2–1.0)	0.83±0.17 (0.5–1.0)	0.06
CCT	568.87±33.71 (516–617)	613.62±65.19 (511–695)	0.11
RNFL	74.2±16.63 (45–95)	81.45±17.67 (55–114)	0.31
Follow-up time (mean±SD)	30.76±20.4	35.02±16.91	0.2

AGV: Ahmed glaucoma valve; PPV: Pars Plana vitrectomy; PDR: Proliferative diabetic retinopathy; BCVA: Best corrected visual acuity; IOP: Intraocular pressure; CCT: Central corneal thickness; RNFL: Retinal nerve fiber layer; SD: Standard deviation; SO: Silicone oil. Categorical data were expressed as n (%).

The median follow-up time was 30.76 months in the trabeculectomy group and 35.02 months in the AGV group (p=0.08). No significant difference was observed in mean IOP between the groups throughout follow-up, except at the 1- and 6-month visits (p=0.04 and p=0.01, respectively), where IOP was lower in the trabeculectomy group (Fig. 1). The number of antiglaucoma medications was significantly lower in the trabeculectomy group at all follow-up visits except for at 1 week (p<0.05 for all, Table 2). BCVA was similar between the groups at all follow-ups (p>0.05 for all).

While the overall success rate was similar between the trabeculectomy (84.0%) and AGV (75.8%) groups, the complete success rate was higher in the trabeculectomy group. The percentage of eyes free of antiglaucoma medication in the trabeculectomy group was 40.0% (10 eyes), compared to 15.2% (5 eyes) in the AGV group (p=0.04). Figure 2 shows the Kaplan–Meier survival curves of complete success rates, and Figure 3 represents the overall success rates of each group (p=0.016 and p=0.69, respectively). The cumulative probability of overall success at 12, 24, and 36 months was 92.0%, 88.0%, and 84.0%, respectively, in the trabeculectomy group,

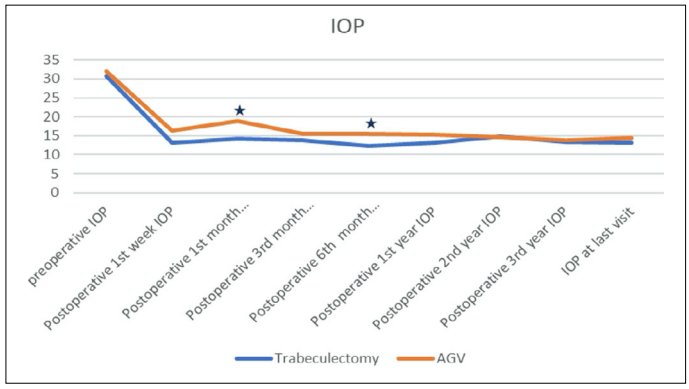

Figure 1. Graphic of intraocular pressure values of both groups in all follow-ups.

AGV: Ahmed glaucoma valve; IOP: Intraocular pressure, statistically significant.

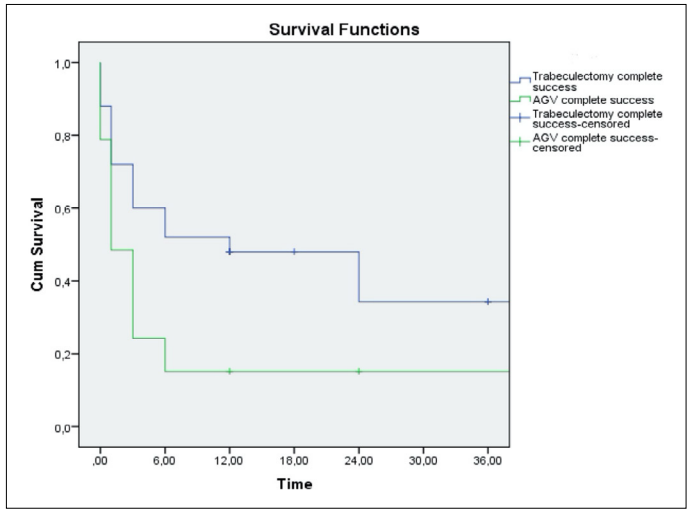

Figure 2. Kaplan–Meier survival graphic showing each group's complete success rates (p=0.016).

Table 2. Mean intraocular pressure values and the number of antiglaucoma medications of both groups in all follow-ups

	Trabeculectomy	AGV	p
Post-operative 1st week IOP	13.08±8.27 (1–35)	16.27±8.73 (2–38)	0.18
Number of antiglaucoma medication in 1st week	0.43±1.04 (0–4)	0.72±1.31 (0–3)	0.39
Post-operative 1st month IOP	14.12±7.78 (2–33)	18.83±8.36 (1–40)	0.04
Number of antiglaucoma medication in 1st month	0.54±0.98 (0–3)	1.46±1.41 (0–3)	0.01
Post-operative 3rd month IOP	13.86±5.81 (8–33)	15.4± 6.83 (2–31)	0.39
Number of antiglaucoma medication in 3rd month	1.08±1.34 (0–4)	2.01±1.34 (0–4)	0.02
Post-operative 6th month IOP	12.2±4.01 (4–24)	15.39±4.99 (8–33)	0.01
Number of antiglaucoma medication in 6th month	1.32±1.43 (0–4)	2.22±1.33 (0–4)	0.02
Post-operative 1st year IOP	13.24±5.55 (2–32)	15.27±4.67 (6–30)	0.14
Number of antiglaucoma medication in 1st year	1.24±1.39 (0–4)	2.06±1.39 (0–4)	0.03
Post-operative 2nd year IOP	14.84±7.79 (4–38)	14.42±3.92 (9–23)	0.82
Number of antiglaucoma medication in 2nd year	1.23±1.42 (0–4)	2.31±1.34 (0–4)	0.03
Post-operative 3rd year IOP	13.31±7.23 (4–34)	13.72±3.57 (7–23)	0.83
Number of antiglaucoma medication in 3rd year	1.23–1.3 (0–3)	2.27±1.31 (0–4)	0.04
IOP at last visit	13.04±6.51 (4–38)	14.48±5.73 (8–30)	0.37
Number of antiglaucoma medication at last visit	1.56±1.55 (0–4)	2.39±1.43 (0–4)	0.04

AGV: Ahmed glaucoma valve; IOP: Intraocular pressure.

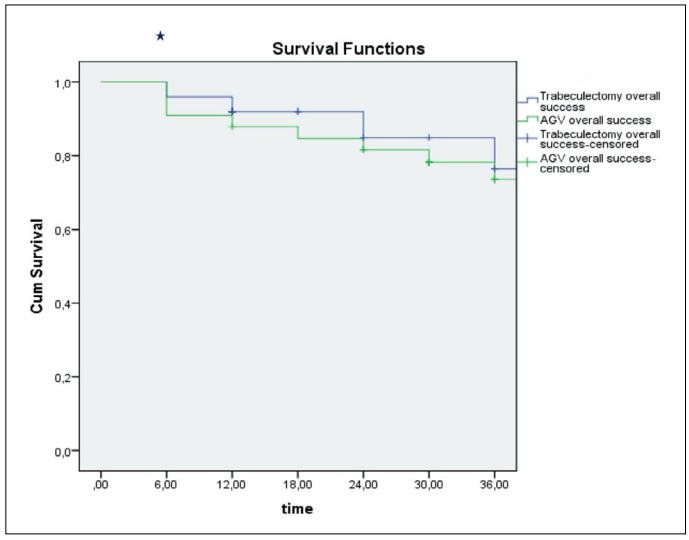

Figure 3. Kaplan–Meier survival graphic showing each group's overall success rates (p=0.69).

and 87.8%, 81.8%, and 75.7%, respectively, in the AGV group.

When eyes were classified based on SO tamponade, the overall success rates following trabeculectomy and AGV were comparable (88.9% vs. 81.8%, respectively; p=0.62); however, complete success was significantly higher in the trabeculectomy group than in the AGV group (50% vs. 9.1%, respectively; p=0.04) among eyes without prior SO. In eyes with prior SO tamponade, the trabeculectomy and AGV groups achieved comparable rates of overall success (71.4% vs. 72.7%, respectively; p=0.9) and complete success (14.3% vs. 18.2%, respectively; p=0.8).

Bleb needling was performed in 2 eyes (8 %) in the trabeculectomy group, and AGV cyst excision was performed in 4 eyes (12.2%) in the AGV group. Surgical failure occurred in 4 eyes (16.0%) in the trabeculectomy group and 8 eyes (24.2%) in the AGV group (p=0.44). In the trabeculectomy group, surgical failure was the result of a final IOP >22 mmHg in 2 eyes (8.0%), a final IOP lower than 5 mmHg in 1 eye (4.0%), and the need for further glaucoma surgery in 1 eye (4.0%). In the AGV group, failure was related to vision loss in 3 eyes (9.1%), final IOP over 22 mmHg in 4 eyes (12.1%), and the need for additional glaucoma surgery in 5 eyes (15.2%) (Table 3).

Post-operative complications were observed in 3 (12.0%) eyes in the trabeculectomy group and 7 eyes (21.2%) in the AGV group (p=0.36). In the trabeculectomy group, post-operative complications included hypotony and choroidal effusion in 1 eye (4.0%), intraocular lens drop in 1 eye (4.0%), cystoid macular edema in 1 eye (4.0%), and cataract formation in 1 eye (4.0%). In the AGV group, hypotony and choroidal effusion were observed in 2 eyes (6.06%), cystoid macular edema in 2 eyes (6.06%), tube exposure in 2 eyes (6.06%), tube obstruction in 1 eye (3.03%), and bullous keratopathy in 1 eye (3.03%). In the single case of tube obstruction, tube extraction was performed due to exposure and obstruction of the tube by the iris; in the single case of bullous keratopathy, evisceration was performed due to vision loss. Two cases of choroidal effusion responded well to topical treatment, while 1 case (3.03%) in the AGV group required viscoelastic substance injection into the anterior chamber due to persistent choroidal detachment (Table 4).

Discussion

An increase in IOP following PPV is common, with even higher incidence noted when SO is used as an endotamponade (5,15). Trabeculectomy remains the gold standard for treating medically refractory glaucoma. This procedure establishes a channel between the anterior chamber and the subconjunctival space, allowing aqueous humor from the an-

Table 4. Post-operative complications in each group

	Trabeculectomy group (n=25) (%)	AGV group (n=33) (%)
Hypotony and choroidal effusion	1 (4.0)	2 (6.06)
IOL drop	1 (4.0)	
CME	1 (4.0)	2 (6.06)
Cataract formation	1 (4.0)	
Tube exposure		2 (6.06)
Obstruction of tube		1 (3.03
Bullous keratopathy		1 (3.03)

AGV: Ahmed glaucoma valve; IOL: Intraocular lens; CME: cystoid macular edema. Categorical data were expressed as n (%).

Table 3. Reasons for failure in each groups

	LP loss	Final IOP >22 mmHg (%)	Final IOP <5 mmHg (%)	Further glaucoma surgery (%)
Trabeculectomy group (n=25)	0	2 (8.0)	1 (4.0)	1 (4.0)
AGV group (n=33)	3 (9.1)	4 (12.1)	0	5 (15.2)

LP: Light perception; AGV: Ahmed glaucoma valve; IOP: Intraocular pressure. Categorical data were expressed as n (%).

terior chamber to drain beneath the conjunctival bleb (16). Success of trabeculectomy largely depends on the long-term viability of the bleb, with post-operative conjunctival scarring posing a substantial risk for failure (7). Thus, trabeculectomy after vitrectomy is often less successful. However, advances in vitrectomy technology have led to more minimally invasive procedures, shorter operation times, and reduced complication rates. These likely contribute to decreased conjunctival fibroblast proliferation, reduced chemical factors in the vitreous, and the presence of fewer inflammatory cells (12).

GDDs are widely used, especially in cases at high risk for bleb failure, such as in patients with neovascular glaucoma (NVG) or those who have undergone vitrectomy or other conjunctival incisional procedures. GDDs include a silicone tube that allows aqueous outflow from the anterior chamber to an endplate. However, they have notable limitations, including restriction of ocular movement, potential tube exposure, a higher rate of early hypotony, corneal touch, and an increased need for penetrating keratoplasty. Consequently, many surgeons reserve GDDs for refractory cases (14,17). Further research on the optimal surgical methods for managing glaucoma in vitrectomized eyes is essential to determine the most effective strategy.

We compared the long-term outcomes of trabeculectomy and AGV implantation in a population of vitrectomized eyes. During an average follow-up of 33.17 months, complete success was achieved in 40.0% of eyes in the trabeculectomy group and 15.2% in the AGV group, while overall success rates were 84.0% and 75.8%, respectively. Complete success was higher in the trabeculectomy group, and 40.0% of eyes remained medication-free at the final follow-up (p=0.04). The cumulative probabilities of success were 92.0% and 87.8% at 1 year, 88.0% and 81.8% at 2 years, and 84.0% and 75.7% at 3 years in the trabeculectomy and AGV groups, respectively.

A previous study reported the success rates of trabeculectomy after vitrectomy as 55.1%, 45.3%, and 43.1% at 1-, 2-, and 3-year post-surgery, respectively. Their lower success rates were attributed to the high prevalence of NVG (67.2%) and uveitis (7.2%) in the cohort (12). Chronic inflammation and NVG are well-established risk factors for trabeculectomy failure (7). Neovascularization is considered to impair post-operative wound healing. In addition, factors such as extensive conjunctival inflammation, scarring, increased influx of vasoactive materials from the vitreous into the anterior chamber, and post-vitrectomy inflammation may contribute to poor outcomes after trabeculectomy in vitrectomized eyes (12,18,19). The trabeculectomy success rates for vitrectomized NVG cases were reported as 62.6% at 1 year and 58.2% at 2 years post-surgery in the study by Takihara et al. (19) In contrast, the success rates demonstrated in the current study were higher than previously reported, which may be attributed to differences in patient populations. Our cohort included eyes that had undergone vitrectomy due to various indications; the single NVG case in the trabeculectomy group failed postoperatively after 12 months. In addition, 2 eyes required bleb needling during follow-up, although this was not regarded as a failure in our study.

Trabeculectomy is considered more likely to fail in eyes where SO was used as the endotamponade during vitrectomy. This is mainly due to conjunctival scarring and emulsified SO, which can induce inflammation and fibrosis (20). Among our patients, 7 eyes (28.0%) had prior SO endotamponade, and none experienced failure in the long term, except for the single NVG case. The rate of prior SO tamponade was more prevalent in the AGV cohort (66.7%). When eyes were subgrouped according to prior SO tamponade, complete success was significantly higher in the trabeculectomy group than in the AGV group among eyes without prior SO. However, in eyes without prior SO, overall success rates were similar between the two groups, and both complete and overall success rates were comparable in eyes with prior SO tamponade. Notably, the median SO removal time in these eyes was 4 months, significantly shorter than the durations reported in the literature (20). In addition, although not statistically significant, SO was removed even sooner in the trabeculectomy group, which may have further contributed to the favorable outcomes.

Previously reported success rates of AGV implantation after vitrectomy range between 62% and 80% at 12- and 24-month follow-up, comparable to our findings (13,14,21,22). Lower visual acuity, higher pre-operative IOP, presence of NVG, and prior glaucoma surgery have all been identified as factors predicting failure in tube shunt procedures (23,24). Meanwhile, in a study comparing outcomes of AGV implantation in vitrectomized eyes with and without SO endotamponade, mean IOP, number of medications, and complication rates were similar between the two groups after 2 years (14). However, the success rate was 70.2% in eyes with SO and 87.2% in eyes without SO, suggesting SO to be a risk factor for AGV failure (14). Early SO removal may facilitate IOP control, but the risk of recurrent retinal detachment often restricts this possibility. In the present study, the overall AGV success rate was 75.8%, and a majority of AGV-implanted eyes (60.6%) required antiglaucoma medications for IOP management, consistent with previous studies (13,14,21,22,25). In our series, 66.7% of AGV-implanted eyes had prior SO endotamponade, which was removed in a median of 7 months.

