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CONTENTS

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EDITORIAL

2018 Issue 3 at a Glance:

For this issue, we have selected five original articles, a review, four case reports, and a letter to the editor representing the research being conducted by ophthalmologists from Turkey and many other countries within the universal rules and principles of science in the service of human health.

The first original study in this issue is by Huseynli and Abdulaliyeva from Baku, Azerbaijan. The authors analyzed the keratometric, topometric, and pachymetric properties of early keratoconic corneas in a Caucasian population using Scheimpflug camera imaging parameters and investigated the utility of different indices to distinguish subclinical keratoconus (ScKC) and keratoconus (KC) eyes from normal eyes. Their results show that Scheimpflug tomography parameters effectively distinguish KC from normal corneas in white subjects, while a combination of different data is necessary to differentiate ScKC (see pages 99-108).

Pseudoexfoliation syndrome (PEX) is a disease involving the basement membrane and is characterized by age-related, progressive accumulation of fibrillar material in various ocular and extraocular tissues. Most patients with PEX develop pseudoexfoliation glaucoma (PEG). Ersöz et al. analyzed the optic nerve heads of PEG patients and healthy volunteers using enhanced depth imaging spectral domain optical coherence tomography (EDI SD-OCT) and assessed associations between disease severity and prelaminar tissue and lamina cribrosa thickness measurements. The authors reported that prelaminar tissue thinning was associated with the presence of PEG but not with glaucoma severity, while lamina cribrosa thickness significantly correlated with PEG severity and progression (see pages 109-114).

Glaucoma is a global public health problem and the second commonest cause of blindness worldwide after cataract. Because it is usually asymptomatic in the early stages, many patients do not realize they have glaucoma until the onset of vision loss. The treatment of diagnosed patients is also an important link in controlling glaucoma. Demirtaş et al. developed a tool called the Glaucoma Knowledge Level Questionnaire, conducted validity and reliability studies for the scale, and are presenting it for use by scientists in our country as a starting point to increase public knowledge of glaucoma and thereby prevent vision loss and reduced quality of life due to glaucoma (see pages 115-121).

Bozkurt Oflaz et al. conducted a study evaluating the correlation between cataract surgery simulator performance and practical experience to assess the value of simulation devices in surgical training. They determined that the results of simulated surgery were consistent with real-life experience and that repeated practice improved performance. The authors concluded that training with simulators is ideal for physicians to increase their self-confidence before real surgeries and to prevent possible complications (see pages 122-126).

Bayraktar et al. evaluated the results of phacoemulsification and posterior chamber intraocular lens implantation in six patients with radiation cataract after undergoing radiotherapy for retinoblastoma. Two patients developed iridocyclitis which responded to treatment and all patients developed posterior capsular opacification. However, all patients had a better final visual acuity compared to preoperative visual acuity, and none exhibited late intraocular recurrence, orbital tumor, systemic metastasis, or secondary cancer. The authors concluded that surgical intervention done after ensuring retinoblastoma control with treatment and waiting at least nine months is safe in terms of tumor recurrence (see pages 127-131).

The esteemed Turkish scientists Türkan Eldem, MD and Bora Eldem, MD have penned this issue's review entitled "Ocular Drug, Gene, and Cellular Delivery Systems and Advanced Therapeutic Medicinal Products", which provides comprehensive and useful information about the basic features, current technological advances, and legal regulations pertaining to various ocular delivery systems and more complex high-risk advanced therapies involving gene or cellular systems, that have been designed to increase the absorption and decrease the metabolism and elimination of drugs, prolong residence time in ocular tissues and compartments, and overcome ocular barriers (see pages 132-141).

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Özbek-Uzman et al. reported a case of late *Candida parapsilosis* fungal keratitis after crescentic lamellar wedge resection for pellucid marginal degeneration. Despite controlling the infection with medical treatment, the patient experienced recurrent infectious episodes and cataract development, which the authors attributed to lens capsule damage and inoculation of the lens with microorganism during injection of antifungal drug. However, they reported achieving good visual acuity in this challenging case with patience and diligent medical and surgical treatment including cataract surgery, amphotericin B administration to the anterior chamber, and corneal cross-linking (see pages 142-145).

Yaşar et al. presented a case of urticaria following the use of nepafenac (Nevanac 0.1%, Alcon), an ophthalmic nonsteroidal anti-inflammatory (NSAI) solution. The authors noted that although the ocular side effects of topical NSAI drugs are known, such a systemic allergic reaction has not been reported previously. Therefore, they emphasized the need for ophthalmologists to keep the possibility of urticaria in mind when prescribing nepafenac, and asserted that their report contributes to the literature the first documented case of urticaria as a side effect of ophthalmic nepafenac use (see pages 146-149).

Visualization of changes secondary to ischemia using optical coherence tomography angiography (OCTA) may be a non-invasive alternative in the diagnosis and follow-up of acute retinal artery branch occlusion. Çelik et al. reported a patient with acute retinal artery branch occlusion who was followed using OCTA, demonstrating that OCTA can facilitate the diagnosis and follow-up of patients with contraindications for fluorescein angiography such as chronic kidney disease (see pages 150-154).

In another case report, Alfaqawi et al. described a patient with refractory cystoid macular edema (CME), which can develop after successful retinal detachment repair and is notoriously difficult to treat. They initially gave repeated intravitreal triamcinolone injections and intravitreal dexamethasone implants to manage the CME, but later switched to an intravitreal steroid fluocinolone acetonide implant (ILUVIEN) due to recurrence. They reported that this treatment resulted in the maintenance of a nonexudative macula and improvement in visual acuity (see pages 155-157).

Finally, we have included a letter to the editor sent by Indiran et al. of India that raises awareness of magnetic resonance imaging (MRI) artifacts and the practical problems they cause. They reported a case in which eye cosmetics caused an MRI artifact that mimicked a ciliary body tumor (see pages 158-159).

Respectfully on behalf of the Editorial Board,
Tomris Şengör, MD

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Turk J Ophthalmol 2018;48:99-108

Original Article

Evaluation of Scheimpflug Tomography Parameters in Subclinical Keratoconus, Clinical Keratoconus, and Normal Caucasian Eyes

Samira Huseynli, Farah Abdulaliyeva
National Ophthalmology Center Named After Academician Zarifa Aliyeva, Ophthalmology Clinic, Baku, Azerbaijan

Abstract

Objectives: To evaluate tomographic and topographic parameters in subclinical and clinical keratoconus eyes by comparing them with normal eyes in a young Caucasian population.

Materials and Methods: This cross-sectional study included 88 normal eyes (control group), bilateral data from the preclinical stage of 24 progressive keratoconus eyes (bilateral subclinical keratoconus group), 40 fellow eyes of patients with unilateral keratoconus (fellow eyes group) and 97 eyes with mild keratoconus (clinical keratoconus group). Topographic and tomographic data, data from enhanced elevation maps and keratoconus indices were measured in all study eyes using Scheimpflug tomography. Receiver operating characteristic (ROC) curve analysis was used to assess individual parameters to discriminate eyes of patients with subclinical and clinical keratoconus from control eyes. The sensitivity and specificity of the main effective parameters were evaluated and optimal cut-off points were identified to differentiate subclinical keratoconus and keratoconus from normal corneas.