El-Saied et al. (13) evaluated four different glaucoma surgeries in vitrectomized eyes using a more homogenous population, in which all eyes had undergone vitrectomy for retinal detachment with SO endotamponade. At 12-month follow-

up, the authors reported the highest success rate with the Ex-Press mini shunt (100%), followed by the AGV implantation (80%). Both trabeculectomy and deep sclerectomy surgeries had a lower success rate (50%) (13). In the present study, overall success rates were comparable between the two groups (84% in the trabeculectomy group and 76% in the AGV group). While the success rate of AGV was consistent with previous studies, trabeculectomy demonstrated a greater success rate than previously reported. This difference may be attributed to the higher proportion of cases with SO endotamponade and a younger mean age in the AGV group compared to the trabeculectomy group in our study.

Previous investigations demonstrate that younger age is an independent risk factor for post-operative failure after both trabeculectomy and AGV implantation. This association is generally attributed to the more pronounced inflammatory response in younger patients, which accelerates bleb scarring and implant encapsulation (12,13,23,24). In our series, the mean age of the trabeculectomy cohort was substantially higher than that of the AGV cohort; this difference may have favorably influenced the surgical outcomes observed in the trabeculectomy group.

Post-operative complications were observed at similar rates in both groups. In vitrectomized eyes, hypotony and choroidal effusion are among the most common complications following glaucoma surgery (13,25). El-Saied et al. (13) report hypotony in 50% of eyes following AGV implantation and in 40% of eyes following trabeculectomy. Pakravan et al. (25) reported choroidal effusion in 4 out of 15 eyes after trabeculectomy and in 2 out of 15 eyes following AGV implantation in a cohort of vitrectomized and aphakic eyes; suprachoroidal hemorrhage occurred in 2 other eyes in their AGV group. In our study, hypotony was observed in 3 (12%) cases in the trabeculectomy group and 3 (9.1%) cases in the AGV group at the 1-month post-surgical visit. However, chronic hypotony had developed in only one trabeculectomy case by the final follow-up, which was considered a surgical failure in our study. Other complications observed in our series included tube exposure and tube obstruction, both of which demanded further surgical intervention.

The primary limitations of this study include the relatively small cohort of patients, the heterogeneity of the groups in terms of PPV indications, its retrospective design, and the lack of patient randomization. The unequal distribution and duration of SO tamponade between the trabeculectomy and AGV groups, as well as the high mean age in the trabeculectomy group, may have influenced surgical outcomes, thereby limiting the generalizability of the comparative results. Nevertheless, the current study's findings suggest that trabeculectomy may have outcomes as favorable as AGV in the long term in selected vitrectomized eyes.

Conclusion

Although both AGV implantation and trabeculectomy demonstrated comparable results in vitrectomized eyes, this finding should be interpreted with caution due to differences in patient characteristics between the groups. The need for post-operative antiglaucoma medications was lower following trabeculectomy, which may indicate its potential as a favorable option in appropriately selected eyes. Ultimately, the decision between these two surgical options should be guided by the surgeon's expertise and an assessment of conjunctival mobility and integrity.

Disclosures

Ethics Committee Approval: This study was approved by the Health Sciences University Hamidiye Scientific Research Ethics Committee (Date: 14.03.2024, Number: 3/37) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from all patients.

Conflict of Interest: None declared.

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Original Article

A 5-Year Analysis of Optical Coherence Tomography Biomarkers in The Visual Outcomes of an As-Needed Treatment Algorithm for Neovascular Age-Related Macular Degeneration

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Abstract

Objectives: This study aimed to predict the visual course of patients with neovascular age-related macular degeneration by analyzing data from a 5-year observational study and to identify biomarkers that have an impact on visual prognosis.

Methods: The present study comprised a total of 104 patients who received the PRN treatment regimen between March 2015 and March 2021. Best-corrected visual acuity (BCVA) and optical coherence tomography findings were evaluated. Multinomial logistic regression models were used to determine predictors of BCVA at 12, 24, and 60 months.

Results: Better BCVA and thicker macula at baseline, decreased BCVA at month 3, and persistence of IRF at month 3 were correlated with decreased BCVA at month 12 (all $p<0.05$). At 24 month, a decline in BCVA was associated with specific baseline characteristics, including better BCVA, absence of pigment epithelial detachment (PED), and presence of intraretinal cystoid fluid (IRF) (all $p<0.01$). Similarly, decreased BCVA and thicker macula in the 3rd month were associated with worse BCVA. At the 60-month visit, better baseline BCVA, absence of PED, presence of IRF at baseline, and persistence of IRF at month 3 were associated with a reduction in BCVA (all $p<0.05$). The visual prognosis had no correlation with the number of injections.

Conclusion: This 5-year real-life study identified prognostic markers that cause a decline in visual acuity. The use of these markers has the potential to be valuable in preserving visual gain, irrespective of the number of injections.

Keywords: Anti-vascular endothelial growth factor, Biomarkers, Neovascular age-related macular degeneration, Real-life, Visual prognosis

Introduction

In the year 2020, age-related macular degeneration (AMD) was listed as one of the primary causes of loss of vision in people aged 50 and over worldwide (18 million cases) (1). In the case of neovascular AMD (nAMD), the development of subretinal or sub-retinal pigment epithelium (RPE) choroidal neovascularization (NV) can irreversibly reduce visual acuity (VA) (2).

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Intravitreal anti-vascular endothelial growth factor (VEGF) injection therapy has been demonstrated to minimize macular complications by suppressing neovascular membrane formation (2-6). However, despite the use of these agents, only some patients achieve the desired VA gain and anatomic improvement. Therefore, some studies have been undertaken to predict the treatment response of patients with nAMD. In these studies, biomarkers (age, genetic factors, initial VA) and optical coherence tomography (OCT)-based markers (status of vitreomacular interface, presence of fibrovascular or serous pigment epithelial detachment (PED), subretinal and intraretinal fluid, hyperreflective foci [HF]) were thoroughly investigated to identify the characteristics of patients requiring intensive treatment (5-7). Personalized disease prognosis can be achieved by describing probable prognostic factors using biomarkers.

The objective of our study was to ascertain the prognostic factors and biomarkers that affect visual outcomes by analyzing real-life data and establishing criteria for creating personalized disease prognoses for treatment-naïve patients. This study represents the first investigation, to the best of our knowledge, to provide 5 years of real-life data in Türkiye, with the aim of identifying biomarkers that can be used to predict visual outcomes of nAMD treatment.

Methods

This retrospective study was conducted in the medical retina department of a tertiary care center between March 2015 and 2021. The medical records of patients who received intravitreal anti-VEGF injections for nAMD were reviewed. The study followed the tenets of the Declaration of Helsinki and it was approved by the ethics committee of Ankara Training and Research Hospital. Informed consent was obtained from all participants. The trial registration number (retrospectively registered) was E-21-687 (August 18, 2021).

The study comprised a series of patients aged 50 years and over who underwent intravitreal injection of anti-VEGFs for nAMD, with a 5-year follow-up period. The study excluded all patients who had any disease causing choroidal neovascular membrane formation other than AMD, any retinal and corneal pathology affecting VA, and image quality. In addition, patients with a history of intraocular surgery, except uncomplicated phacoemulsification with intraocular lens implantation, and a history of uveitis and any hereditary retinal disease were excluded.

Following the administration of 3-month loading doses of aflibercept (Eylea®, Bayer, Berlin, Germany) or ranibizumab (Lucentis®; Genentech/Roche, USA), the treatment algorithm was adapted to an as-needed (PRN) basis. OCT follow-ups were conducted at 4–6-week intervals to monitor patient progress. We performed retreatment when there was a decrease of one or more lines in VA due to disease activity, persistence of intraretinal or subretinal fluid (SRF), an increase of more than 100 µm in central macular thickness (CMT), or development of new-onset macular hemorrhage. A decreased VA due to central atrophy was not an indication for injection.

All patients underwent a complete ophthalmic examination, including medical and family history, best-corrected visual acuity (BCVA, measured on an early treatment diabetic retinopathy study [ETDRS] chart converted to logarithm of the minimum angle of resolution [logMAR]), intraocular pressure measurement, slit-lamp biomicroscopy, and dilated fundus examination using a 90 D lens during the follow-up. OCT (Heidelberg Engineering, Franklin, MA 02038, USA) and fundus fluorescein angiography (Carl Zeiss Meditec, Inc., Dublin, CA) were performed in all patients with AMD. The types of choroidal NV (CNV) were recorded. CMT measurements were obtained using spectral domain OCT. The BCVA and CMT values, as well as the OCT findings (presence of PED, intraretinal, and SRF), were evaluated at the baseline visit and at 3, 6, 12, 24, and 60 months. The extent of VA (logMAR) changes over time was determined by calculating the differences between eye-specific logMAR averages at initial and at every visit. The total number of injections administered and the total number of visits made by patients were meticulously calculated.

Cross-sectional images were analyzed using built-in software, and automated software was used to segment the retinal layers in foveal scans. Retinal thickness map analysis was performed using spectralis software on nine subfields according to the ETDRS definitions. CMT was measured as the average of all points within the inner circle of 1 mm radius. The presence of SRF, intraretinal cystoid fluid, PED, and HF was evaluated on OCT scans within 3 mm fovea at the baseline visit. The vitreomacular interface was classified according to the classification system established by the ınternational vitreomacular traction (VMT) study group. This classification was based on OCT images. OCT markers were evaluated for their effects on VA at 12, 24, and 60th months.

The clinical factors assessed included the patient's age, sex, and visual acuity as well as the findings of the OCT scan at baseline and at 3 months. The influence of these factors on the final visual outcomes at 12, 24, and 60 months was analyzed.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 27 software. (SPSS, Inc. Chicago, IL). Descriptive statistics are given as mean±standard deviation or median (minimum-maximum) for continuous variables and frequency (%) for categorical variables. The assessment of normality was conducted by Kolmogorov–

Smirnov test. Multinomial logistic regression models were used to identify predictors of VA at 12, 24, and 60 months. Patients were categorized into three groups according to the degree of change in their BCVAs, as outlined in the following sentence. An absolute difference of <0.2 logMAR was deemed to be a non-clinically relevant change, whereas an increase of 0.2 logMAR or greater was considered a decrease in VA, and a decrease of 0.2 logMAR or greater was regarded as an improvement in VA (7). The dependent variables were the BCVA status at 12, 24, and 60 months (decreased was defined as "1," a non-clinically relevant change was defined as "2," and increased was defined as "3"). The independent variables were baseline clinical and OCT findings. Numerical values (e.g., baseline BCVA, age, CMT) were included as continuous variables in the multinominal regression analysis. P<0.05 was considered to be statistically significant.

Results

A total of 223 patients who were followed up in the retina outpatient clinic and received regular treatment between March 2015 and March 2021 were identified. However, the current study incorporated a total of 104 eyes from 104 patients, with consistent longitudinal follow-up for 5 years. Fifty patients were male and 54 were female; the mean age of the patients was 71.66±9.28 (51–92) years. Angiographically, the CNV lesions were occult in 45%, minimally classic in 28.9%, predominantly classic in 17.7%, and retinal angiomatous proliferation in 8.4%. Table 1 presents a comprehensive overview of the patients' demographic characteristics, while Figure 1 illustrates the mean number of visits and injections.

The mean BCVA was 0.40 (0.00–3.0) logMAR at baseline. The mean VA changes at 3, 6, 12, 24, and 60th months were −0.07, −0.09, −0.05, 0.0, and +0.025 logMAR, respectively. The

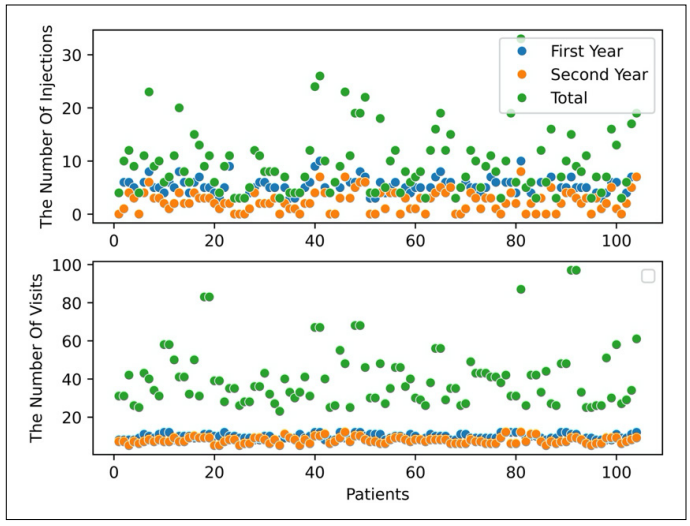

Figure 1. The mean number of visits and injections.

Table 1. Summary of the data of the study group

No. of patients/eyes at the beginning of study	**104/104**
Mean age (range, year)	71.66±9.28 (51–93)
Gender Male/Female (%)	50/54 (48/52)
Type of CNV lesion	
Type 1	47 eyes (45.1%)
Type 2	30 eyes (28.8% minimally classic)
	19 eyes (18.2% predominantly classic)
Type 3	8 eyes (8.2% RAP)
Anti-VEGF agents	
Ranibizumab/Aflibercept/(eyes)	93/11
The mean number of injections (mean±SD/median, minimum-maximum)	
1st year	5.2±1.5/5 (3–10)
2nd year	2.6±2.0/2.5 (0–8)
During the follow-up period	9.75±5.9/9 (3–33)
The mean number of visits (mean±SD/median, minimum-maximum)	
1st year	9.8±1.4/9.5 (8–12)
2nd year	7.6±1.7/7 (5–12)
During the follow-up period	40.16±15.5/38 (22–97)

SD: Standard deviation; VEGF: Vascular endothelial growth factor; CNV: Choroidal neovascularization; RAP: Retinal angiomatous proliferation.

mean baseline CMT was 302.5 (204–948) µm, and the mean CMT change at 3, 6, 12, 24, and 60th months after treatment was −27.50, −11, −6.5,+14.50, +7.50 µm, respectively (Fig. 2).

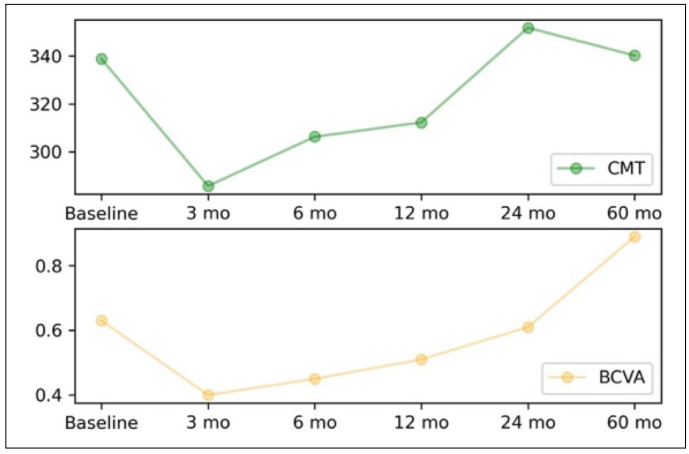

Figure 2. The mean visual acuity and central macular thickness changes during the follow-up.

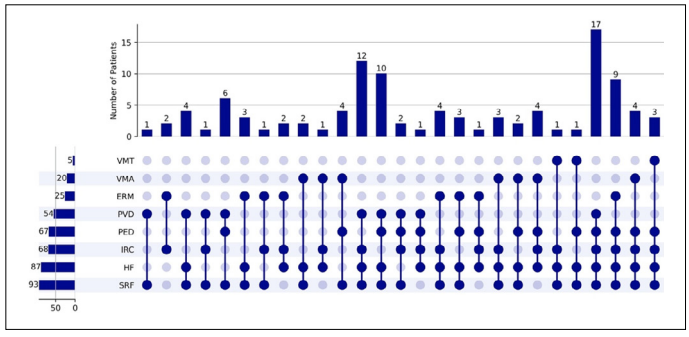

Figure 3. OCT findings of the patients at baseline visit.

OCT: Optical coherence tomography, PED: Pigment epithelial detachment, IRC: Intraretinal cystoid fluid, SRF: Subretinal fluid, HF: Hyper-reflective foci, ERM: Epiretinal membrane, PVD: Posterior vitreous detachment, VMA: Vitreomacular adhesion, VMT: Vitreomacular traction.

The most common OCT findings at baseline visit were SRF (91.6%), HF (79.4%), PED (57%), and intraretinal fluid/cyst (54.1%). Figure 3 shows the OCT findings of patients at the baseline visit.

Multinomial logistic regression analysis was conducted to evaluate the combined impact of clinical and OCT biomarkers at baseline and after 3 monthly loading doses on BCVA status at 12, 24, and 60 months. Better baseline BCVA ($p<0.001$), thicker macula at baseline ($p=0.013$), decreased BCVA at the 3rd month ($p<0.001$), and IRF resistance at month 3 ($p<0.001$) were found to be associated with decreased BCVA at the 12th month. At the 24 months, a statistically significant correlation was observed between the decreased BCVA and several baseline characteristics. These included better baseline BCVA ($p<0.001$), absence of PED ($p=0.008$), and presence of IRF ($p=0.006$). Furthermore, decreased BCVA ($p=0.005$), thicker CMT ($p=0.017$) at the 3rd month, and persistence of IRF at the 3rd month were identified as significant factors associated with decreased BCVA. At the 60 months, a better baseline BCVA ($p=0.01$), absence of PED ($p=0.026$), presence of IRF ($p=0.019$) at baseline, and persistence of IRF at month 3 ($p=0.002$) were linked to a decline in BCVA (Table 2 and Fig. 4).

Discussion

In this study, the real-world data of anti-VEGF agents used in the treatment of AMD over a 5-year follow-up period were evaluated. Furthermore, we identified biomarkers and OCT markers that may affect BCVA at 12, 24, and 60 months.

An extensive number of studies have been conducted to evaluate the outcomes of PRN and Treat-and-Extend (T and E) regimens, as compared with monthly injections. The number of injections in PRN studies was lower than that in T and E regimens. Almost all previous studies demon-

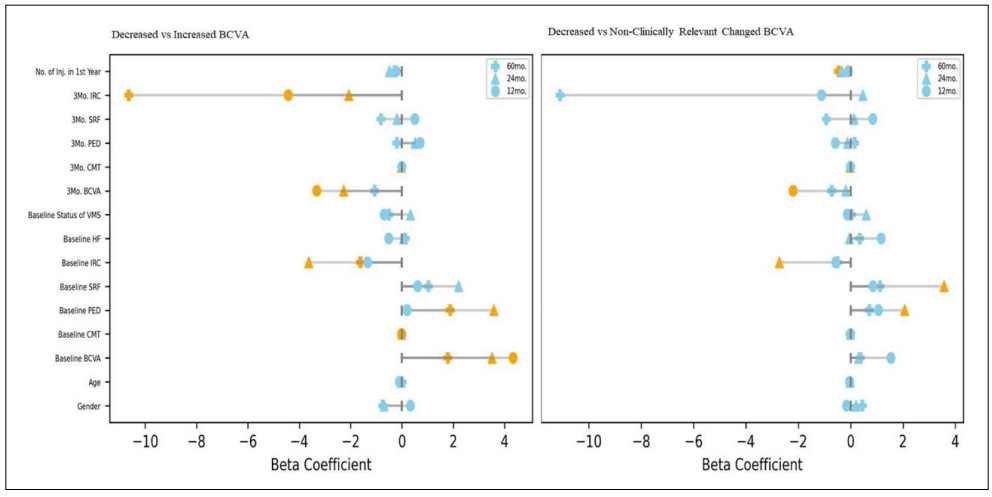

Figure 4. The results of the multinomial logistic regression analysis (The statistical significance of the results is indicated by the use of orange icons, while non-significant results are represented by blue icons).

Table 2. The results of multinominal regression analysis

	Decreased BCVA versus Increased BCVA						Decreased BCVA versus Unchanged BCVA					
	12 Mo		24 Mo		60 Mo		12 Mo		24 Mo		60 Mo	
	p	Odds ratio	p	Odds ratio	p	Odds ratio	p	Odds ratio	p	Odds ratio	p	Odds ratio
Gender	0.74	1.39	0.52	0.50	0.35	0.48	0.83	0.86	0.79	1.23	0.49	1.57
Age	0.08	0.91	0.62	0.97	0.95	1.00	0.42	0.97	0.68	0.98	0.26	0.96
Baseline BCVA	0.00	76.09	0.00	33.54	0.01	5.98	0.32	4.67	0.82	1.36	0.63	1.45
Baseline CMT	0.02	0.98	0.58	1.00	0.43	1.00	0.37	1.00	0.48	1.00	0.01	0.99
Baseline PED	0.85	1.22	0.01	36.02	0.02	6.56	0.16	2.90	0.02	7.87	0.30	2.06
Baseline SRF	0.62	1.85	0.16	9.13	0.43	2.80	0.37	2.36	0.01	35.55	0.21	3.07
Baseline IRC	0.21	0.26	0.01	0.03	0.04	0.20	0.47	0.57	0.02	0.07	0.47	0.61
Baseline HF	0.63	0.60	0.96	1.07	0.88	1.14	0.17	3.22	0.97	0.96	0.66	1.42
Baseline status of the vitreomacular surface	0.25	0.50	0.60	1.40	0.28	0.60	0.77	0.88	0.24	1.81	0.92	1.04
3 Mo. BCVA	0.00	0.04	0.01	0.10	0.27	0.35	0.04	0.11	0.87	0.83	0.47	0.49
3Mo. CMT	0.47	0.99	0.02	0.98	0.92	1.00	0.30	0.99	0.01	0.98	0.68	1.00
3Mo. PED	0.55	2.04	0.66	1.68	0.81	0.82	0.52	0.56	0.90	0.89	0.84	1.16
3Mo. SRF	0.69	1.66	0.88	0.82	0.40	0.44	0.39	2.34	0.90	1.14	0.28	0.39
3Mo. IRC	0.03	0.01	0.04	0.13	0.04	0.00	0.45	0.33	0.75	1.60	0.80	0.00
No. of injections in 1st year	0.49	0.80	0.19	0.61	0.23	0.75	0.74	0.92	0.27	0.71	0.04	0.63

BCVA: Best-corrected visual acuity, PED: Pigment epithelial detachment, IRC: Intraretinal cystoid fluid, SRF: Subretinal fluid, CMT: Central macular thickness, Mo: month, HF: Hyper-reflective foci.

strated that as injections increased, patients gained more letters and demonstrated excellent vision maintenance (5-7). The mean number of injections in the initial year of treatment was 5.2, which is consistent with the findings of other studies (8,9). In the subsequent year under the PRN regimen, this number decreased to an average of 2.6 injections. The findings of this study indicate that the number of injections in the 1st year of treatment has no effect on visual prognosis. However, although visual acuity stability was maintained during the first 2 years of treatment, it was not sustained at 60 months. One potential strategy to address this issue could be to determine the frequency of injections based on the prognostic factors identified in the present study.

We analyzed prognostic indicators at baseline and at month 3 to predict individual treatment prognosis. In previous studies, patient age has been reported as a biomarker of treatment response. In most of these studies, younger patient age was correlated with good final VA results (2,3,5,10,11). In the current study, patient age was not correlated with BCVA during follow-up. The mean age of our patients was 71.66 and the proportion of patients aged <65 years was only 23%, indicating that our patients predominantly comprised elderly individuals.

Wang et al.(12) reported that men exhibited a 2.19-fold increased risk of reinjection than women. Similarly, the 5-year follow-up results of the comparison of AMD treatment trial (CATT) study demonstrated that, compared to men, women were more likely to gain a minimum of 15 letters (13). In the current study, there was no difference in the follow-up between females and males. These results match those observed in previous studies (14,15).

Another important predictor of visual improvement was the baseline VA level. A number of studies correlated poor baseline VA with better visual outcomes at year 1 and year 2; however, some studies reported better baseline VA as a predictor of better final VA (4,5,16,17). In our study, poor baseline VA had a significantly positive effect on VA level in all visits. However, even if patients with poor baseline VA seem to gain more VA, they will have poorer final VA. Several reports have shown that initiating treatment early is one of the significant factors for improved visual outcomes (18,19).

As demonstrated in preceding studies, the BCVA level following three loading doses has been identified as a significant predictor of the final visual outcome (5,11). The present study's findings provide further evidence in support of this hypothesis, thereby demonstrating a positive correlation between VA levels following three loading doses and VA levels at 12, 24, and 60 months. The BCVA level achieved after three loading doses was valuable for predicting long-term visual prognosis.

OCT-based biomarkers are used to predict visual prognosis while assessing treatment response. At present, CMT is not used as a monitoring or retreatment indicator. Therefore, evaluating CMT alone is insufficient to distinguish subtle changes in retinal compartments. Furthermore, there was a weak correlation between VA and retinal thickness. Our results indicate that baseline CMT significantly affects VA at month 12, but not at 24 and 60 months. However, a thick macula after three loading doses affected the BCVA at month 24. A thicker central macula may unfortunately lead to morphological changes in the retinal layers, resulting in a poorer long-term visual prognosis.

Another significant biomarker investigated in previous studies is the location of fluid within the retinal layers, including intraretinal and SRF. In most of the previous studies, the presence of SRF at baseline and during follow-up was associated with favorable visual outcomes (20,21). While there are studies showing that SRF <200 μm can be tolerated with no negative effect on VA, there are also studies showing a progressive decrease in retinal sensitivity in eyes with SRF (22,23). The present study found no statistically significant correlation between the presence of SRF at baseline or at 3 months and subsequent visual prognosis during follow-up. In contrast, a number of earlier studies have shown that the existence of IRF at baseline and throughout the follow-up period is indicative of a poor final visual prognosis (13,14,21). Our findings align with those of numerous preceding studies, which have demonstrated a correlation between the presence of baseline IRF and a decline in BCVA over time. Similarly, the results of the multinomial logistic regression analysis in our study indicated that the presence of IRF following loading doses has a negative predictive value for visual gain.

The presence of PED and its persistence after loading are prognostic factors evaluated in previous studies. The association between the presence of PED at the baseline visit and visual outcomes has been reported in previous studies (14). Some reports indicate no significant association with the risk of inferior visual outcomes, whereas others specifically state that PED width predicts disease progression (24,25). In addition, it has been documented that fibrovascular or vascularized PED may result in a less favorable visual outcome. Nonetheless, certain studies have indicated a possibility that the presence or persistence of PED may be associated with relatively good VA (26). The present study found that the presence of PED at baseline had no effect on VA at 12 months. However, it was linked to better VA at 24 and 60 months. The present study did not concentrate on a comparison between serous and fibrovascular PEDs; however, the majority of the observed PEDs in the current study fell under the serous category.

The vitreomacular interface status has been considered an important risk factor in previous reports. In the literature, eyes with vitreomacular adhesion (VMA) had lower VA than those with PVD; these eyes also required more intensive treatment (14,27). Post hoc analysis of the MONT BLANC and CATT studies showed that there was no significant change in BCVA gains among the VMA, VMT, and RELEASE groups, but eyes with VMA and VMT required an increased number of injections to obtain favorable visual outcomes (22,28). In this study, the most common vitreomacular interface change was VMA. No correlation was observed between vitreomacular interface status at baseline and mean BCVA during the 60-month follow-up. In accordance with the existing literature, eyes with VMA, VMT, and epiretinal membrane required a higher average number of injections during follow-up than eyes with PVD (10 vs. 8 injections), although this was not statistically significant.

HF, another OCT finding, are small, well-defined dots located in the neurosensory retina and within the RPE (29,30). Coscas et al.(31) reported that poor BCVA at baseline was significantly correlated with the continuation of HFs after intravitreal injections. Some studies noted that HFs could be a biomarker of less VA gain, especially if they did not resolve with treatment (29-31). The presence of HF was found to have no effect on VA at 12, 24, and 60 months in this study. This study did not investigate the persistence of HF after injection but rather the relationship between the presence of HF at baseline and short- and long-term visual outcomes. These findings indicate that there is insufficient evidence to conclude that HF has an effect on visual prognosis.

The retrospective design of the study constitutes its primary limitation. Second, the potential effects of different anti-VEGF drugs were not addressed. Moreover, while a qualitative assessment of OCT parameters, including fluid, PED, and HF, was performed, a quantitative analysis of subretinal and intraretinal fluid volume, PED, and HF was not conducted. It may be useful to adopt a quantitative assessment approach to quantify the effectiveness of anti-VEGF treatment and the progression of AMD.

Conclusion

This study identified prognostic factors and OCT biomarkers affecting visual outcomes over a 5-year follow-up period in a real-world setting. The results indicated that lower baseline VA, absence of IRF, presence of PED at baseline, and lower macular thickness at baseline were predictive of better VA in the initial years following injections. Similarly, better BCVA at 3 months, absence of intraretinal fluid and the presence of PED, and reduced CMT at 3 months were significant prognostic markers for favorable visual outcomes in the initial 2 years following injections. The findings of our study indicate that the number of 1st year injections had no discernible effect on either short or long-term visual prognosis. In the present study, as in real-life studies, a decline in VA in patients treated with PRN regimens in the latter years of treatment was also observed. However, the use of favorable prognostic indicators, such as improved BCVA, absence of IRF, and a thinner macula following three loading doses, in conjunction with poor prognostic markers, including better baseline BCVA, absence of PED, and presence of IRF at the initial visit, may prove beneficial in preserving VA, regardless of the number of injections administered. This enables the creation of a personalized visual prognosis. Furthermore, when deciding on retreatment in a PRN regimen, it may be helpful to consider indicators affecting the visual prognosis. These indicators include the presence of IRF and its persistence after loading doses, thick macula persistence at 3 months, and inadequate visual improvement after loading doses. For this purpose, longitudinal studies with follow-up periods exceeding 5 years should be conducted with larger patient populations.

Disclosures

Ethics Committee Approval: This study was approved by the Ankara Training and Research Hospital Ethics Committee (Date:18.08.2021 Number: E-21-687).

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

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Original Article

The Role of Botulinum Toxin in Dry Eye Disease and Meibomian Gland Dysfunction Associated with Hemifacial Spasm

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Abstract

Objectives: To investigate the signs and symptoms of dry eye disease (DED) in patients with hemifacial spasm (HFS) through the evaluation of ocular surface measurements and meibomian gland function, and to assess the effects of botulinum toxin type A (BTX-A) injection on ocular surface health.

Methods: This prospective study included patients with unilateral HFS who underwent BTX-A injection as treatment. Eyes on the same side as the spasm were defined as the HFS group, whereas the contralateral, unaffected eyes were used as controls. Ocular surface assessments included the ocular surface disease ındex (OSDI) score, Schirmer's I test, tear break-up time (TBUT), corneal surface staining, eyelid margin abnormalities, and meibomian gland function. All evaluations were repeated at 1, 3, and 6 months following BTX-A injection.

Results: Compared to the control group, the HFS group demonstrated significantly higher OSDI scores, corneal surface staining, eyelid margin abnormalities, meibomian gland expression scores, meibography scores, and meibomian gland loss, whereas TBUT and Schirmer's I test values were significantly lower ($p<0.05$). A significant correlation was observed between the severity of HFS and ocular surface dysfunction, including meibomian gland dysfunction (MGD) ($p<0.05$). Following BTX-A injection, ocular surface parameters showed significant improvement at 1 month ($p<0.05$) and 3 months ($p<0.05$) compared to pre-injection values.

Conclusion: We found an association between HFS and DED, which was correlated with the severity of HFS. In addition, BTX-A injection led to a temporary improvement in dry eye signs and symptoms, including MGD.

Keywords: Botulinum toxin, dry eye, hemifacial spasm, meibomian gland, ocular surface

Introduction

Hemifacial spasm (HFS) refers to a chronic condition involving unilateral, involuntary facial muscle contractions due to irritation or compression of the facial nerve. Although HFS is primarily known as a motor disorder, emerging evidence suggests a significant association with ocular surface dysfunction. Patients with HFS frequently report symptoms suggestive of dry eye disease (DED), such as irritation, tearing, and eye discomfort, likely due to irregular blinking patterns and persistent orbicularis oculi muscle hyperactivity (1).