Results: Comparison of all subclinical and clinical keratoconus eyes from the normal group revealed significant differences in most diagnostic parameters. The ROC curve analysis showed high overall predictive accuracy of several Pentacam parameters (overall D value, anterior and posterior elevations and difference elevations, pachymetry progression index, index of surface variance, index of height decentration and keratoconus index) in discriminating ectatic corneas from normal ones. These outcomes were proportionally less pronounced in all subclinical keratoconus eyes than in the clinical keratoconus eyes. Pachymetric readings were progressively lower in the bilateral subclinical keratoconus eyes and sensitivity and specificity of the analyzed tomographic and topographic parameters were higher than the fellow eyes group when differentiating subclinical keratoconus from healthy corneas.

Conclusion: Scheimpflug tomography parameters such as D value, elevation parameters, progression index and several surface indices can effectively differentiate keratoconus from normal corneas in a Caucasian population. Nevertheless, a combination of different data is required to distinguish subclinical keratoconus.

Keywords: Subclinical keratoconus, keratoconus, Scheimpflug tomography, Pentacam

Introduction

Keratoconus (KC) is a corneal ectatic disorder, usually bilateral in most cases, characterized by progressive corneal thinning resulting in corneal protrusion, irregular astigmatism and decreased vision.[1,2] Modern advances in computer-based technologies and imaging techniques have increased our ability to diagnose KC. Thus, determining the incidence of subclinical KC (ScKC) and clinical KC will provide a more accurate estimation of the impact of such new treatment options on healthcare costs.[3] The incidence of KC varies depending on factors such as ethnicity and the criteria used to establish the diagnosis; most estimates place the incidence in the general population between 50 and 230 per 100,000, though rates vary greatly in different geographic regions.[4] Screening for clinical KC is not difficult due to its corneal topography and biomicroscopic, retinoscopic and pachymetric findings. However, detection of this ectatic disorder is difficult at the very early or preclinical stages.

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The identification of corneas at higher risk or susceptibility represents a major challenge for refractive surgeons.[5]

Early detection of KC is closely related to the clinical care of these patients. These patients should not be assigned to refractive laser treatment but rather should undergo further screening for an ectatic disorder to detect progressive ectasia. Abnormal preoperative topography and age were reported to be the most significant predictive variables for ectasia development.[6]

The term ScKC describes the very early preclinical stage of KC that can only be detected with diagnostic examinations such as corneal topography. Much effort has been made to implement these data for patient screening in refractive surgery and several different approaches have been attempted to discriminate a cornea with ScKC and a normal cornea using corneal topography.[7] However, exact diagnosis of ScKC is still difficult, as there is a lack of defined threshold criteria. A major reason for that difficulty is that persons with suspected bilateral KC continue in their suspected status until definitive KC develops in one eye. Nevertheless, due to lack of symptoms in the early stages, patients often present with advanced KC. Studies revealed differences in the corneal topographic pattern between normal eyes and eyes with presumed ScKC, as represented by fellow eyes or eyes of family members of KC patient, or eyes that developed postLASIK ectasia.[8,9,10]

The Scheimpflug camera we used is considered to be the most sensitive device to detect early forms of KC. It uses various indices derived from tomographic thickness evaluation parameters, such as the corneal thickness spatial profile, the percentage of thickness increase and Belin/Ambrosio Enhanced Ectasia Display (BAD). BAD utilizes both anterior and posterior elevation data and pachymetric data to screen for ectatic change.[11,12,13] The purpose of this study was to analyze the keratometric, topometric and pachymetric properties of early keratoconic corneas of Caucasian eyes with the Scheimpflug imaging camera and to study the usefulness of different indices in differentiating ScKC and clinical KC eyes from normal eyes.

Materials and Methods

In this cross-sectional study, we evaluated patients who visited the clinic and underwent Pentacam HR examination. The local ethics committee of the Zarifa Aliyeva National Ophthalmology Center approved the study and it was conducted according to the principles set forth in the Declaration of Helsinki. Prior to examination, every participant gave his/her informed consent and the patient anonymity was preserved. Inclusion criteria were minimum age of 17 years and definitive findings consistent with KC, such as those described by the Collaborative Longitudinal Evaluation of Keratoconus group.[14] ScKC was diagnosed using criteria defined in previous studies,[15,16,17,18,19,20,21,22,23] including corneal topography with abnormal localized steepening or an asymmetric bow-tie pattern, a normal-appearing cornea on slit-lamp biomicroscopy and at least 1 of the following signs: steep keratometric curvature (>47.0 overall deviation [D]), oblique cylinder >1.5 D, central corneal thickness less than 500 mm and being the fellow eye of clinical KC, with or without abnormal topography. According to the Scheimpflug KC indices, ScKC eyes were categorized as being normal, with a Pentacam KC system indication of 0.

Control cases were selected from a database of candidates for refractive surgery with normal corneas and myopia or myopic astigmatism. Eyes were considered normal if they had no ocular pathology, no previous ocular surgery and no irregular corneal pattern on corneal tomography. One eye was randomly selected from each candidate for inclusion in this study. Exclusion criteria included a history of corneal surgery, significant corneal scarring and significant ophthalmic disease that might potentially affect the outcomes.

In the study we used the WaveLight Oculyzer II (Alcon Surgical, Ft Worth, Texas), a Pentacam High-Resolution Scheimpflug imaging camera 26 (Oculus Optikgeräte GmbH, Wetzlar, Germany), running on software version 1.17r47. The readings were taken as recommended in the instruction manual of the instrument.[24] Image quality was checked and for each eye only one examination with a high quality factor was recorded. Various parameters were derived from topographic and topometric maps and the BAD as described below.

Data obtained from topographic maps: mean keratometric readings along the flattest (K1) and steepest (K2) meridians, topographic astigmatism (cylinder) and asphericity for the anterior corneal surfaces, maximum curvature power on front of the cornea with vertical, horizontal location absolute distance from apex in mm, corneal thickness at the center (central corneal thickness) and at the thinnest point of the cornea (thinnest corneal thickness). The absolute distances from the corneal apex to the thinnest point of the cornea were determined.

Data obtained from the BAD: Corneal height data measurement was followed by evaluation of elevation of the thinnest point from 8 mm anterior and posterior, by using a conventional best-fit sphere (BFS) as the reference surface (in μm) and corneal elevation difference values were taken as the differential changes in corneal elevation between the BFS and the enhanced BFS (with exclusion of a 3.5-mm optical zone in the thinnest portion of the cornea).

The BAD also contains five new terms (D values for standard deviation [SD] from the mean) representing the front surface, back surface, pachymetric progression, thinnest point and thinnest point displacement. The D is the final overall map reading taking each of the five parameters into account. Each individual parameter D and the final D reported as SDs from the mean were also recorded. Progression index is calculated as the average progression value at different pachymetric rings, referenced to the mean curve. The average, minimum and maximum pachymetric progression indexes were recorded.

Corneal volume (CV) is reported as the volume of the cornea in a diameter of 3, 5 and 7 mm, centered on the anterior corneal apex.