Previous research on ocular surface alterations in movement disorders has primarily focused on blepharospasm,

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which shares similar clinical features with HFS, including increased blink frequency and forceful eyelid closure (2,3). However, data specific to HFS remain limited (4,5). In particular, the role of meibomian gland dysfunction (MGD) in the pathogenesis of DED among patients with HFS remains poorly understood (4,5).

Botulinum toxin type A (BTX-A) is the mainstay treatment for HFS, offering temporary relief from muscle spasms by inhibiting acetylcholine release at neuromuscular junctions (1). While its efficacy in reducing motor symptoms is well documented, evidence regarding its effects on the ocular surface and meibomian gland function has yielded inconsistent results (3,6,7).

This research was designed to provide a comprehensive evaluation of DED among HFS patients, incorporating both patient-reported outcomes (ocular surface disease index (OSDI)) and clinical findings (tear break-up time (TBUT), Schirmer's I test, corneal staining, and meibomian gland assessment. Furthermore, we investigated the short- and midterm effects of periocular BTX-A injections on these parameters at 1-, 3-, and 6-month follow-up visits. By comparing findings from affected and contralateral eyes, this study also sought to clarify the localized impact of HFS on ocular surface homeostasis.

Methods

This prospective, cross-sectional observational study was carried out in the ophthalmology department of Dokuz Eylul University Hospital and included patients diagnosed with unilateral HFS. HFS was diagnosed based on standard criteria and confirmed by a neurology specialist (8). Exclusion criteria included the presence of ocular surface diseases other than DED, neurologic disorders other than HFS, eyelid malposition, punctal occlusion, glaucoma, contact lens wear, systemic comorbidities, prior ocular surgeries or trauma, medication use affecting tear production, and refractive errors >±4.00 diopters. The eye on the same side as the HFS was designated as the affected (homolateral) eye, whereas the non-affected (contralateral) eye served as an internal control. The study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Dokuz Eylul University (approval number: 2024/08-19). Informed consent was obtained in writing from all participants before study enrollment.

Demographic and clinical data were recorded for all patients. HFS severity was graded on a 4-point scale (0–4) based on the rating system established by Lee et al. (9) (Table 1) A single examiner performed a standardized ophthalmologic evaluation on all subjects, including both the HFS-affected and contralateral eyes, following completion of the OSDI questionnaire. The assessment protocol included Schirmer's I test, TBUT, corneal surface staining, eyelid margin grading, meibomian gland expression evaluation, and imaging with infrared meibography. Data from both eyes of each participant were included in the analysis. OSDI is a widely used, validated questionnaire comprising 12 items that assess the frequency and severity of symptoms associated with DED (10). Each item is scored on a scale from 0 (none of the time) to 4 (all of the time). The total score is determined by the following equation: (Sum of scores for all answered questions × 100)/(total number of questions answered × 4), with higher scores indicating more severe symptoms. Schirmer's I test was performed under non-anesthetized conditions using a standardized strip positioned at the outer one-third of the lower eyelid to measure tear production. The strip remained in place for 5 min, and the length of the wetted area (in millimeters) was recorded. TBUT was measured after using a minimally moistened fluorescein strip after instilling fluorescein dye into the conjunctival sac. After several blinks to evenly disperse the dye, the duration between the last complete blink and the first visible corneal dry spot was measured using cobalt blue illumination. Corneal fluorescein staining was used to evaluate superficial punctate keratopathy (11). The cornea was divided into five regions, each graded on a scale from 0 to 3, where 0 indicated no staining, 1 represented punctate staining, 2 denoted linear or ball staining, and 3 corresponded to coalesced staining. Eyelid margin abnormalities were graded on a 0–4 scale based on specific features, including lid margin irregularity, plugging of the meibomian gland orifices, vascular engorgement, and mucocutaneous junction displacement (12). Digital pressure was applied to the nasal and central regions of both

Table 1. Grading system for hemifacial spasm

Grade	Detailed description
1	Localized spasm around the periocular area
2	Involuntary movement spreads to other parts of the ipsilateral face and affects other muscle groups: The orbicularis oris, zygomaticus, frontalis, and platysma muscles
3	Interference with vision because of frequent tonic spasms
4	Disfiguring asymmetry: Continuous contraction of the orbicularis oculi muscles affects the opening of the eye

the upper and lower eyelids to evaluate meibomian gland expression. Expression quality was graded as follows: Grade 0 indicated clear meibum easily expressed, Grade 1 indicated cloudy meibum expressed with mild pressure, Grade 2 referred to cloudy meibum requiring moderate pressure, and Grade 3 indicated no expression despite firm pressure (13). Meibomian gland loss was assessed through infrared meibography and calculated as the percentage of gland dropout relative to the total area of the tarsal plate (14). Gland loss was scored using a five-grade meiboscore system: Grade 0 represented no gland loss, Grade 1 indicated <25% loss, Grade 2 indicated 25–50% loss, Grade 3 indicated 50–75% loss, and Grade 4 indicated more than 75% gland loss. The overall meiboscore was obtained by adding the individual scores of the upper and lower eyelids.

DED was diagnosed by the DEWS II guidelines, which require an OSDI score of ≥13 and at least one abnormal clinical test result, including Schirmer's I test (≤5 mm), positive corneal staining, or TBUT <10 s.(15) Patients with HFS were treated with onabotulinumtoxin A (100U, Botox, Allergan, Irvine, CA, USA) injections prepared and administered by a single clinician (Fig. 1). Each vial was reconstituted using 2 mL of preservative-free sterile saline, which produced a final concentration of 5 units/0.1 mL. The injections were performed using a 30-gauge needle at four sites in the medial and lateral pretarsal orbicularis oculi muscle and into the corrugator and procerus muscles between the eyebrows. An additional injection targeted the zygomaticus major muscle and was administered approximately 1–2 cm below the zygomatic arch along an anatomical line from the zygomatic bone to the oral commissure. A standardized total dose of 20 units of onabotulinumtoxinA was administered to the affected side in all patients. The dose was distributed as follows: 2.5 units were injected into both the medial and lateral portions of the pretarsal orbicularis oculi (totaling 5 units per eye for the periocular region), 5 units into the corrugator muscle, 5 units into the procerus muscle, and 5 units into the zygomaticus major muscle. This dosing regimen was consistent for all study participants and was not adjusted based on individual patient factors. All patients underwent ophthalmic examinations at baseline and 1, 3, and 6 months following BTX-A injections. No topical or systemic treatments for DED were administered to any patients with HFS throughout the study period.

Data analysis was performed using the Statistical Package for the Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean±standard deviation, and categorical variables were reported as frequencies and percentages. The Shapiro–Wilk test was applied to assess the normality of the data distribution. Independent samples t-tests were utilized for comparing continuous variables between different groups, and paired samples t-tests were conducted for within-group analyses. Chi-square tests were conducted for comparisons involving categorical data. Pearson's correlation coefficient was applied to quantify associations between continuous variables. Statistical significance was defined as a $p<0.05$. Post hoc power analysis performed with G*Power (v3.1.9.2) indicated that the study had more than 80% power to detect significant effects at the 0.05 alpha level.

Results

In this study, the 27 eyes affected by HFS were included in the HFS group, and the contralateral unaffected eyes of the same patients were used as the control group. Sixteen patients were female, 11 were male, and the mean age was 62.1±10.2 years. DED was diagnosed in 17 (44.4%) patients with HFS. The clinical characteristics and ocular surface measurements for the control and HFS groups are presented in Table 2.

In ocular surface assessments, the HFS group demonstrated significantly higher OSDI scores ($p<0.001$), shorter TBUT values ($p=0.001$), reduced Schirmer's I test results ($p<0.001$), and increased corneal surface staining scores ($p<0.001$) compared to the control group. Eyelid margin abnormality scores were also significantly more severe in the HFS group ($p<0.001$). Moreover, irregular eyelid margins ($p=0.013$), vascular engorgement ($p=0.002$), plugged meibomian gland orifices ($p=0.001$), and mucocutaneous junction displacement ($p=0.033$) were all significantly more prevalent in the HFS group than in controls. The HFS group exhibited significantly greater impairment in meibomian gland function compared to controls. This was reflected in elevated meibomian gland expression scores (upper, lower, and total; all $p<0.001$), increased meibography scores (upper, lower, and total; all $p<0.001$), and more extensive gland loss areas (upper, lower, and total; all $p<0.001$).

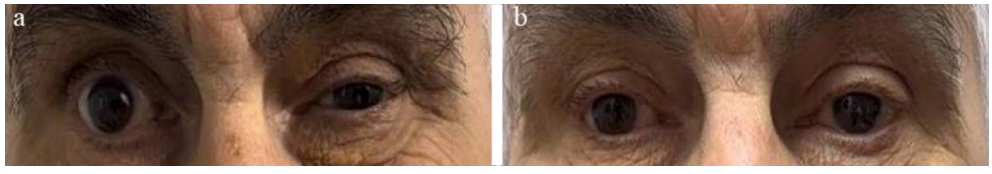

Figure 1. A patient with right-sided hemifacial spasm before **(a)** and after **(b)** botulinum toxin injections. Improved symmetry in eye opening is observed following treatment.

Table 2. Comparison of the clinical characteristics and ocular surface parameters of study groups

	Baseline			Post-BTX-A injection		
	Control (n=27)	Hemifacial spasm (n=27)	p	1 m (n=27)	3 m (n=27)	6 m (n=27)
Age (y)	62.1±10.2	62.1±10.2	1.0	62.1±10.2	62.1±10.2	62.1±10.2
Gender (Female/Male)	16/11	16/11	1.0	16/11	16/11	16/11
Body mass index (kg/m2)	26.3±3.8	26.3±3.8	1.0	26.3±3.8	26.3±3.8	26.3±3.8
Laterality (%)						
Right eye	17 (63)	10 (37)	0.057	10 (37)	10 (37)	10 (37)
Left eye	10 (37)	17 (63)		17 (63)	17 (63)	17 (63)
DED, n (%)	0 (0)	12 (44.4)	<0.001	3 (11.1)	5 (18.5)	8 (29.6)
OSDI score	15.3±8.3	27.1±12.6	<0.001	18.7±10.5	20.9±11.8	23.5±12.3
Tear break-up time (s)	9.33±5.7	5.48±3.1	0.001	8.70±5.3	7.85±4.9	6.44±4.6
Schirmer's I test (mm)	12.48±6.2	7.2±3.5	<0.001	10.5±4.9	9.63±4.6	8.7±4.3
Corneal surface staining score	1.9±1.5	7.5±3.7	<0.001	4.7±2.3	4.2±1.8	6.3±2.6
Eyelid margin abnormality score (%)	0.5±0.6	1.9±1.3	<0.001	1.1±0.8	1.3±0.9	1.6±1.1
Irregular eyelid margin	3 (11.1)	11 (40.7)	0.013	4 (14.8)	6 (22.2)	9 (33.3)
Vascular engorgement	2 (7.4)	12 (44.4)	0.002	4 (14.8)	4 (14.8)	8 (29.6)
Plugged meibomian gland orifices	3 (11.1)	14 (51.8)	0.001	3 (11.1)	5 (18.5)	11 (40.7)
Shift in the mucocutaneous junction	4 (14.8)	11 (40.7)	0.033	5 (18.5)	8 (29.6)	9 (33.3)
Meibomian expression						
Upper eyelid	0.7±0.7	1.9±1.3	<0.001	1.2±0.8	1.3±0.8	1.7±0.9
Lower eyelid	0.6±0.5	1.7±1.1	<0.001	1.0±0.9	1.1±0.9	1.6±0.9
Total	1.3±0.8	3.7±1.9	<0.001	2.2±1.5	2.5±1.6	3.3±1.8
Meibography score						
Upper eyelid	1.1±0.6	2.1±0.9	<0.001	1.4±0.8	1.5±0.8	1.7±0.8
Lower eyelid	0.9±0.5	1.9±0.9	<0.001	1.2±0.8	1.3±0.8	1.6±0.8
Total	2.1±0.9	4.1±1.2	<0.001	2.6±1.0	2.8±1.0	3.3±1.1
Area of meibomian gland loss						
Upper eyelid	17.8±7.1	40.5±19.4	<0.001	24.7±15.1	29.3±16.9	35.7±14.4
Lower eyelid	19.4±7.5	42.8±20.1	<0.001	30.3±17.1	32.4±17.9	37.6±18.1
Total	37.3±17.5	83.3±26.9	<0.001	55.1±22.3	61.7±23.4	73.3±25.9

BTX-A: Botulinum toxin A; DED: Dry eye disease; OSDI: Ocular surface disease index.

As shown in Table 3, correlation analysis was utilized to investigate the link between HFS severity and ocular surface indicators, including MGD parameters. There were significant positive correlations between the severity of HFS and several ocular surface parameters, including OSDI (r=0.506, p=0.001), corneal surface staining (r=0.537, p<0.001), meibomian gland expression (upper: r=0.543, p<0.001; lower: r=0.509, p=0.001; total: r=0.584, p<0.001), meibography scores (upper: r=0.427, p=0.016; lower: r=0.489, p=0.001; total: r=0.463, p=0.002), and the area of meibomian gland loss (upper: r=0.552, p<0.001; lower: r=0.506, p<0.001; total: r=0.538, p<0.001). In contrast, significant negative correlations were observed between HFS severity and TBUT (r=−0.454, p=0.008) as well as Schirmer's I test scores (r=−0.412, p=0.012).

A detailed comparison of ocular surface measurements and MGD in eyes with HFS at baseline and at 1, 3, and 6 months after BTX-A injection is presented in Table 4 and Figure 2. Among patients with HFS, OSDI, TBUT, Schirmer's I test, eyelid margin abnormality score, meibography scores

Table 3. The relationship between the hemifacial spasm severity and ocular surface parameters

	Hemifacial spasm severity	
	r	p
OSDI score	0.506	0.001
Tear break-up time (s)	-0.454	0.008
Schirmer's I test (mm)	-0.412	0.012
Cornea surface staining score	0.537	<0.001
Eyelid margin abnormality score	0.385	0.098
Meibomian expression		
Upper eyelid	0.543	<0.001
Lower eyelid	0.509	0.001
Total	0.584	<0.001
Meibography score		
Upper eyelid	0.427	0.016
Lower eyelid	0.489	0.001
Total	0.463	0.002
Area of meibomian gland loss		
Upper eyelid	0.552	<0.001
Lower eyelid	0.506	<0.001
Total	0.538	<0.001

OSDI: Ocular surface disease index.

(upper, lower, and total), and the extent of meibomian gland loss (upper, lower, and total) showed significant improvement at 1 ($p<0.05$) and 3 months ($p<0.05$) after BTX-A injection compared to pre-injection values. However, these improvements were no longer statistically significant 6 months after injection ($p>0.05$). Two (7.4%) eyes in our study developed a minor hematoma, which gradually resolved within 2 weeks after the injection.

Discussion

Our findings indicate a significant association between HFS and signs and symptoms of DED. A positive correlation was observed between the clinical severity of HFS and the degree of ocular surface alterations, including MGD. In addition, periocular administration of BTX-A alleviated the motor symptoms of HFS and resulted in significant improvements in ocular surface health.

In our study, the prevalence of DED among eyes affected by HFS was 44.4%. This is in line with findings by Raj et al.,(16) who reported that 8 out of 17 patients with HFS (47.06%) were diagnosed with DED, and by Pellegrini et al.,(5) who documented a prevalence of 42% (5,16). In contrast, Jariyokasol et al.(4) reported a DED prevalence of 37.93% in HFS-affected eyes, which was not statistically significantly different from that in the contralateral eyes (27.6%), despite a nearly 10% absolute difference that may be of clinical relevance (4). Differences in diagnostic criteria may explain the lower prevalence reported by Jariyokosol et al. (4) At the same time, their study employed the Asia Dry Eye Society criteria. Our study and those by Raj et al. (16) and Pellegrini et al. (5) utilized the DEWS criteria, which may be more sensitive in detecting DED.