Data obtained from topometric maps: Corneal parameters such as index of surface variance, index of vertical asymmetry, keratoconus index (KI), central keratoconus index, index of

height asymmetry and index of height decentration were evaluated as additional tools in differentiating KC from healthy eyes with thin corneas.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA). ANOVA was used to test differences for age among the groups. Considering all indices in the KC group were non-normally distributed, the analyzed parameters were compared among the groups using the non-parametric Kruskal-Wallis test, post hoc analysis was done with Mann-Whitney U test with Bonferroni correction to compare each pair of groups. The results are expressed as mean ± SD and a value of $p<0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curves were used to determine the overall predictive accuracy of the parameters when used as a test to identify eyes with KC. The diagnostic specificity and sensitivity of the 10 most effective parameters were evaluated and compared with ROC and cut-off points were presented.

Results

Ninety-seven eyes of 97 patients (80 males/17 females) with mild KC (KC group, Pentacam system indication TKC 1), 88 eyes of 64 patients (60 males/4 females) with ScKC (ScKC group; Pentacam system indication TKC 0) and 88 eyes of 88 candidates for refractive surgery (55 males/33 females) with normal corneas (normal group) were analyzed. Mean age was 22.19±2.97, 21.5±3.13 and 21.5±2.95 years respectively in the KC, ScKC and normal groups. Among the ScKC patients, 24 eyes of 12 patients were included in the bilateral ScKC subgroup and 40 eyes in the unilateral ScKC subgroup. Preclinical stage data of both eyes in patients with documented progressive KC were included in the bilateral ScKC group. All eyes in the bilateral ScKC group had suspicious tomography and topography findings and a 1- to 3-year follow-up period showed KC progression in 1 or both eyes. Patients who were diagnosed with clinical KC in 1 eye and had no slit-lamp findings and no topography finding significant enough to be diagnosed as clinical KC in the fellow eye were included in unilateral ScKC subgroup. The mean Pentacam parameters and the differences between clinical and ScKC patients are shown in Tables 1 and 2.

We found no significant differences in terms of mean and maximum keratometry or astigmatism between the ScKC and control eyes ($p\geq0.07$, Kruskal-Wallis test). However, all other values were significantly different between the analyzed groups (Table 2).

Comparison of bilateral ScKC eyes to the fellow eyes of clinical KC eyes revealed significant differences in corneal thickness variables (CCT, ThCT) ($p<0.01$, Mann-Whitney U test). The CV (CV 3-7) values showed lower distribution in the bilateral ScKC group than in the unilateral KC group ($p<0.01$, Kruskal-Wallis test). However, other diagnostic variables showed no significant differences between the groups.

Pairwise comparisons among the clinical KC and other groups of eyes revealed the following significant differences: keratoconic versus normal eyes, all variables ($p<0.01$, Mann-Whitney U test); keratoconic versus fellow eyes, all variables except Thin L.Dist Abs, CV7; and KC versus bilateral ScKC eyes, all variables except flat keratometry, astigmatism and volume values.

Receiver Operating Characteristic Curve Analysis

When discriminating fellow eyes with ScKC from control eyes, the D value showed the highest AUC (0.904), followed by posterior elevation (0.887) (Table 3).

In discriminating between bilateral ScKC eyes and control eyes, most parameters had high AUCs (Table 3); however, corneal thickness and volume parameters showed higher AUCs than in other groups.

Between the clinical KC and normal groups, the diagnostic efficiency of most characteristic parameters increased significantly (all AUC>0.9), indicating their excellent discrimination capacity. However, posterior elevation at the thinnest point, the overall D value and KI showed the highest AUCs (Table 3).

Table 4 shows the cut-off points and sensitivity and specificity values of the main effective Pentacam parameters derived from ROC curve analysis in all study groups.

Figure 1 presents graphical representations of the ROC curves of main effective Pentacam parameters with higher predictive accuracy to detect subclinical and clinical KC.

Discussion

The pathogenesis of primary KC remains unclear. As known from the literature, KC is generally a bilateral disorder, although initially only one eye might be affected. We also know that approximately 50% of the unaffected fellow eyes will progress to KC within 16 years. In a study by Li et al.[9] more than one-third of clinically normal eyes in patients with unilateral KC developed manifest KC during the 8-year follow-up period. Several studies investigated early screening and diagnosis of KC using the Pentacam device in different ethnic populations.[16,17,18,19,20,21,22,25,26,27,28,29,30,31] Results varied in different populations related to race, geographic location and size of the study population (Table 5).

Most such studies differ from each other by the criteria used to diagnose subclinical/forme fruste KC.[16,17,18,19,20,21]

The aim of the present study was to identify and compare characteristics of the subtle morphologic changes in bilateral KC-suspect eyes and clinically normal fellow eyes of patients with KC. In our study, all subclinical eyes had no clinical signs of KC but had abnormal topographic features with asymmetric bowtie and focal or inferior steepening pattern. According to the Scheimpflug camera, KC indices of these eyes were categorized as being normal (with system indication "0"). Thus, analysis of these eyes might help to identify at-risk corneas, especially in refractive surgery candidates.

In this study, D value was the most characteristic index between all analyzed groups and showed the highest area under the ROC curve, followed by posterior and anterior elevation. We found that the best cut-off for D value to differentiate

Table 1. Mean Pentacam parameters between subclinical, clinical keratoconus and normal eyes

Pentacam parameters	Control group (n=30) mean ± SD	Fellow eye ScKC (n=40) mean ± SD	Bilateral ScKC (n=24) mean ± SD	Clinical KC (n=97) mean ± SD
K1	42.51±1.4	42.46±1.47	43.12±1.4	43.48±1.9
K2	44.23±1.4	44.06±1.49	44,8±2.1	46.66±2.4
Kmean	43.45±1.22	43.22±1.31	43.97±1.6	45.0±1.99
Astig	-1.73±1.02	-1.34±1.66	-1.6±1.7	-2.19±2.9
Q value	0.48±0.12	0.64±1.11	0.54±0.16	0.67±0.32
K max	44.6±1.24	45.18±1.7	45.7±2.1	50.09±3.36
AP (µm)	547.33±33.55	520.45±34	502.5±22.56	493.49±56.4
TP (µm)	545.23±33.3	512.7±34.5	494.25±20.84	485.69±34.63
ThinL.A (mm)	0.62±0.24	0.91±0.22	0.92±0.17	0.94±0.225
PPI, average	0.957±0.138	1.14±0.16	1.2±0.26	1.63±0.4
PPI, minimum	0.697±0.142	0.82±0.15	0.88±0.22	1.27±0.37
PPI, maximum	1.17±0.17	1.57±0.38	1.6±0.5	2.27±0.59
CV3	4.06±0.23	3.76±0.23	3.6±0.15	3.6±0.23
CV5	11.66±0.7	11.05±0.7	10.67±0.49	10.78±0.66
CV7	24.99±1.48	23.71±1.5	23.05±1.1	23.33±1.42
EA (µm)	2.31±1.51	5.18±3.0	5.37±2.42	13.63±5.45
EA dif (µm)	2.67±1.23	4.5±1.9	5.5±1.95	10.14±4.37
EP (µm)	3.3±2.41	11.36±6.8	10.8±7.8	30.55±10.28
EP dif (µm)	3.4±2.6	8.42±4.7	8.5±4.9	21.88±11.88
D	0.71±0.58	2.21±1.004	2.7±1.24	5.6±2.06
ISV	20.9±7.28	24.9±10.03	28.79±9.3	51.9±14.68
IVA	0.12±0.051	0.21±0.09	0.22±0.1	0.52±0.2
KI	1.01±0.015	1.04±0.023	1.03±0.035	1.12±0.047
CKI	1.0056±0.05	1.0078±0.01	1.007±0.007	1.03±0.32
IHA	4.3±3.4	7.48±0.28	5.95±4.6	19.67±14.1
IHD	0.007±0.003	0.013±0.07	0.015±0.008	0.042±0.02
Rmin	7.4±0.21	7.44±0.31	7.39±0.36	6.76±0.44

SD: Standard deviation, n: number of eyes, ScKC: Subclinical keratokonus, Astig: Central astigmatism, Kmax: Maximum curvature power on front of cornea, ThinL.A: Thinnest location absolute distance from apex, PPI: Pachymetric progression index, EA: Anterior elevation at the thinnest point, EP: Posterior elevation at the thinnest point, D: Overall deviation, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Central keratoconus index, IHA: Index of height asymmetry, IHD: Index of height decentration, Rmin: Minimum sagittal curvature

Table 2. Comparison of Pentacam parameters between normal, bilateral subclinical keratokonus, fellow eye of the unilateral keratokonus and clinical keratoconus eyes

Pentacam parameters	Fellow eye ScKC vs normal p value	Bilateral ScKC vs normal p value	Fellow eye ScKC vs bilateral ScKC p value	Fellow eye ScKC vs KC group p value	Bilateral ScKC subgroup vs KC group p value	KC vs normal group p value
K1	0.880	0.220	0.199	0.004	0.301	0.022
K2	0.636	0.272	0.187	<0.001	0.001	<0.001
Kmean	0.403	0.264	0.163	<0.001	0.013	<0.001
Astigmatism	0.07	0.190	0.652	0.005	0.076	0.005
Q value	0.567	0.042	0.285	<0.001	0.004	<0.001
Kmax	0.043	0.013	0.305	<0.001	<0.001	<0.001
CCT (µm)	<0.001	<0.001	0.013	<0.001	0.273	<0.001
ThCT (µm)	<0.001	<0.001	0.013	<0.001	0.088	<0.001
ThinL.Abs (mm)	<0.001	<0.001	0.707	0.642	<0.001	<0.001
PPI, average	<0.001	<0.001	0.675	<0.001	<0.001	<0.001
PPI, minimum	<0.001	<0.001	0.525	<0.001	<0.001	<0.001
PPI, maximum	<0.001	<0.001	0.811	<0.001	<0.001	<0.001
CV3	<0.001	<0.001	0.010	0.004	0.971	<0.001
CV5	<0.001	<0.001	0.015	0.021	0.479	<0.001
CV7	<0.001	<0.001	0.052	0.106	0.433	<0.001
EA (µm)	<0.001	<0.001	0.798	<0.001	<0.001	<0.001
EA dif (µm)	<0.001	<0.001	0.058	<0.001	<0.001	<0.001
EP (µm)	<0.001	<0.001	0.304	<0.001	<0.001	<0.001
EP dif (µm)	<0.001	<0.001	0.925	<0.001	<0.001	<0.001
D	<0.001	<0.001	0.133	<0.001	<0.001	<0.001
ISV	0.029	0.001	0.062	<0.001	<0.001	<0.001
IVA	<0.001	0.001	0.509	<0.001	<0.001	<0.001
KI	<0.001	0.001	0.579	<0.001	<0.001	<0.001
CKI	0.345	0.073	0.697	<0.001	<0.001	<0.001
IHA	0.07	0.119	0.519	<0.001	<0.001	<0.001
IHD	<0.001	<0.001	0.284	<0.001	<0.001	<0.001
Rmin	0.123	0.085	0.308	<0.001	<0.001	<0.001

P value: Mann-Whitney U, ScKC: Subclinical keratokonus, Astig: Central astigmatism, Kmax: Maximum curvature power on front of cornea, ThinL.A: Thinnest location absolute distance from apex, PPI: Pachymetric progression index, EA: Anterior elevation at the thinnest point, EP: Posterior elevation at the thinnest point, D: Overall deviation, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Central keratoconus index, IHA: Index of height asymmetry, IHD: Index of height decentration, Rmin: Minimum sagittal curvature

clinical KC from controls was 1.83 with 100% sensitivity and 96.0% specificity. On the other hand, the best cut-off for D value in differentiating eyes with bilateral ScKC from normal eyes was 1.73 with a sensitivity of 96.7% and specificity of 79%, suggesting excellent sensitivity and specificity. However, when differentiating fellow eyes of unilateral KC eyes from normal eyes, the best cut-off for D value was 1.59 with excellent sensitivity (95.5%) but limited specificity (73.7%).

The D value is a multimetric combination parameter composed of keratometric, pachymetric, pachymetric progression and posterior elevation parameters. Mufuoglu et al.[18] showed that among the keratometric, pachymetric (including progression indices) and posterior elevation indices, D value had the best areas under the ROC curve to differentiate between clinical and ScKC eyes and control eyes. They found that the best cut-off for D value to differentiate KC from controls was 2.1, with 100% sensitivity and 100% specificity. This result suggests that the new D index can be valuable as a sole parameter in diagnosing

Table 3. Receiver operating characteristic curve analysis for subclinical and clinical keratoconus eyes versus normal eyes