Patients with HFS had significantly higher OSDI and corneal staining scores and significantly lower Schirmer's I test values and TBUT compared to their unaffected fellow eyes. In addition to prior research, our study presents a novel finding that eyes with HFS exhibited a higher incidence of MGD than the controls (4,5). A significant association was also observed between higher HFS severity scores and more significant impairment in subjective and objective dry eye parameters. While comparisons can be drawn between our results in HFS patients and previous findings in blepharospasm due to shared clinical characteristics, it is critical to recognize that the available literature on the effect of blepharospasm on DED lacks consistency and is marked by substantial variability (3,6,7).

Irregular and forceful blinking patterns in HFS may contribute to the pathogenesis of DED by disrupting tear film stability and reducing adequate lubrication between the ocular surfaces (17). Inadequate separation and lubrication of the eyelid and ocular surfaces can lead to repeated microtrauma during eyelid movements, particularly of the upper lid (17). This microtrauma may trigger an inflammatory cascade through the mechanism of the Lewis triple response (18). The resulting tear hyperosmolarity and mechanical stress on the epithelium may further stimulate the release of proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin-1 at the ocular surface (19).

The meibomian glands are essential in preserving the homeostasis of the tear film's lipid layer, and any dysfunction may lead to increased tear evaporation and the subsequent development of DED. Our impaired meibomian gland function findings in HFS patients may be explained by morphological and functional disruptions secondary to sustained eyelid muscle spasms. Lin et al. (20) demonstrated that repetitive forced blinking and sustained spasms in blepharospasm patients were associated with reduced acinar area, lower meibum reflectivity, and increased acinar irregularity, likely reflecting diminished lipid storage. In addition, impaired Riolan muscle function may reduce gland orifice diameter, compromising lipid secretion.

Table 4. Comparison of measurements during the 6-month follow-up in the hemifacial spasm group

	Hemifacial spasm					
	Pre-injection versus			1 month versus		3 month versus
	1 month	3 month	6 month	3 month	6 month	6 month
DED, n (%)	0.006	0.040	0.259	0.443	0.091	0.339
OSDI score	0.009	0.028	0.207	0.393	0.086	0.268
Tear break-up time (s)	0.014	0.034	0.314	0.554	0.102	0.228
Schirmer's I test (mm)	0.007	0.036	0.166	0.497	0.153	0.442
Cornea surface staining score	0.002	<0.001	0.152	0.396	0.022	0.001
Eyelid margin abnormality score	0.012	0.042	0.320	0.526	0.106	0.281
Irregular eyelid margin	0.033	0.143	0.573	0.483	0.111	0.362
Vascular engorgement	0.017	0.017	0.259	1.0	0.190	0.190
Plugged meibomian gland orifices	0.001	0.010	0.412	0.443	0.013	0.074
Shift in the mucocutaneous junction	0.074	0.392	0.573	0.339	0.214	0.769
Meibomian expression						
Upper eyelid	0.004	0.015	0.464	0.476	0.006	0.027
Lower eyelid	0.001	0.010	0.326	0.344	0.004	0.032
Total	0.001	0.008	0.285	0.307	0.001	0.014
Meibography score						
Upper eyelid	0.002	0.011	0.103	0.522	0.188	0.465
Lower eyelid	0.005	0.008	0.056	0.413	0.159	0.407
Total	0.001	0.001	0.084	0.417	0.161	0.384
Area of meibomian gland loss						
Upper eyelid	0.001	0.028	0.309	0.297	0.008	0.140
Lower eyelid	<0.001	0.001	0.084	0.255	0.001	0.062
Total	<0.001	0.001	0.128	0.267	0.004	0.106

DED: Dry eye disease; OSDI: Ocular surface disease index.

The present study showed a significant improvement in OSDI scores, corneal surface staining, meibum expressibility, meibography scores, and meibomian gland loss 1 month following periocular BTX-A injection. Six months post-treatment, the observed benefits were no longer statistically significant, consistent with the temporary duration of BTX-A's neuromuscular blockade. Horwath-Winter J et al. (21) investigated the effects of standard periorbital BTX-A injections on dry eye symptoms over 3 months in patients with essential blepharospasm. According to the study, Schirmer test scores decreased significantly over time, with notable reductions recorded at 1 week, 1 month, and 3 months after the injection (21). This difference in Schirmer's results might be explained by the type of BTX-A used in their study. Specifically, abobotulinumtoxinA, known for its higher diffusion rate compared to onabotulinumtoxinA, may have caused a more widespread distribution of the toxin to the lacrimal glands, leading to a reduction in tear production as observed in the Schirmer test (22). Although Jariyakasol et al.(4) reported no statistically significant differences in tear function parameters – including basal secretion, reflex tearing, and delayed clearance – between HFS-affected and unaffected eyes based on fluorescein clearance testing, they observed higher Oxford scheme grades in the affected eyes, suggesting potential HFS-related epithelial compromise (4). BTX-A may impact tear dynamics through multiple pathways, including reduced lacrimal gland output, altered lipid layer composition, and changes in tear volume and film stability (23). These effects are likely modulated by factors such as the concentration and dose of BTX-A, the injection site, technique, and the extent of its diffusion into surrounding tissues.

Various oral medications have been investigated for managing HFS, including anticonvulsants, baclofen, anticholinergics, and haloperidol (1). However, limited reliable evidence

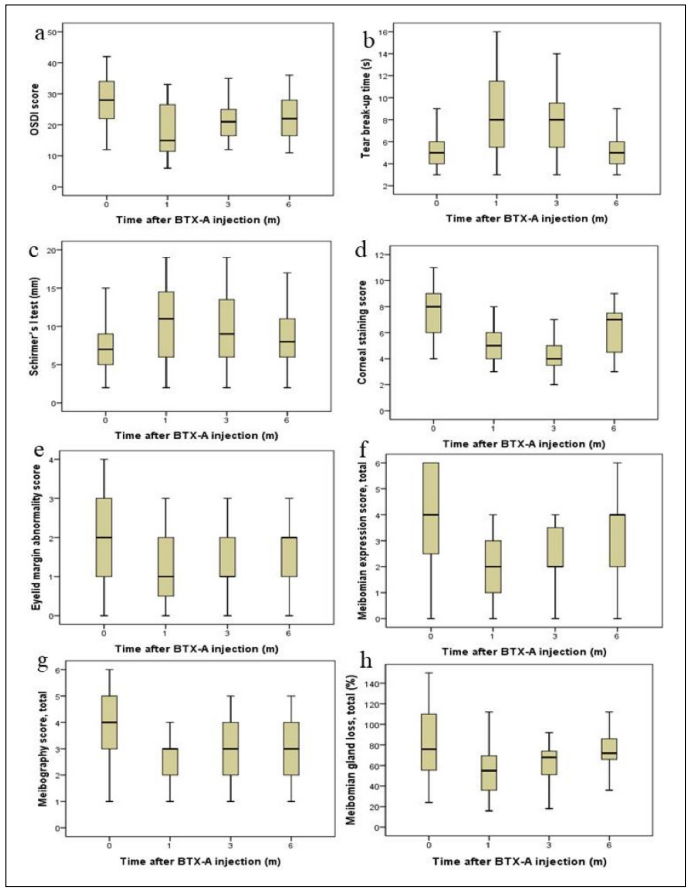

Figure 2. Ocular surface parameters before and at 1, 3, and 6 months after botulinum toxin injection: **(a)** Ocular surface disease ındex score; **(b)** tear break-up time; **(c)** Schirmer's I test; **(d)** corneal staining score; **(e)** eyelid margin abnormality score; **(f)** total meibomian gland expression score; **(g)** total meibography score; **(h)** total area of meibomian gland loss.

supports their efficacy, and treatment is often accompanied by undesirable side effects such as sedation and fatigue (1). Botulinum toxin has emerged as the most effective therapeutic intervention for HFS. The transient improvements observed in ocular surface measurements and meibomian gland function following BTX-A injections in patients with HFS may be attributed to several interconnected mechanisms. These include reducing involuntary muscle contractions, decreasing blink amplitude and frequency, prolonged ocular surface exposure, and reduced tear clearance (24). Gameiro et al. (24) demonstrated that BTX-A significantly decreased blink frequency, amplitude, and maximal eyelid closure velocity. Reduced blinking frequency may also lead to prolonged tear residence time on the ocular surface. As Sahlin et al. (25) have shown, each blink clears a measurable volume of tears, and decreased blinking may enhance tear retention, explaining the improved Schirmer's test results in our cohort. On the other hand, reports by Horwath-Winter et al.(21) and Dutton et al.(26) underscore a paradoxical reduction in tear secretion and increased ocular staining post-BTX-A, likely due to autonomic suppression of lacrimal gland function, particularly when the toxin is delivered laterally in the upper eyelid.

Our study demonstrated a favorable safety profile, with hematoma being the only complication in just 7.4% of patients. Unlike our findings, prior investigations have reported a broader range of complications, including visual disturbances, epiphora, lagophthalmos, diplopia, and ptosis (27). This relatively low complication rate may be attributed to using the pretarsal injection technique for administering BTX-A to the orbicularis oculi muscle rather than the preseptal approach. This improved performance is likely due to the functional role of the pretarsal orbicularis oculi, which is primarily responsible for involuntary blinking. In contrast, the preseptal portion facilitates voluntary, forceful eyelid closure (28,29). Furthermore, anatomical studies have shown that the pretarsal region contains more skeletal muscle fibers and greater neuronal innervation density per surface area than the preseptal region (28). The muscle fiber composition – predominantly short, type II fibers – may also promote more uniform diffusion of BTX-A across neuromuscular junctions, even at lower doses, thereby enhancing therapeutic efficiency while minimizing systemic exposure (28,30,31).

There are several limitations in this study that should be considered. The generalizability of the results to other, larger, or more diverse populations may be limited by the relatively small sample size and the single-center nature of the study. However, given the HFS's rarity, this study's sample size is relatively robust compared to previous research. Second, while using the contralateral eye as an internal control helps mitigate inter-individual variability, subtle bilateral changes or sympathetic effects may have influenced the results. Third, the cross-sectional design of the study restricts our ability to draw definitive conclusions regarding the causal relationship between HFS severity and ocular surface alterations or the long-term efficacy of BTX-A treatment. Fourth, we did not evaluate tear osmolarity, cytokine profiles, or goblet cell density, which might have provided additional mechanistic insight into the inflammatory and tear film-related changes in HFS patients. One of our study's strengths lies in using the contralateral, non-affected eyes as internal controls, which allowed for effective control of inter-individual variability and potential confounding factors. Variables known to influence dry eye, such as age, gender, race, environmental exposure, and smoking status, were inherently matched between the study and control eyes. An additional strength of the study is its focus on assessing how the clinical severity of HFS correlates with various ocular surface measures.

Conclusion

Our findings indicate that patients with HFS exhibit more severe ocular surface damage, which worsens with increasing disease severity. MGD is a contributing factor to the development of DED in this population. Our findings further suggest that BTX-A injections benefit tear film stability and meibomian gland function, offering therapeutic value beyond motor symptom relief.

Disclosures

Ethics Committee Approval: This study was approved by the Dokuz Eylul University Ethics Committee (Date:15.08.2024 Number: 2024/08-19).

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

Conflict of Interest: None declared.

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Original Article

A Novel Multimodal Large Language Model for Interpreting Image-Based Ophthalmology Case Questions: Comparative Analysis of Multiple-Choice and Open-Ended Response

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Abstract

Objectives: The objective of the study is to evaluate the performance of Claude 3.5 Sonnet, a novel multimodal large language model, in interpreting image-based ophthalmology case questions.

Methods: A total of 174 image-based ophthalmology questions from a comprehensive ophthalmology education platform were analyzed by Claude 3.5 Sonnet. Each question was presented in both multiple-choice and open-ended formats. Questions were categorized into six subspecialties: Retina and uveitis; external eye and cornea; orbit and oculoplastics; neuroophthalmology; glaucoma and cataract; and strabismus, pediatric ophthalmology, and genetics. Performance was evaluated by two board-certified ophthalmologists.

Results: Claude 3.5 Sonnet demonstrated an overall accuracy rate of 89.65% in multiple-choice questions and a comparable 87.93% in open-ended questions, with no statistically significant difference between formats (p=0.72). Performance showed slight variations among subspecialties, with the highest accuracy in external eye and cornea cases (95.65% in both formats) and lower accuracy in strabismus, pediatric ophthalmology, and genetics (87.50% in multiple-choice and 84.38% in open-ended).

Conclusion: Claude 3.5 Sonnet showed strong capabilities in interpreting image-based ophthalmology questions across all subspecialties, with consistent performance between different question formats. These findings suggest potential applications in ophthalmology education and board examination preparation; however, validation of its utility in real-world clinical scenarios needs further evaluation.

Keywords: Artificial intelligence, Claude 3.5 Sonnet, ophthalmology board examinations

Introduction

Artificial intelligence (AI) has begun to play a pivotal role in the field of medicine, with remarkable improvements recently, especially the development of large language models (LLMs) (1,2). LLMs are defined as a type of generative AI that uses conversation-based technology and allows users to receive contextually appropriate textual responses to their questions (3). A recent innovation in LLM technology is the addition of image interpretation capabilities. These multimodal LLMs, also referred to as vision-language models (VLMs), have the potential to lead a new era in medicine by processing and interpreting both visual and textual con-

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tent (4). Claude 3.5 Sonnet (Anthropic, California, United States), a multimodal LLM released in early 2024, has the capability to analyze both textual and image data inputs (5).

In recent years, internationally recognized qualifications such as the European Board of Ophthalmology and the Fellowship of the Royal College of Ophthalmologists (FRCOphth) examinations have gained great popularity among young ophthalmologists, particularly ophthalmology residents, in our country. In preparation for these examinations, candidates frequently use question banks, as these resources closely resemble the format and content of the actual examinations. "Cybersight" is a comprehensive online training and mentorship platform for eye health professionals worldwide, with a particular focus on regions where access to learning resources is limited. Cybersight aims to improve the knowledge, skills, and expertise of eye care professionals globally. The platform offers a robust question bank that includes case-based scenarios with high-quality ophthalmic images across various subspecialties. This resource serves as an effective tool for ophthalmologists preparing for board examinations, providing them with opportunities to enhance their diagnostic and management skills through practical case scenarios (6). While previous studies have investigated the performance of LLMs in text-based ophthalmology board examination practice questions (2,7,8), no study up to date has evaluated the image-based case questions. Given that ophthalmology is a subspecialty heavily reliant on multimodal imaging and visual data interpretation, multimodal LLMs capable of image analysis are gaining increasing significance.

The present study aims to evaluate the performance of the novel multimodal LLM, Claude 3.5 Sonnet, in interpreting image-based ophthalmology case questions. The study utilizes case-based scenarios sourced from the "Cybersight" educational platform, which provides comprehensive coverage across ophthalmology subspecialties.

Methods

Claude 3.5 Sonnet (Anthropic, California, United States), a multimodal LLM released on June 21, 2024, was used to evaluate its performance on image-based case questions. The study utilized visual case questions from "Cybersight," a comprehensive online training and mentorship platform for eye care professionals. A total of 174 image-based questions were selected for this study from the Cybersight question bank.

The questions were categorized into six subspecialties: "Retina and Uveitis" (n=30); "External Eye and Cornea" (n=23); "Orbit and Oculoplastics" (n=28); "Neuroophthalmology" (n=31); "Glaucoma and Cataract" (n=30); and "Strabismus, Pediatric Ophthalmology, and Genetics" (n=32).

While the original questions in Cybersight were presented in multiple-choice format, we conducted the study by presenting each identical question in two different formats: (1) Presenting the complete question with multiple-choice options as originally designed and (2) presenting only the case scenario and images without the answer choices to assess whether Claude 3.5 Sonnet could generate correct open-ended responses. This approach allowed for direct comparison of the model's performance on the same clinical scenarios in both multiple-choice and open-ended formats.

To standardize the input process, all questions were formatted using Microsoft Word, following the methodology described by Gilson et al. (9) For each question, the visual stem and relevant text were combined into a single paragraph. In multiple-choice questions, answer choices were placed on separate lines, with two empty lines inserted between the question stem and the choices. For open-ended evaluation, the same case descriptions and images were presented without the multiple-choice options. The images used in the study were directly obtained from the Cybersight question bank without any modifications. These images represented a comprehensive range of ophthalmological imaging modalities commonly used in clinical practice, including anterior segment photographs, slit-lamp images, fundus photographs, optical coherence tomography (OCT) scans, orbital imaging, and other diagnostic images typically used in clinical practice. Image quality varied but was consistently of diagnostic standard, with sufficient resolution and clarity to allow for identification of key pathological features. The diversity of imaging techniques across the different subspecialties provided an opportunity to evaluate Claude 3.5 Sonnet's performance across the full spectrum of visual data encountered in ophthalmology practice.

A new account was created specifically for this study to eliminate potential bias from previous conversations. The conversation history was cleared, and the chatbot was refreshed before each new question to prevent carryover effects. All question inputs were performed by a single researcher (P.K.) to ensure consistency.

Researchers manually reviewed all answers to evaluate Claude 3.5 Sonnet's performance. The answers provided by Claude 3.5 Sonnet were independently evaluated by two board-certified ophthalmologists. The evaluation was conducted by comparing Claude's responses against the validated answers and explanations provided in our reference source material. Each evaluator assessed the accuracy and clinical appropriateness of the model's responses utilizing the official answer key. Responses were recorded as correct or incorrect based on the official solutions provided by the Cybersight platform. This dual-review process ensured a consistent and objective assessment of the model's performance across all subspecialty domains. The percentage of correct answers was calculated overall and for each subspecialty. Re-

sponses were scored as correct only if they demonstrated accurate identification of the pathology, correct diagnosis, and appropriate management consistent with the reference answers provided by the question bank.

Official permission was obtained from the Cybersight platform to use their questions for this research purpose. As this study did not involve human participants, institutional review board approval was not required.

The primary outcome measure was Claude 3.5 Sonnet's performance in providing correct responses to image-based ophthalmology practice questions. Secondary outcomes included comparisons of performance across the six ophthalmology subspecialties.

Statistical Analysis

IBM the Statistical Package for the Social Sciences version 25 (SPSS Inc., Chicago, IL, USA) was used for statistical purposes. Categorical variables were expressed as frequencies and percentages, and numerical variables were expressed as means and standard deviations. Researchers recorded the answers as correct or incorrect and the percentage of correct answers was calculated overall and for each subspecialty. Kolmogorov–Smirnov tests were used to determine whether the data were normally distributed. Independent t-test was performed to determine the differences in the normality of the distribution or Mann–Whitney U test was performed to determine differences in non-normal distribution. A P-value under 0.05 was considered statistically significant.

Results

The performance of Claude 3.5 Sonnet was evaluated in both multiple-choice and open-ended image-based questions (n=174), with further analysis by subspecialty.

For multiple-choice image-based questions, Claude 3.5 Sonnet demonstrated an 89.65% accuracy rate based on the images. In an open-ended format using the same questions, the model achieved a slightly lower but comparable 87.93% accuracy rate.

The model's performance across different subspecialties is detailed in Table 1, showing both multiple-choice and open-ended results. In both formats, "external eye and cornea" showed the highest accuracy (95.65% in both formats). The lowest performance was observed in "Strabismus and pediatric ophthalmology and genetics" (87.50% in multiple-choice and 84.38% in open-ended).

The difference in performance between multiple-choice and open-ended formats was not statistically significant overall (p=0.72) or within any individual subspecialty (all p>0.05), suggesting that Claude 3.5 Sonnet's diagnostic capabilities remain consistent regardless of question format.

Discussion

The present study evaluated the performance of Claude 3.5 Sonnet, a multimodal LLM, in interpreting image-based ophthalmology practice questions in various subspecialties. We compared its performance in both multiple-choice and open-ended question formats using identical clinical scenarios.

Claude 3.5 Sonnet demonstrated strong performance in interpreting ophthalmic images, with an overall accuracy of 89.65% in multiple-choice format and a comparable 87.93% in open-ended format.

To the best of our knowledge, this study represents the first comprehensive evaluation of Claude 3.5 Sonnet's performance specifically in ophthalmology-related images across all major subspecialties. The model's performance in ophthalmology significantly exceeds its previously reported capabilities in other medical imaging domains. In a recent study by Kurokawa et al., (10) Claude 3.5 Sonnet successfully diagnosed only 30.1% of radiology case questions with key images. In addition, another study reported that Claude 3.5 Sonnet achieved a 59% success rate in diagnosing breast ultrasound images (11).

Although previous studies have evaluated the performance of LLMs on text-based ophthalmology board practice questions, up to date, no study has specifically evaluated

Table 1. Comparison of Claude 3.5 Sonnets' performance between multiple-choice and open-ended formats across ophthalmology subspecialties

Subspecialties	Number of questions	Multiple-choice format Correct/Total (%)	Open-ended format Correct/Total (%)	p
Retina and uveitis	30	26/30 (86.67)	27/30 (90.00)	0.69
External eye and cornea	23	22/23 (95.65)	22/23 (95.65)	1.00
Orbit and oculoplastics	28	25/28 (89.29)	24/28 (85.71)	0.71
Neuroophthalmology	31	28/31 (90.32)	27/31 (87.10)	0.68
Glaucoma and cataract	30	27/30 (90.00)	26/30 (86.67)	0.72
Strabismus and Ped. Oph. and genetics	32	28/32 (87.50)	27/32(84.38)	0.73
Overall	174	156/174 (89.65)	153/174 (87.93)	0.72

LLMs' performance on ophthalmology-related image-based case questions. Previous studies assessing text-based ophthalmology board practice questions have reported that ChatGPT, a popular LLM, achieved success rates ranging from 60% to 80% in various practice question sources (2,7,8). Recently, attempts have been made to evaluate LLMs in interpreting ophthalmological images. A study by Mihalache et al. (12) evaluated LLMs' ability to interpret OCT images. In this study, 448 OCT images were analyzed and their model demonstrated a 65% success rate in correct detection. In another study by Antaki et al., (13) the diagnostic capabilities of the LLMs-Gemini Pro model in interpreting OCT images were evaluated. The research included 50 patients with various retinal pathologies. In that study, the LLMs-Gemini Pro model showed a correct diagnosis rate of 34%.

Claude 3.5 Sonnet showed remarkably consistent performance between multiple-choice (89.65% accuracy) and open-ended questions (87.93% accuracy). This consistency in performance between different question formats is worth analyzing, given the structural differences between these types of questions. Multiple-choice questions, with their predefined options, typically align closely with the pattern recognition and classification algorithms intrinsic to many AI models (14). Open-ended questions, on the other hand, necessitate a more complex set of cognitive processes. The model must not only recognize and classify the pathology present in the image but also generate a coherent, relevant response without the guidance of predefined options. This involves a higher level of language understanding and generation capabilities, requiring the model to respond in a flexible manner, drawing from its training across medical knowledge domains. The consistently strong performance across both question types with no statistically significant difference highlights Claude 3.5 Sonnet's versatility in medical image interpretation regardless of the response format required. This suggests that the model possesses not only strong pattern recognition capabilities for identifying ophthalmic pathologies but also robust medical reasoning abilities that allow it to independently formulate accurate diagnostic and management recommendations when no options are provided. This capability shows a remarkable improvement in AI-related medical image interpretation, potentially paving the way for more comprehensive clinical decision support. However, it is imperative to emphasize that the images used in this study were sourced from board examination preparation materials which represent a standardized set of clinical scenarios and they may not fully capture the complexity of real-world clinical presentations.

The successful performance of Claude 3.5 Sonnet in cornea and external eye cases (95.65% accuracy in both open-ended and multiple-choice questions) compared to other subspecialties is an important finding. Several factors may contribute to this higher performance. Corneal and external eye conditions often present with more visually distinct features which may align better with the pattern recognition capabilities of AI models. In addition, clear views typically offered by external eye photographs and slit-lamp photography might enable more accurate interpretation. The relatively lower performance in "Strabismus, Pediatric Ophthalmology, and Genetics" (84.38% in open-ended and 87.50% in multiple-choice) may be attributed to several factors. First, this subspecialty often involves complex alignment issues that require a three-dimensional understanding from two-dimensional images. Second, pediatric ophthalmology cases frequently require integration of age-specific considerations and developmental factors that may not be as prominently featured in the training data. Third, genetic conditions in ophthalmology often present with subtle clinical manifestations that may be challenging to distinguish from static images alone.

In contrast to this current study, Minalache et al.'s study (12) evaluated both image-based and non-image-based case scenarios in ophthalmology and their LLMs showed the highest performance in the retina category (77% correct responses) and the lowest in neuro-ophthalmology (58% correct responses). Our findings differ significantly, with external eye and cornea showing the highest performance (95.65% accuracy in both open-ended and multiple-choice questions) and Strabismus and Pediatric Ophthalmology and Genetics showing the lowest (84.38% in open-ended and 87.50% in multiple-choice). Importantly, our study demonstrates substantially higher accuracy across all subspecialties. In addition, their research did not evaluate image-based questions related to cornea and external eye diseases or orbital-oculoplastic pathologies, which were included in our comprehensive analysis of six major ophthalmology subspecialties.

The performance of Claude 3.5 Sonnet suggests potential applications in both ophthalmology education and clinical practice. The model's high accuracy in board-style questions suggests its potential use in examination preparation, allowing students and residents to practice image interpretation and receive immediate feedback. Moreover, the model's ability to handle both multiple-choice and open-ended questions with similar accuracy could support a variety of learning styles and formats. However, it is crucial to emphasize that AI should be only complementary, not a replacement for traditional clinical education methods. In this current study, the aim was also to emphasize the potential of LLMs, and Claude 3.5 Sonnet's ability to efficiently analyze high volumes of images in busy clinical departments might offer an advantage in image-intensive

subspecialties like ophthalmology and it might serve as a valuable diagnostic tool. However, this research also highlights the need for cautious implementation to reduce the risk of over-reliance on it.

The current study has several limitations. First, the questions were derived from ophthalmology examination practice materials, which may not fully represent the complexity of real-world clinical scenarios. Second, while we achieved a more balanced distribution of questions across subspecialties, there were still slight variations in sample sizes between subspecialties that may have influenced performance comparisons. Third, our evaluation focused on a single multimodal LLM when the number of LLMs capable of processing medical images at this level was quite limited. Fourth, we did not include a comparative analysis with human ophthalmologists at different training levels, which would have provided valuable context for interpreting the model's performance relative to human experts.

Future research should include comparative analyses with human experts at various training levels (residents, fellows, and attending physicians) to provide valuable context about the model's relative capabilities across different ophthalmological issues. In addition, head-to-head comparisons between multiple LLMs with different architectures would help understand their relative strengths and limitations in ophthalmological image interpretation. Further work should explore how these models perform with more complex, ambiguous cases or rare conditions that might not be well-represented in standard question banks. Investigating how these models might be optimized specifically for ophthalmological applications through fine-tuning or specialized training could potentially enhance their performance in this domain.

Conclusion

These results demonstrate that Claude 3.5 Sonnet shows strong performance in interpreting ophthalmic images across all major ophthalmology subspecialties, with comparable accuracy in both multiple-choice (89.65%) and open-ended question formats (87.93%).

The model performed most effectively in the cornea and external eye subspecialty, while showing slightly lower but still impressive accuracy in strabismus, pediatric ophthalmology, and genetics cases. The consistent performance across different question formats highlights Claude 3.5 Sonnet's versatility in medical image interpretation and reasoning. These findings suggest potential applications in ophthalmology education, board examination preparation, and as a complementary tool in clinical settings. However, further research is imperative to validate the model's utility in real-world clinical scenarios and to compare its performance with that of ophthalmologists at various training levels.

Disclosures

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Surgical Technique

Large Inferior Rectus Recession without Lower Eyelid Retraction in Thyroid Eye Disease

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Abstract

Objectives: In this study, a new technique that does not cause lower eyelid retraction in patients with excessive limitation of movement and vertical strabismus due to inferior rectus (IR) fibrosis in thyroid eye disease was introduced.

Methods: There were six patients with their six eyes with their mid-term results.

Operation Technique: According to the deviation amount, a 7–14 mm length bovine pericardium (Tutopatch®) was inserted between the distal end of the tendon and the beginning of the muscle fibers, which are located between the tendon's distal end and the tendon muscle junction to the IR with 6/0 non-absorbable suture.

Results: There were six cases with a mean 19.5±5.2 PD (PD: prism diopters) (14–26 PD) vertical deviation and severe up-gaze limitations with a mean −4.1±0.75. The post-operative vertical deviation was a mean of 3.5±1.22 PD, and the limitation of upgaze was a mean of −1.3±0.4.

Conclusion: This procedure provides effective results in reducing gaze limitation and vertical deviation in thyroid patients without causing any problems in the eyelids.

Keywords: Bovine pericardium, thyroid eye disease, vertical strabismus

Introduction

The inferior rectus (IR) inserts in the vertical meridian, approximately 6.5 mm from the limbus and 9.8 mm wide at its insertion on the globe. The tendon is 7 mm in length, measured from the origin (1). The IR also interacts with the lower eyelid via a fascial connection from its sheath. Weakening or recession of the IR more than 4.5–5 mm may widen the palpebral fissure, and this can cause lower lid droop (2).

Although various techniques have been described to prevent this, these usually require post-operative lower eyelid surgery. Although the previously described technique of recessing the deep fibers of the IR allows for large recessions without causing lower eyelid retraction, this technique cannot be applied to fibrotic muscles (3,4).

Different from the neurogenic extraocular paralysis, motility problems in patients with thyroid eye disease (TED) occur due to fibrosis in the muscles. This limitation will restrict the eye movements. The treatment of strabismus in these patients, first of all, will be by recession of this fibrotic muscle.

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The technique has previously been presented at various meetings. (Gokyigit B et al. TOA 52. Annual meeting 2018; Inal A, Karabulut GO, Ocak OB, Gokyigit B. AAO annual meeting 2018).

We were inspired by the three publications in developing the technique (5-7). However, in all three publications, the Tutopatch was placed between the muscle insertion and the beginning of the tendon.

In this study, we introduce a new technique that does not cause lower eyelid retraction in TED patients with the results of six cases.

Methods

This retrospective study was approved by the Ethics Committee of Okmeydanı Training and Research Hospital, with the number 967, and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patients following a detailed explanation of the study objectives and protocol.

There were six patients with their six eyes in this study. All patients underwent detailed anterior and posterior segment examination. Besides vertical and horizontal deviation amounts, we noted their lower lid retraction, scleral show amounts, limitation of elevation, and globe elevation from the mid-horizontal line amounts.

The lower eyelid retraction was measured with the scleral show method. Postoperatively, if the scleral show amount was found to be ≤0.5 mm, it was accepted as successful, between 0.5 and 1 mm as partial success, and ≥1mm as failure. Ductions were graded on an ordinal scale from −4 (underaction) to +4 (overaction). Postoperatively, if the globe passed the mid-horizontal line or the limitation was ≤−1, it was considered successful; if the limitation was −2, it was considered partial success; and if it was −3 or above, it was considered unsuccessful.

Operation Technique

According to the deviation amount, 7–14 mm length bovine pericardium (Tutopatch®) was inserted between the distal end of the tendon and the beginning of the muscle fibers, which are located between the tendon's distal end and tendon muscle junction to the IR with 6/0 non-absorbable suture. The non-absorbable sutures (Dacron® 6-0 suture) were left at the same length on both sides of the Tutopatch as protection against any possible dissolution later. There is no processing performed on the IR insertion. Placing the pericardium distal edge to the beginning of IR fibers, as shown in Figure 1, the final perspective from the operation is shown in Figure 2.

All surgeries were performed by a single surgeon. (BG)

Figure 1. Placing the pericardium distal edge at the beginning of the inferior rectus fibers.