	Fellow eye ScKC vs normal			Bilateral ScKC vs normal			KC vs normal		
Values	**AUC**	**SE**	**CI 95%**	**AUC**	**SE**	**CI 95%**	**AUC**	**SE**	**CI 95%**
K1	0.474	0.057	0.376-0.602	0.577	0.065	0.467-0.726	0.653	0.041	0.572-0.733
K2	0.448	0.060	0.318-0.578	0.570	0.077	0.413-0.715	0.827	0.032	0.765-0.889
Kmean	0.452	0.057	0.338-0.575	0.593	0.067	0.466-0.732	0.766	0.036	0.696-0.836
Astiq	0.389	0.059	0.273-0.505	0.414	0.076	0.265-0.0564	0.619	0.044	0.534-0.735
Q value	0.522	0.061	0.476-0.714	0.638	0.065	0.424-0.719	0.750	0.038	0.675-0.825
CCT	0.691	0.051	0.400-0.681	0.895	0.041	0.521-0.818	0.872	0.026	0.821-0.923
ThCT	0.730	0.049	0.680-0.865	0.931	0.032	0.848-0.985	0.899	0.023	0.854-0.944
Kmax	0.612	0.063	0.727-0.924	0.681	0.076	0.912-0.1.0	0.952	0.018	0.917-987
ThinL.Abs	0.823	0.039	0.731-0.895	0.863	0.035	0.775-0.929	0.776	0.035	0.708-845
PPI average	0.834	0.040	0.798-0.946	0.836	0.048	0.785-0.960	0.960	0.015	0.931-0.990
PPI minimum	0.745	0.050	0.679-0.875	0.783	0.056	0.710-0.921	0.944	0.019	0.907-0.982
PPi maximum	0.844	0.044	0.785-0.942	0.835	0.050	0.772-0.955	0.975	0.012	0.952-0.997
CV3	0.752	0.050	0.712-0.914	0.917	0.036	0.866-0.991	0.861	0.027	.807-.915
CV5	0.706	0.052	0.651-0.849	0.872	0.043	0.833-0.985	0.811	0.032	0.748-0.873
CV7	0.697	0.053	0.637-0.842	0.850	0.046	0.813-.978	0.778	0.035	0.710-0.847
EA	0.815	0.047	0.745-0.928	0.905	0.033	.859-981	0.988	0.007	0.974-1.0
EA diffirent	0.790	0.046	0.692-0.878	0.893	0.038	0.810-996	0.984	0.011	0.963-1.0
EP	0.887	0.041	0.800-0.966	0.888	0.041	0.793-0.962	0.999	0.001	0.996-1.0
EP diffirent	0.829	0.045	0.739-0.918	0.838	0.050	0.743-0.932	0.994	0.003	0.988-1.0
D	0.904	0.031	0.831-0.958	0.973	0.014	0.926-0.998	0.993	0.005	0.983-1.0
ISV	0.617	0.054	0.518-0.735	0.756	0.050	0.656-0.859	0.974	0.010	0.953-1.0
IVA	0.844	0.041	0.748-0.916	0.857	0.046	0.747-0.940	0.996	0.003	0.990-1.0
KI	0.810	0.045	0.785-0.965	0.732	0.067	0.618-0.882	0.994	0.004	0.986-1.0
CKI	0.531	0.062	0.415-0.668	0.603	0.064	0.483-0.741	0.782	0.036	0.710-0.853
IHA	0.659	0.057	0.538-0.765	0.606	0.068	0463-0.732	0.884	0.026	0834-0.934
IHD	0.782	0.045	0.679-0.866	0.830	0.050	0.719-0.923	0.979	0.011	0.957-1.0
Rmin	0.579	0.056	0.369-0.608	0.471	0.074	0.433-0.728	0.904	0.024	0.858-0.950

AUC: Area under curve, SE: Spherical equivalent, CI: Confidence interval, ScKC: Subclinical keratokonus, Astig: Central astigmatism, Kmax: Maximum curvature power on front of cornea, ThinL.Abs: Thinnest location absolute distance from apex, PPI: Pachymetric progression index, EA: Anterior elevation at the thinnest point, EP: Posterior elevation at the thinnest point, D: Overall deviation, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Central keratoconus index, IHA: Index of height asymmetry, IHD: Index of height decentration, Rmin: Minimum sagittal curvature

KC. But the best cut-off for the D value in differentiating eyes with ScKC from normal eyes was 1.3, with 60% sensitivity and 90% specificity, suggesting good specificity to diagnose ScKC but limited sensitivity.

In another study population, the Pentacam's suspicious cut-off for overall D value was >1.61 as optimal for their particular keratoconic sample.[20] Considering a suspicious D value (>1.6 SD) as positive in order to maximize sensitivity while sacrificing specificity, they preferred to falsely flag a cornea as ectatic than to miss a ScKC case during the preoperative evaluation of refractive surgery candidates.

In our study, the D value was significantly different in the KC, ScKC and healthy groups; these results are very comparable to those of other studies.[18,20,21] However, our study included only patients diagnosed with mild KC.

Posterior elevation was the most discriminating parameter between eyes with ScKC and controls in our study, consistent with a report by de Sanctis et al.[25] In their study, posterior elevation showed high predictive accuracy for ScKC compared to the controls (AUC=0.93) and the optimal cut-off was 29 µm, with 68% sensitivity and 90.8% specificity. Due to differencesin acquiring points of the device, Du et al.[26] reported a much

Table 4. Cut-off points, sensitivity and specificity of the main effective Pentacam parameters derived from receiver operating characteristic curve analysis

	Fellow eye ScKC vs normal			Bilateral ScKC vs normal				KC vs normal	
Values	**Sensitivty**	**Specificity**	**Cut-off**	**Sensitivity**	**Specificity**	**Cut-off**	**Sensitivity**	**Specificiy**	**Cut-off**
D	0.955	0.737	>1.59	0.977	0.792	>1.73	100	0.959	>1.83
EP	0.955	0.763	>8.0	0.955	0.583	>8.0	100	0.994	>11
EA	0.933	0.553	>5.0	0.933	0.667	>5.0	0.978	0.948	>6.0
PPI average	0.933	0.474	>1.14	0.989	0.417	>1.20	0.978	0.907	>1.21
PPI maximum	0.966	0.579	>1.28	0.978	0.417	>1.51	0.978	0.938	>1.54
IVA	0.921	0.525	>0.15	0.944	0.500	>0.22	0.978	0.958	>0.24
KI	0.867	0.875	>1.03	0.867	0.667	>1.03	0.933	0.979	>1.04
IHD	0.823	0.650	>0.008	0.900	0.750	>0.012	0.967	0.969	>0.013

D: Overall deviation, EA: Anterior elevation at the thinnest point, EP: Posterior elevation at the thinnest point, PPI: Pachymetric progression index, IVA: Index of vertical asymmetry, KI: Keratoconus index, IHD: Index of height decentration

Table 5. Summary of the studies of effective Pentacam parameters to detect subclinical keratoconus eyes

Study	Total number of eyes	Sample country	Age (years)	Pentacam parameters (AUC; cut-off)
Uçakhan et al.[17]	151	Turkey	28.3±7.3	PPI average (0.84; >1.15) AED (0.77; >18.5) PED (0.77; >46.5) IVA (0.76; >0.195) ISV (0.79; >24.5)
Muftuoglu et al.[18]	112	Turkey	29.0±8.8	PE (0.71;>11 µm) PED (0.76; >8 µm) D (0.83; >1.31) PPI average (0.62: >1.15)
Bae et al.[19]	48	South Korea	25.08±6.4	AED (0.734; >5.5 µm) PED (0.735; >11.1 µm) IVA (0.733; > 0.16) IHD (0.748; >0.008)
Ruisenor Vazquez et al.[20]	244	Argentina	32.5±11.7	D (0.93; >1.61) PPI max (0.92; >1.4) PPI average (0.86; >1.09)
Hashemi et al.[21]	359	Iran	32.02±10.5	D (0.86; >1.54) IVA (0.86; >0.14) ISV (0.80; >22)
de Sanctis et al.[25]	164	Italy	35±14	PE (0.93; >29.0 µm)
Du et al.[26]	213	China	20.7±5.5	PE (0.882; >7.5 µm) AE (0.774; >3.5 µm) CCT (0.852; <523.5 µm)
Current study†	213	Azerbaijan	21.5±3.13	D (0.904; 1.59) PE (0.87; >8.0 µm) AE (0.815; >5.0 µm) PPI average (0.834; >1.14) IVA (0.844; >0.15) KI (0.810; >1.03)

†This table contains comparison between fellow eyes subclinical keratoconus vs normal eyes from this study
AUC: Area under curve, D: Overall deviation, IVA: Index of vertical asymmetry, ISV: Index of surface variance, PPI: Pachymetric progression index