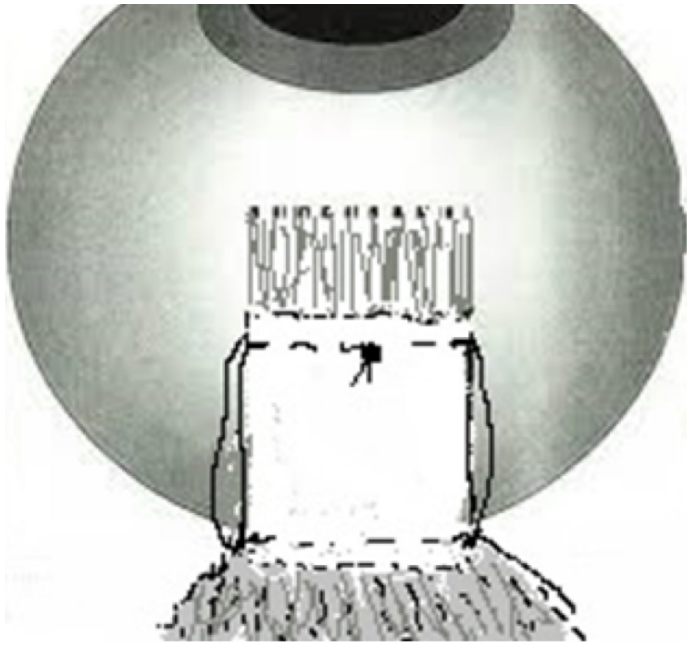

Figure 2. Final perspective from the operation.

Results

There were four males and two females. Their ages were between 35 and 62 (mean 47.5±12.07) years, and their vertical deviations were between 14 and 26 PD (mean 19.5±5.2). The elevation limitation was found between −3 and −5. While there was a slightly lower lid retraction in three patients, there was no retraction in the others.

Patients' post-operative mean vertical deviations were found to be 3.5±1.22 PD, and the limitation of elevation was found to be −1.3±0.4. While eyelid retraction was under 0.5

Table 1. Patients' demographics, pre-operative and post-operative findings

No.	Gender	Age (year)	Vert. deviation		Lim. of elevation		Lower lid retr.		Follow up (m)
			Preop	Postop	Preop	Postop	Preop	Postop	
1.	Male	41	14	2	-4	0	-	-	14
2.	Male	61	25	4	-5	-1 (-2)	±	±	14
3.	Male	62	26	5	-5	-1 (-2)	±	±	18
4.	Female	36	18	2	-4	-1	-	-	13
5.	Female	35	14	4	-3	-1	-	-	24
6.	Male	50	20	4	-4	-1 (-2)	±	±	10

Vert: Vertical; Lim: Limitation; retr: Retraction; m: Month; preop: Pre-operative; Postop: Post-operative; Limited abduction levels: -5, no abduction to 0, normal abduction.

mm in 3 patients, no retraction was detected in the others, and there was no change in the amount of lower eyelid retraction after surgery.

The follow-up of all the patients was over a year (15.5±4.88 months). Patients' demographics, pre-operative and post-operative findings are shown in Table 1. None of the patients required a second surgery.

The limitations of this study are the small number of patients and the fact that all of our patients were affected and operated on only one eye. Therefore, the results of applying the surgical technique to both eyes could not be evaluated.

Discussion

Esser, Schittkowski, and Eckstein performed recession of the IR muscle in 10 patients with simultaneous suturing of bovine pericardium (Tutopatch) (5). The new technique of tendon elongation using a bovine pericardium graft is applicable in large vertical squint angles (with or without prior bony orbital decompression) as well as for corrections after insufficient simple recessions (by realignment of the muscle and secondary suturing of the graft). Their dosing formula: 1 mm IR recession [including graft] leads to 2.0° vertical angle reduction. We performed the adding Tutopatch operation not between the insertion and the beginning of the tendon, but at the end of the tendon and the beginning of the muscle. Thus, we left the IR sheath and lower eyelid retractors outside the operating area.

Conclusion

Tendon elongation with tissues was used previously, but these cases needed additional lower lid procedures to prevent lower lid retraction from time to time. In this new approach, tissues are not inserted between the tendon and its insertion, but located between the tendon's distal end and the tendon muscle junction.

In conclusion, this operation does not affect the lower lid retractor, and the operation has both effective results and no lid problems.

Disclosures

Ethics Committee Approval: This study was approved by the Okmeydanı Training and Research Hospital Ethics Committee (Date: 10.08.2018, Number: 967) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from all patients.

Conflict of Interest: None declared.

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Peer-review: Externally peer-reviewed.

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Case Report

Tamoxifen Retinopathy and Macular Telangiectasia Type 2: Case-Based Differential Diagnosis

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Abstract

Tamoxifen is a widely used agent for the treatment of breast cancer worldwide. Despite its significant efficacy in breast cancer, serious side effects may occur with long-term or high-dose use. One of these side effects is tamoxifen retinopathy (TR). Tamoxifen retinopathy typically presents with bilateral visual impairment, crystalline deposits, and changes in the foveal reflex during fundus examination. Although characteristic features can be observed with multimodal imaging, it may be confused with various retinal pathologies. One of the primary conditions considered in the differential diagnosis of TR is macular telangiectasia type 2 (Mac-Tel 2). In this case presentation, we aim to share the differential diagnosis process of TR and highlight the distinguishing features from Mac-Tel 2 in a female patient who presented with decreased vision, based on the patient's history, detailed fundoscopic examination findings, and multimodal imaging.

Keywords: Macular telangiectasia, multimodal imaging, optical coherence tomography, tamoxifen retinopathy

Introduction

Tamoxifen is a non-steroidal estrogen receptor antagonist. It is widely used as adjuvant therapy for estrogen receptor-positive breast cancer worldwide. In standard protocols, the duration of tamoxifen treatment can extend to 5–10 years (1). Due to its long-term use, systemic and ocular side effects of tamoxifen have become prominent. The ocular toxicity of tamoxifen was first described by Kaiser-Kupfer and Lippman in 1978 (2). Although the doses used in the first cases reported were much higher than those used today, tamoxifen toxicity can still occur due to prolonged use and individual patient characteristics (3).

Currently, with the help of multimodal imaging techniques and typical examination findings, a diagnosis of TR can be established. However, in some patients, even with detailed examination and imaging, TR can be confused with other retinal pathologies. One of the retinal conditions most commonly confused with TR is Mac-Tel 2. Mac-Tel 2 is a progressive, bilateral retinal neurodegenerative disease associated with telangiectatic changes (4). Distinguishing between TR and Mac-Tel 2 is crucial for deciding whether to discontinue tamoxifen therapy and for planning ophthalmological interventions if the disease progresses.

In this case report, we present a differential diagnosis of tamoxifen retinopathy based on the patient's history, examination, and the distinguishing features observed through multimodal imaging.

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Case Report

A 47-year-old female patient presented to our clinic with blurred vision in both eyes for the past 2–3 months. The patient had received radiotherapy due to breast cancer and had been using 20 milligrams per day of an estrogen receptor antagonist (tamoxifen) and a gonadotropin-releasing hormone agonist (goserelin) for five years. She had no other known systemic or ophthalmologic diseases.

A detailed ophthalmological examination was performed. Best-corrected visual acuity (BCVA) was 8/20 in both eyes according to the Snellen chart. Intraocular pressures were within normal limits in both eyes. Biomicroscopic examination revealed a normal anterior segment in both eyes. After pupil dilation with 0.05% tropicamide, fundus examination showed normal optic discs and vascular structures bilaterally. Refractive crystalline deposits were observed in the bilateral central macula, while the peripheral retina appeared normal.

Optical coherence tomography (OCT) revealed a central macular thickness of 227 microns in the right eye and 257 microns in the left eye, with intraretinal cavitation and disruption of the ellipsoid zone bilaterally (Fig. 1). Retinal nerve fiber layer thicknesses were within normal limits. Fundus autofluorescence (FAF) imaging showed increased hyperreflectivity at the fovea bilaterally (Fig. 2). Optical coherence tomography angiography (OCT-A) showed no significant microvascular changes. Fundus fluorescein angiography (FFA) revealed no vascular leakage or telangiectatic changes.

Based on the patient's history of tamoxifen use, fundoscopic findings, and characteristic multimodal imaging features, a diagnosis of TR was established, and the patient was referred to the Department of Medical Oncology. Tamoxifen therapy was discontinued, and a new treatment was planned by Medical Oncology. No significant change was observed in the patient's visual acuity and retinal findings during the six-month follow-up after discontinuation of tamoxifen treatment.

Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

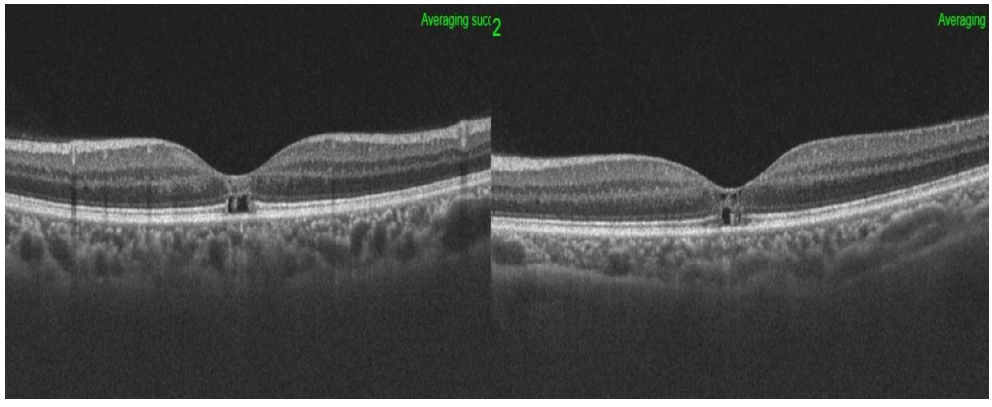

Figure 1. Foveal cavitation and disruption of the ellipsoid zone are observed in the OCT images of the patient's right and left eyes.

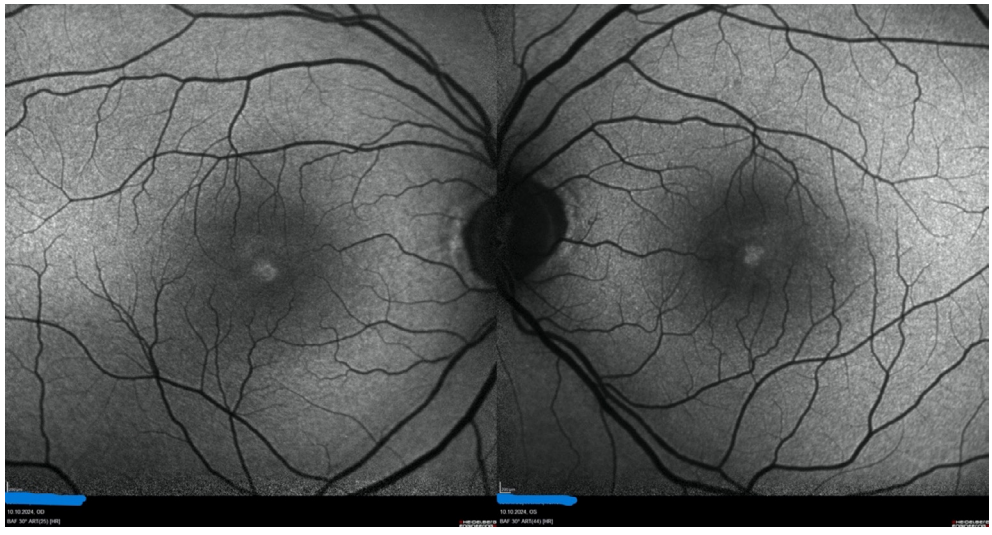

Figure 2. Foveal hyperautofluorescence is observed in the FAF images of the patient's right and left eyes.

Discussion

Tamoxifen retinopathy is a toxic maculopathy that develops due to the long-term or high-dose use of tamoxifen and can be irreversible (5). In our case, the patient's history of tamoxifen use, decreased visual acuity, and multimodal imaging findings were consistent with TR. Imaging, particularly OCT, revealed foveal cavitation, ellipsoid zone disruption, and refractive deposits, suggestive of TR (6). One of the leading differential diagnoses for TR is Mac-Tel 2, a retinal disease with similar clinical and imaging characteristics. These phenotypic similarities may be related to Müller cell involvement in both diseases (4).

In Mac-Tel 2, foveal cavitation, outer retinal layer disruption, and crystalline-like deposits in the fundus can also be observed, necessitating careful differential diagnosis. However, Mac-Tel 2 typically presents with progressive bilateral neurodegeneration, telangiectatic changes in the retina, and subretinal neovascularization in advanced stages (7). In TR, the degenerative process is predominantly related to toxicity, and a history of tamoxifen use is typically present. Fundus autofluorescence (FAF) imaging can show foveal changes in both diseases. In TR, hyperautofluorescent foci at the fovea generally correspond to crystalline deposits, whereas in Mac-Tel 2, there are typically foveal hyperautofluorescence and autofluorescence changes associated with parafoveal vascular changes (8–9). In our case, the hyperreflectivity observed at the fovea on FAF was consistent with TR findings.

In Mac-Tel 2, OCT-A typically reveals telangiectatic vascular structures at the level of the deep capillary plexus and subretinal neovascularization in later stages (10). In contrast, significant vascular abnormalities are not typical in TR on OCT-A, although early microvascular irregularities resembling Mac-Tel 2 have been reported (11). The absence of notable capillary telangiectasia or neovascular membranes in OCT-A in our case helped to exclude Mac-Tel 2.

Fundus fluorescein angiography in Mac-Tel 2 characteristically shows late-phase hyperfluorescence and vascular leakage around the temporal fovea (Fig. 3) (12). In TR, typical findings on FFA are usually absent, and nonspecific changes may be seen (13). In our case, the absence of vascular leakage or telangiectatic structures on FFA supported the diagnosis of TR.

Conclusion

In conclusion, despite clinical and imaging similarities between TR and Mac-Tel 2, patient history and multimodal imaging findings play a critical role in establishing the correct diagnosis. Specifically, hyperautofluorescence corresponding to crystalline deposits on FAF, foveal cavitation with ellipsoid zone disruption on OCT, and the absence of vascular abnormalities typical for Mac-Tel 2 on OCT-A and FFA strongly support a diagnosis of TR. Following diagnosis, consulting the Department of Medical Oncology to discontinue tamoxifen treatment is crucial to prevent disease progression. Therefore, routine comprehensive retinal evaluations are essential for early diagnosis in patients using tamoxifen.

Disclosures

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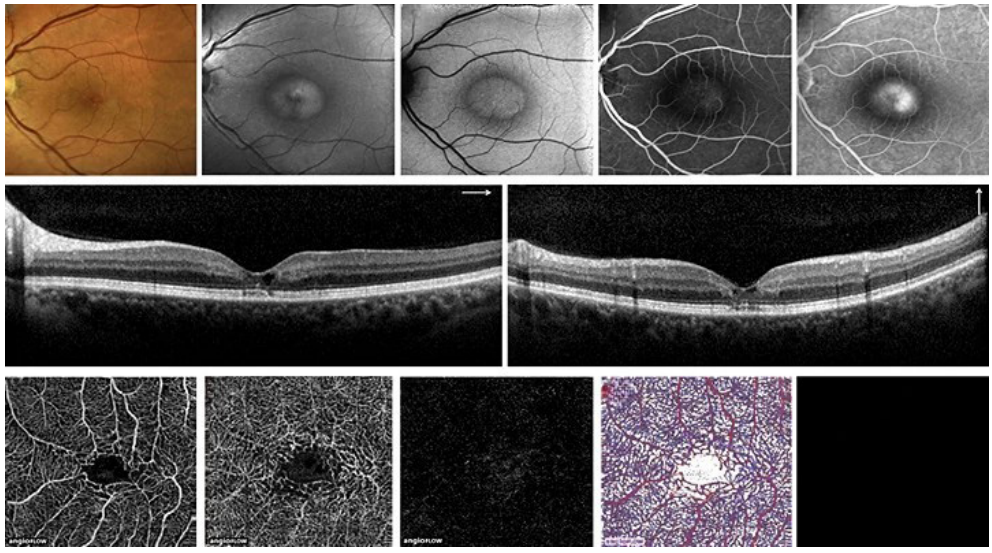

Figure 3. Color fundus photograph, FAF, FFA, OCT, and OCT angiography images of a Mac-Tel 2 case (14).

Author Contributions: Concept – A.E., S.A.D.; Design – A.E., S.A.D.; Supervision – A.E., S.A.D.; Resource – A.E., S.A.D.; Materials – A.E., S.A.D.; Data Collection and/or Processing – A.E., S.A.D.; Analysis and/or Interpretation – A.E., S.A.D.; Literature Search – A.E., S.A.D.; Writing – A.E., S.A.D.; Critical Reviews – A.E., S.A.D.

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Case Report

An Ophthalmic Entity More Than Liver Disease, Alagille Syndrome: A Genetically Confirmed Case Report

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Abstract

Alagille syndrome (ALGS) is a rare autosomal dominant disease that mainly affects the bile ducts and the liver. This syndrome may be associated with ophthalmic anomalies, but systemic diseases are often so obvious compared to ocular findings that many patients are referred to eye clinics after diagnosis. The diagnosis of ALGS is based on medical history and clinical findings. In this report, we describe and present a systemic disease of an undiagnosed ALGS based on eye findings. Papilledema and posterior embryotoxon were detected in the patient who was investigated due to headache. The diagnosis was made based on ophthalmological findings and was confirmed by genetic consultation. Missense mutations of the jagged canonical Notch ligand 1 gene located on chromosome 20p12.2 were detected. The patient benefited from treatment aimed at increasing intracranial pressure, and the etiology of symptoms related to other systems was clarified. The aim of this report is to support a clinical approach that evaluates possible common and rare comorbidities in ALGS from an ophthalmic perspective. We also emphasize the diversity of clinical presentation. ALGS affects multiple systems, so an integrative approach is important.

Keywords: Alagille syndrome, Jagged canonical Notch ligand 1 gene, Papilledema, Posterior embryotoxon

Introduction

Alagille syndrome (ALGS) is a rare autosomal dominant disease that mainly affects the bile ducts and the liver. This syndrome may be associated with ophthalmic anomalies, especially posterior embryotoxon (PE), iris abnormalities, abnormal fundus pigmentation, and optic disc pathologies. ALGS is generally recognized in pediatric age with hepatic, renal, cardiac, pulmonary, or skeletal abnormalities. Many patients are referred to eye clinics after diagnosis.

The presence of PE requires a detailed medical history. Papilledema is an accompanying finding of ALGS. Increased intracranial pressure (ICP) accompanying endocrine diseases such as polycystic ovaries is one of the causes of papilledema. The coincidence of papilledema and PE may aid in diagnosis and protect against life-threatening conditions (e.g., ICP or vasculopathy).

Based on eye findings, we identified the systemic disease of an undiagnosed ALGS. In this presentation, we demonstrate the ophthalmic findings of the case and introduce the accompanying systemic findings.

We wanted to emphasize the importance of an integrative approach to the patient. We underline the vasculopathic nature of the syndrome, which may be helpful in understanding the cause of ophthalmological findings in different ocular tissues.

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Case Report

A 28-year-old female patient was referred to our clinic from the neurology department to investigate her headache. She had a broad forehead, a triangular facial appearance, deep-set eyes, and a bulbous nasal tip (Fig. 1).

In her medical history, she had prolonged jaundice in the neonatal period, but she did not receive any treatment for this reason, and the patient's jaundice improved with age.

There was no known diagnosis of ALGS in her family, but there was a sibling lost in the early childhood period.

She had been followed in the gynecology clinic for 2 years due to menstrual irregularity.

She had received dermatological treatment for oily scalp and seborrhoeic dermatitis. She applied to the ear, nose, and throat clinic several times due to nosebleeds, but due to her young age, a hypertensive cause was not considered and was not investigated from this perspective.

In her gastrointestinal system history, she felt severe indigestion and bloating in the abdominal area after eating for a long time. The gastroenterology clinic, which she went to with these complaints, had applied symptomatic treatment to regulate stomach movements and acid secretion, but no evaluation or imaging was performed in terms of portal hypertension, liver, and bile disorders.

She complained of pain in her neck and lumbar area for a long time, and she was followed up by orthopedics and neurosurgery clinics. C4-C5-C6 mild disc herniation and flattening of cervical lordosis were detected. There was a disc protrusion in L4-L5 and S1. She did not receive any treatment other than painkillers for these complaints.

Although the findings of several different systems mentioned before were indicative of ALGS, they were not pathognomonic for any clinician, and it was not suspected that the findings were part of a syndrome until the eye examination.

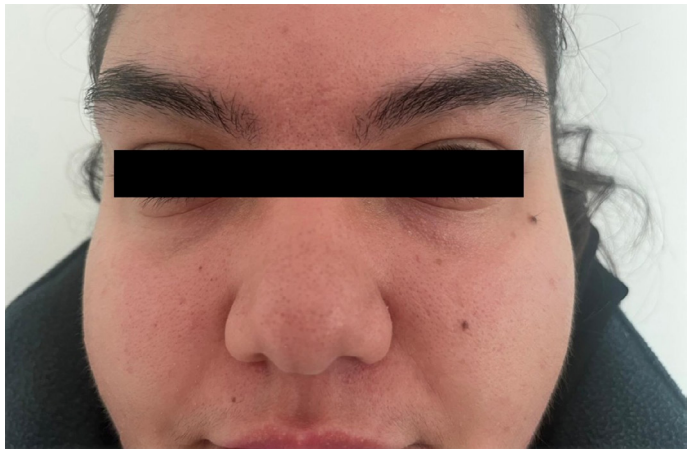

Figure 1. The broad forehead, triangular face appearance, deep-set eyes, and a bulbous nasal tip.

This report was prepared in accordance with the CARE case report guidelines and with patient-informed consent. The patient underwent routine eye examinations and imaging.

The refractive error was +0.25 in both eyes (Topcon KR-8900 Auto Kerato-Refractometer, Topcon Corporation, Japan). At the first examination, visual acuity was 0.9 in both eyes. Intraocular pressures were normotone (applanation tonometry). The cornea was transparent, and its shape and diameters were normal.

There was PE in both eyes (Fig. 2). The iris surface was regular, and pigmentation was normal. Light reflex was normal. The crystalline lens was clear. There was bilateral grade 2–3 papilledema on fundus examination (Fig. 3). Retinal nerve fiber layer analysis (Cirrus –HD 5,000 OCT, Carl Zeiss Meditec, Dublin, California) was performed at each follow-up (Fig. 4). Although retinal pigmentation was generally normal during retinal examination, spotty pigmentation changes were observed at the periphery (Fig. 5).

After detection of papilledema, she was re-evaluated in neurology with the enlightenment of the eye clinic, with the preliminary diagnosis of ICP accompanying polycystic ovaries. In the lumbar puncture performed in the neurology clinic, the opening pressure was reported as 50 mmHg. The patient was hospitalized and treated, and after medical treatment, the headache resolved, and the papilledema gradually improved. In genetic consultation, missense mutations of

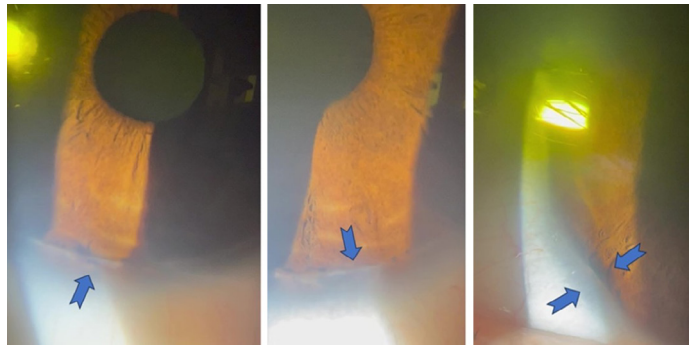

Figure 2. As seen on slit-lamp biomicroscopy, the gray-white Schwalbe's line is concentric with and anterior to the limbus.

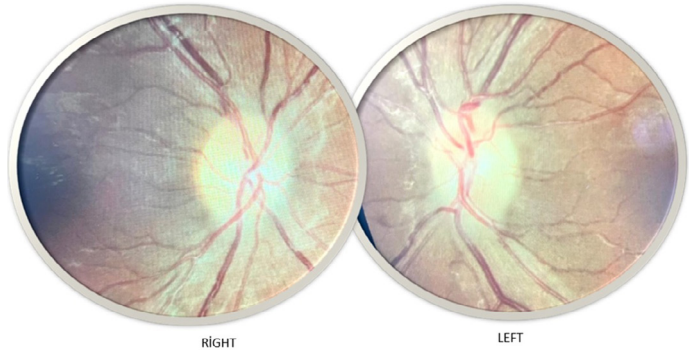

Figure 3. Grade 2–3 papilledema on fundus photograph.

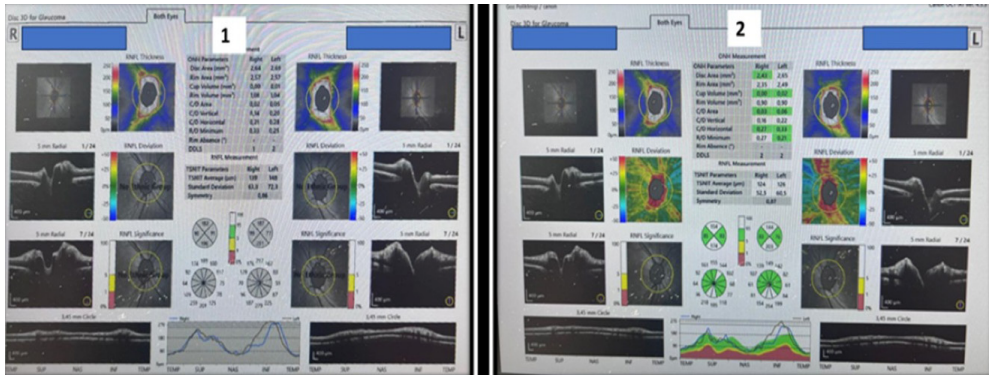

Figure 4. Retinal nerve fiber layer (RNFL) image numbered 1 is the first follow-up RNFL image numbered 2 is after treatment for increased intracranial pressure.

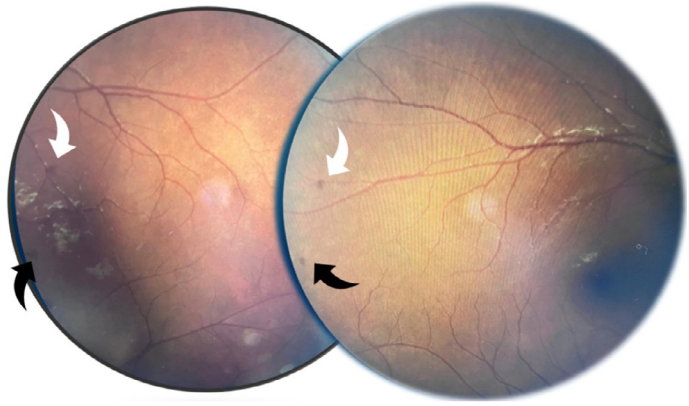

Figure 5. Fundus photo: Spot-like pigmentation on the retina periphery.

the jagged canonical Notch ligand 1 (JAG1) gene located on chromosome 20p12.2 were detected. The patient was referred back to the clinics she had previously attended to be re-evaluated with her new diagnosis. Ophthalmic follow-up continues.

Discussion

When ALGS was first described by French pediatrician Daniel Alagille in 1969, it was a clinical entity with unknown genetics (1). ALGS is characterized by five major clinical criteria: cholestasis with bile duct paucity on liver biopsy, congenital cardiac defects (with particular involvement of the pulmonary arteries), PE in the eye, characteristic facial features, and butterfly vertebrae. The clinical spectrum is often wider. ALGS cases presenting with renal abnormalities, hyperandrogenism, and polycystic ovary syndrome have also been reported (2). Three of the five main criteria must be present.

In our case, at least three criteria were present. Although there was a history and clinical picture of cholestasis, the diagnosis of ALGS was not considered, and a liver biopsy was not performed. There was no medical record regarding congenital cardiac defects. Characteristic facial features were present. Findings related to spinal problems were considered butterfly vertebrae after the diagnosis of ALGS was confirmed. PE in the eye was detected by us.

The most common ocular abnormality is PE (95%) in patients with ALGS, but a group of ocular findings is associated with ALGS. Many different tissues can be affected in the eye, such as the cornea, iris, retina, and optic disc. Iris abnormalities, especially stromal hypoplasia (45%), diffuse fundus hypopigmentation (57%), speckling of the retinal pigment epithelium (33%), optic disc anomalies (76%), microcornea, and congenital maculopathy are other ocular findings (3).

PE refers to an anteriorly displaced and thickened Schwalbe's line. PE most often occurs with Axenfeld–Rieger syndrome and ALGS. In our case, PE was also evident and became the cornerstone in making the diagnosis. If the diagnosis is suspected, other ocular findings should be investigated in detail. For example, in this case, spot-like (speckling) pigmentation was observed in the retinal periphery, a rare finding of ALGS.

ALGS can cause ICP and papilledema, and its frequency is between 7% and 10% (4). Pseudopapilledema associated with optic disc drusen has been reported more frequently in publications (5). However, in this case, there was papilledema due to actual ICP (50 mmHg). ICP accompanying endocrine diseases, such as polycystic ovaries, is one of the causes of papilledema. The coincidence of papilledema and PE may aid in diagnosis. After medical treatment, the papilledema improved. We believe that diagnosis is protective against life-threatening situations.

While ALGS was initially just a group of symptoms, with the detection of the autosomal dominant pattern, genetic research accelerated. Gene analysis revealed that there was a problem with the JAG1 gene in most of the cases. The disease is caused by mutations that disrupt the Notch signaling pathway. Mutations in JAG1 have been identified in ~70% of patients with ALGS (6-8). In our case, we achieved genetic confirmation based on clinical findings.

According to some researchers, ALGS is primarily a vasculopathy, and at least some of the Notch signaling pathway effects are caused by abnormalities of angiogenesis and the vascular system (9). For example, the abnormal formation of mature bile ducts could be the result of abnormal development of the intrahepatic arterial network (10). It is known that the Notch signaling pathway plays a major role in angiogenesis, providing support for this idea and possibly explaining the pathophysiology of the disease.

During cranial neural crest development, iridocorneal microarteritic infarcts can cause PE and possibly trigger microcornea by impairing corneal nutrition. It is reasonable that pigmentations in the retina periphery may be related to microarteritic obstructions. In the presented case, there were PE and retinal anomalies.

ALGS is usually caused by a single mutation in the JAG1, and manifests with liver disease and cardiovascular symptoms that are a direct consequence of JAG1 haploinsufficiency. In the presented case, de novo JAG1 gene mutation was detected without a family history. Phenotypic findings were found to be compatible with the angiopathic theory explaining the etiopathogenesis.

In this study, we present the ocular and systemic findings of ALGS. This report does not reflect all gene mutation types and phenotypes. The case report we present is limited and should be supported by more case numbers and phenotypes.

Conclusion

The aim of this report is to support a clinical approach that evaluates possible common and rare comorbidities in ALGS from an ophthalmic perspective. We also emphasize the diversity of clinical presentation. Ophthalmologists should be aware that a delay in the diagnosis of ALGS can be life-threatening. Therefore, the importance of an integrative, multidisciplinary approach should not be forgotten.

Disclosures

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

Conflict of Interest: None declared.

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News

Subject: Great News for the Turkish Ophthalmology Community!

Dear Ophthalmology Specialists,

We are delighted to announce that as of October 15, 2025, the Beyoglu Eye Journal has been officially indexed in the Web of Science.

All articles published from the 2023 issues onward will now be included in this prestigious index.

This remarkable milestone reflects the dedication and vision of our editorial team.

We extend our deepest gratitude to our Editor-in-Chief, Prof. Dr. Muhittin Taşkapılı, and Editor, Prof. Dr. Çiğdem Altan, for their outstanding contributions that have guided the journal's growth and ensured its inclusion in leading international indexes since its foundation a decade ago.

We also sincerely thank our editorial board members, reviewers, and authors for their continuous support and valuable contributions to the journal's success.

Thank you for being part of this journey toward academic excellence.

Sincerely,

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