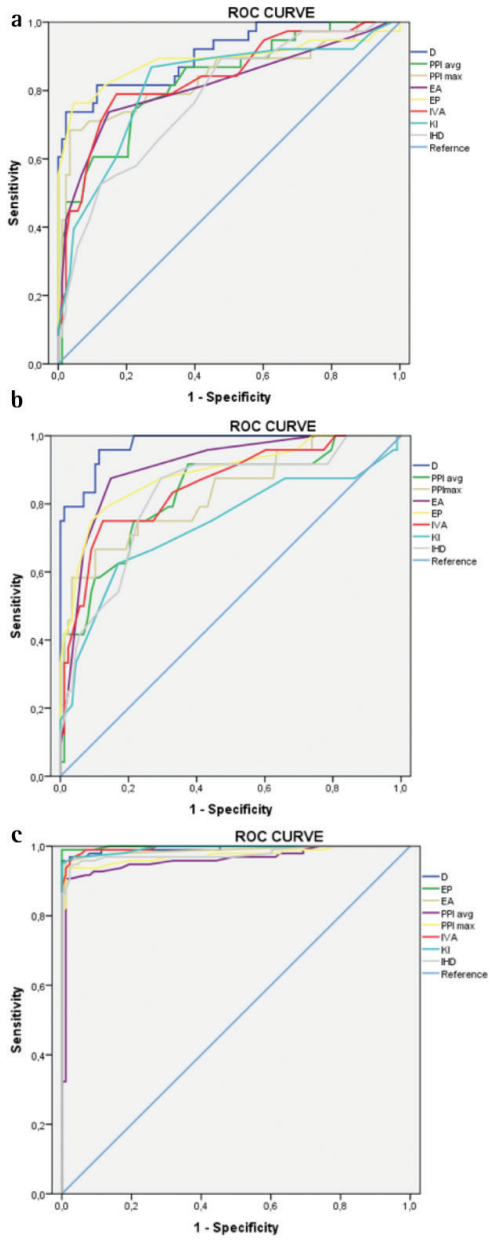

Figure 1. Receiver operating characteristic curves of main effective Pentacam parameters to detect unilateral subclinical keratoconus (a), bilateral subclinical keratoconus (b) and clinical keratoconus (c)

D: Overall deviation, EA: Anterior elevation at the thinnest point, EP: Posterior elevation at the thinnest point, PPI: Pachymetric progression index, IVA: Index of vertical asymmetry, KI: Keratoconus index, IHD: Index of height decentration

smaller cut-off value for posterior elevation (7.5 µm) but with a comparable sensitivity (70.7%) and specificity (93.8%). In our study, anterior and posterior elevations in the analyzed study groups were significantly different; however, as displayed in Table 5, we obtained much lower values than those reported in other studies, especially in the KC group. This may be explained by the use of newer software and the fact that we utilized elevation indices at the thinnest point from 8 mm BFS. Uçakhan et al.[17] evaluated Pentacam parameters in ScKC compared with normal eyes. They defined ScKC as the fellow eye of KC and found that corneal thickness distribution indices and posterior elevation are more helpful than anterior curvature data in identifying eyes with ScKC. Additionally, they also evaluated the anterior/posterior elevation depression difference and suggested that posterior elevation difference was the strongest discriminating factor, followed by anterior elevation depression. The anterior and posterior elevation difference values were available in the BAD display software for the Pentacam proposed by Villavicencio et al.[13] Anterior and posterior corneal elevation differences determined with enhanced BFS may provide more accurate diagnostic information for KC than the amounts of anterior and posterior corneal elevation themselves determined with conventional BFS.[17,18,19,25,26,27,28,29,30]

Kamiya et al.[30] observed in Japanese patients that anterior and posterior elevation measurements tended to have a higher accuracy at the earlier stages of KC, so they concluded that elevation and elevation difference measurements might provide useful information to improve the diagnostic accuracy in early KC. They detected that posterior elevation (0.980) and anterior elevation (0.977) showed the highest areas under the ROC curve. Their results are highly comparable to ours in AUROC of indices.

Pinero et al.[16] reported progressively lower pachymetric readings in eyes with subclinical, early, or moderate KC ($p<0.01$). The CV was significantly lower in the moderate KC group than in the subclinical and mild groups. A possible explanation for this finding may be that at early stages of KC a redistribution of CV occurs with no loss of tissue. As discussed, we found significant differences in CCT, ThCT, CV3, CV5 and CV7 between normal eyes and eyes with subclinical or clinical KC.

Additionally, in our study the bilateral ScKC group showed lower distribution in corneal thickness parameters and CV (CV 3-7) values than fellow eyes of the clinical KC eyes and these parameters had higher predictive accuracy than when comparing the fellow eye group to normal eyes. An explanation of this finding could be that subclinical eyes with low pachymetric reading showed a greater tendency toward progression. Using the Pentacam, Bae et al.[19] evaluated topographic and tomographic changes in fellow eyes of Asian patients with unilateral KC to compare them with normal eyes. Previous research indicates that true unilateral KC is very rare, thus the normal fellow eye may be the ideal model for the mildest form of ScKC. The group found that fellow eyes in unilateral KC patients showed differences in several parameters that were not detectable with the Pentacam detection program. In their study on ROC curve analysis, keratometric asymmetry and topometric index were best at discriminating fellow eyes from normal, followed by elevation differences on the posterior and anterior corneal surface. In our study from anterior surface Pentacam-derived topometric indices, the index of surface variance, index of height decentration and KI were the most sensitive and specific

criteria to diagnose ScKC. This is comparable to some previous studies.[21,22]

In this study we found significantly increased topographic elevation, pachymetry and topometric values in bilateral suspect eyes and fellow eyes of patients with unilateral KC compared with the values in control eyes. We also found that corneal topography and tomography outcomes were proportionally less pronounced in all ScKC eyes than in clinical KC eyes. Comparing bilateral suspect eyes from fellow eyes of patients with unilateral KC, we found that eyes in the former subgroup have more cornea tissue alteration than the latter subgroup. Furthermore, sensitivity and specificity of the analyzed tomographic and topographic parameters were significantly higher in the former subgroup than the latter group compared to the values in control eyes.

This study has some limitations, including a higher proportion of males than females in the study group. The preponderance towards males in the population is consistent with the authors' clinical experience of the male/female incidence in keratoconic patients and KC incidence studies and thus, this is unlikely to skew the results of this study.[22,31]

Conclusion

In conclusion, this study showed that several Petacam parameters, such as BAD D value, anterior and posterior elevation and difference elevation, pachymetry progression index, index of surface variance, index of height decentration and KI are very effective in discriminating KC from normal corneas. The current study supports findings previously reported on the usefulness of Scheimpflug imaging to assess subclinical keratoconic eyes in different population and confirm results indicating that any single parameter taken alone is not sufficient to distinguish normal cornea from one with ScKC, as the studied parameters showed some degree of overlap in normal and pathologic corneas. Further studies with a larger number of patients and with controls composed of a relevant clinical population and simultaneous evaluation of the corneal biomechanics and wavefront aberrations would be useful to diagnose early KC in the Caucasian population.

Ethics

Ethics Committee Approval: The local ethics committee of the Zarifa Aliyeva National Ophthalmology Center approved the study and it was conducted according to the principles set forth in the Declaration of Helsinki.

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Samira Huseynli, Farah Abdulaliyeva, Design: Samira Huseynli, Farah Abdulaliyeva, Data Collection or Processing: Samira Huseynli, Farah Abdulaliyeva, Analysis or Interpretation: Samira Huseynli, Literature Search: Samira Huseynli, Farah Abdulaliyeva, Writing: Samira Huseynli.

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Original Article

Evaluation of Prelaminar Region and Lamina Cribrosa with Enhanced Depth Imaging Optical Coherence Tomography in Pseudoexfoliation Glaucoma

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Abstract

Objectives: To analyze optic nerve head images of pseudoexfoliative glaucoma (PXG) patients and healthy volunteers obtained with enhanced depth imaging spectral domain-optical coherence tomography (SD-OCT).

Materials and Methods: Seventy patients with PXG and 68 age- and gender-matched healthy subjects were included in this prospective study. The prelaminar tissue and lamina cribrosa were imaged using spectralis OCT with the enhanced depth imaging technique. PXG disease stage was determined with visual field to evaluate relationships between prelaminar tissue thickness (PTT), lamina cribrosa thickness (LT) and disease severity.

Results: There was no significant difference between the PXG group and control group with regard to age, gender, central corneal thickness, or axial length. The mean PTT (93.1±44.5 µm, $p<0.05$) and LT (206.3±33.6 µm $p<0.05$) values of the PXG group were significantly lower compared to the control group in enhanced depth imaging OCT measurements. The PXG patients were divided into stages according to visual field defect severity. While a significant difference was not detected in PTT based on disease stage ($p>0.05$), a statistically significant difference was detected between stages for LT ($p<0.05$).

Conclusion: A thinner PTT was correlated with the presence of PXG but not with the severity of glaucoma. In addition, LT has a stronger relationship with disease severity and progression compared to PTT.

Keywords: Enhanced depth imaging, lamina cribrosa, optical coherence tomography, prelaminar tissue, pseudoexfoliation glaucoma

Introduction

Pseudoexfoliation syndrome (PEX) is an age-related generalized basal membrane disease. It is characterized by the excessive and progressive accumulation of fibrillary material in various ocular and extraocular tissues.[1] Pseudoexfoliative glaucoma (PXG) develops in the vast majority of patients with PEX.[2] PXG is the most common form of secondary open angle glaucoma types.[3] It is characterized by high intraocular pressure (IOP), severe fluctuation of IOP, rapid progression, poor prognosis.[4] The structural changes in lamina cribrosa (LC) beside elevated IOP and severe fluctuation were suggested to be associated with poor prognosis.[5,6,7] Elastotic changes were detected in the LC of eyes with PXG.[7] In a study conducted with atomic force microscopy, the stiffness of the LC was reported to decrease in pseudoexfoliative eyes.[8] In addition, LC deformation may lead to ischemia through the compressive effect on the laminar capillary.[9,10] Since laminar region has been considered the primary site of axonal injury in glaucoma, these alterations may contribute to the rapid progression of PXG.[3] The prelaminar region which covers the LC is composed of retinal ganglion cells, axon bundles, astrocytes, capillaries and extraocular material.

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Its thickness may reduce as the result of ischemia.[11] Prelaminar tissue thickness (PTT) was also shown to decrease as a response to acute[12] and chronic[13] IOP elevation.

Although optical coherence tomography (OCT) can visualize the anterior margins of LC and prelaminar tissue, it cannot visualize the posterior margins of the LC. It is possible to safely visualize the posterior margins of the LC and optic nerve head (ONH) with enhanced depth imaging (EDI), which is present in spectral domain (SD)-OCT.[14,15,16,17]

In our study, we analyzed ONH images of PXG patients and healthy volunteers obtained with EDI SD-OCT. We aimed to investigate the presence of a significant difference between the PXG group and control group with regard to PTT and LC thickness (LT). We also planned to investigate the relationship between PTT, LC and PXG disease stage determined with visual field, retinal nerve fiber layer (RNFL) thickness and vertical cup/disc ratio.

Materials and Methods

This prospective study was approved by the Medical Ethics Committee of İzmir Tepecik Training and Research Hospital. The study was carried out in adherence to the tenets of the Declaration of Helsinki and written informed consent was obtained from all participants. Seventy patients with PXG and 68 age- and gender-matched healthy subjects were recruited from October 2014 to May 2015. Medical histories and demographic data of all participants were noted. All subjects underwent ophthalmic examination including best-corrected visual acuity, central corneal thickness with non-contact specular microscope (sp-2000p, Topcon, Japan), axial length (Lenstar LS900, Haag-Streit AG, Koeniz, Switzerland), Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, dilated fundus photography, visual field test with Octopus 101 automated perimetry (Interzeag AG, Schlieren, Switzerland) using G2 program (central 30-2 threshold strategy) and SD-OCT scanning (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). The vertical cup/disc ratio was noted on dilated fundus examination.

PXG was diagnosed when baseline IOP >21 mmHg, open anterior chamber, glaucomatous optic neuropathy, visual field defects typical of glaucoma and pseudoexfoliation material on the anterior lens capsule, pupillary margin, or both. The Hodapp-Anderson-Parrish system modified for Octopus perimetry was used to classify patients with glaucoma.[18] PXG patients were stratified into five groups according to the severity of visual field defects. Stage 1 (early) glaucoma was characterized by a mean deviation score (MDS) of -0.7 to +4.4 dB; stage 2 (moderate) glaucoma by an MDS of +4.5 to +9.4 dB; stage 3 (advanced) glaucoma by an MDS of +9.5 to +15.3 dB; stage 4 (severe) glaucoma by an MDS of +15.4 to +23.1 dB and stage 5 (end-stage) glaucoma by an MDS of ≥ +23.2.

The inclusion criteria for eyes were a best-corrected visual acuity of 20/40 or better, spherical refraction within ±5.0 diopters and cylinder correction within ±3 diopters. At least two visual field tests were performed to minimize the learning effect. Only reliable (false positive/negative under 15% and reliability factor under 15) and compatible visual field results were included. The control group participants had normal eye exam and perimetry. The exclusion criteria included cardiovascular disease, diabetes, head trauma, Alzheimer's disease, history of stroke, claustrophobia, ocular trauma and other ocular disease affecting visual field and RNFL. Patients whose IOP could not be controlled with medical treatment and end-stage patients were excluded. If both eyes had PXG, one eye was randomly selected for inclusion in the study.

Peripapillary RNFL Measurement with Spectral Domain-Optical Coherence Tomography

All OCT assessments involved in the study were performed by the same experienced ophthalmologist. For OCT examination, the RNFL thicknesses were assessed by scanning a peripapillary circle with a diameter of 3.4 mm and 768 A-scans. Only well-centered images with a signal strength of >20 dB were used. The RNFL thicknesses were automatically segmented and measured using Spectralis software version 5.3.3.0.

Measurement of Prelaminar Tissue Thickness and Lamina Cribrosa Thickness by Spectral Domain-Optical Coherence Tomography Enhanced Depth Imaging

The prelaminar tissue and LC were imaged using the Spectralis OCT with the EDI technique. An internal nasal fixation light was used to center the disc in the 10×15° rectangle. This rectangle was scanned with 97 sections (384 A-scans) with an interval of 30 µm. An average of 45 frames was produced for each cross-sectional B-scan. Thickness measurements were done using Spectralis software version 5.3.3.0. LT and PTT were measured at the vertical center of ONH of 3 B-scans (mid-superior, center, mid-inferior). The center of the ONH was identified as the point where central retinal vessels originate from the ONH. Mid-superior and mid-inferior locations were determined as the midpoints between the center and the margins of the optic disc (Figure 1A). LT was defined as the distance between the anterior and posterior borders of the LC. The borders of the LC were considered to be where the highly reflective region started and finished. Prelaminar tissue was defined as the reflective field on the anterior margin of the LC (Figure 1B). For each patient, the mean of the measurements at the mid-superior, center and mid-inferior locations were regarded as the average PTT and LT. The average PTT and LT were used for statistical analyses. The relationship between PTT, LC and PXG disease stage was determined with visual field, RNFL thickness and vertical cup/disc ratio.

Statistical Analysis

All statistical analyses were performed with Statistical Packages for the Social Sciences (SPSS, version 22, IBM corp., Armonk, New York, USA). A p value <0.05 was considered statistically significant. For comparison of groups, independent t test was used for continuous variables and chi-square test was used for categorical data. Comparison of the patients in different disease stages in the PXG group was done with Kruskal-Wallis test. Pearson correlation analysis was used for correlation analysis.

Results

ONH EDI OCT images of 70 PXG patients and 68 healthy volunteers were analyzed. Two patients in the PXG group and 3 patients in the control group were excluded from the study because the posterior margins of the LC were not visualized clearly. Sixty-eight patients in the PXG group and 65 patients in the control group were included in the statistical analysis.

There was no significant difference between PXG group and control group with regard to age, gender, central corneal thickness, or axial length. Baseline characteristics of the participants are shown in Table 1.

Mean PTT ($p<0.05$) and LT ($p<0.05$) values of the PXG group were seen to be statistically significantly lower compared to the control group in EDI OCT measurements. While mean PTT was 93.1±44.5 µm in the PXG group, it was 213.9±141.1 µm in the control group. Mean LT was calculated as 206.3±33.6 µm in the PXG group and 269.1±24.1 µm in the control group.

The PXG patients were divided into stages according to visual field defect severity. There were 16 patients (23.5%) in early stage, 21 patients (30.9%) in moderate stage, 18 patients (26.5%) in advanced stage and 13 patients (19.1%) in severe stage. While a significant difference was not detected in PTT in comparison of disease stages ($p>0.05$), a statistically significant difference was detected between stages for LT ($p<0.05$). Post hoc multiple comparison results for LT are shown in Table 2.

While a weak correlation was detected with vertical cup/disc ratio in correlation analysis done for PTT, a correlation was not detected with average of RNFL thicknesses (RNFLav). LT was found to be negatively correlated with vertical cup/disc ratio, positively correlated with RNFLav (Table 3, Figure 2).

Table 1. Baseline characteristics of the pseudoexfoliation glaucoma and control groups

	Pseudoexfoliation glaucoma group	Control group	p
Age*	63.7±8.7	61.8±7.6	0.589
Gender‡	35 women/33 men	32 women/33 men	0.796
CCT (µm)*	530.3±33.6	524.7±32.5	0.329
AXL (mm)*	23.1±0.9	22,9±0.7	0.276

*Independent t test, ‡Chi-square test
AXL: Axial length, CCT: Central corneal thickness, p: Significance value

Table 2. Multiple comparison of lamina cribrosa thickness of each group

	Mean ± SD (µm)	p*
Early/Moderate	233.62±22.34/217.2±11.94	0.329
Early/Advanced	233.62±22.34/198.38±23.99	0.001
Early/Severe	233.62±22.34/166.0±39.83	<0.001
Moderate/Advanced	217.2±11.94/198.38±23.99	0.157
Moderate/Severe	217.2±11.94/166.0±39.83	0.001
Advanced/Severe	198.38±23.99/166.0±39.83	0.465

*Kruskal-Wallis test post hoc multiple comparison
p: Significance value, SD: Standard deviation

Table 3. Correlation between enhanced depth imaging optical coherence tomography measurements vs. vertical cup/disc ratio and average retina nerve fiber layer thickness

	Prelaminar tissue thickness		Laminar thickness	
	r	p	r	p
Vertical cup/Disc ratio	-0.327	0.006	-0.613	<0.001
RNFLav	0.208	0.089	0.700	<0.001

p: Significance value, r: Pearson correlation coefficient, RNFLav: Average of retina nerve fiber layer thickness thicknesses

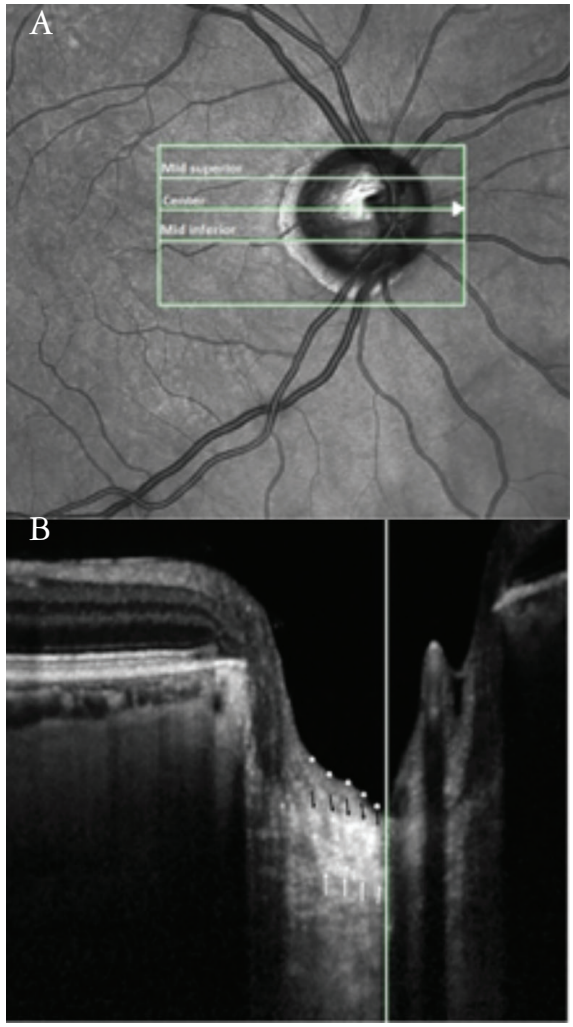

Figure 1. Simultaneous images of a pseudoexfoliation glaucoma patient. a) The measurement of prelaminar tissue thickness and laminar thickness (LT) were performed at the presumed vertical center of each of the 3 B-scans (mid-superior, center, mid-inferior). The short vertical line crossing the center horizontal line corresponds to the long white vertical line in the next image. B) The image shows a horizontal cross-sectional B-scan of the optic nerve head at the center line. The vertical white line marks the vertical center of the optic nerve head. The borders of the highly reflective region were accepted as the borders of the lamina cribrosa (LC); white arrows indicate the posterior borders and black arrows indicate the anterior borders of the LC. LT was defined as the distance between the anterior and posterior LC borders. Prelaminar tissue was defined as the reflective field on the anterior margin of the LC. White dots delineate the anterior borders of the prelaminar tissue

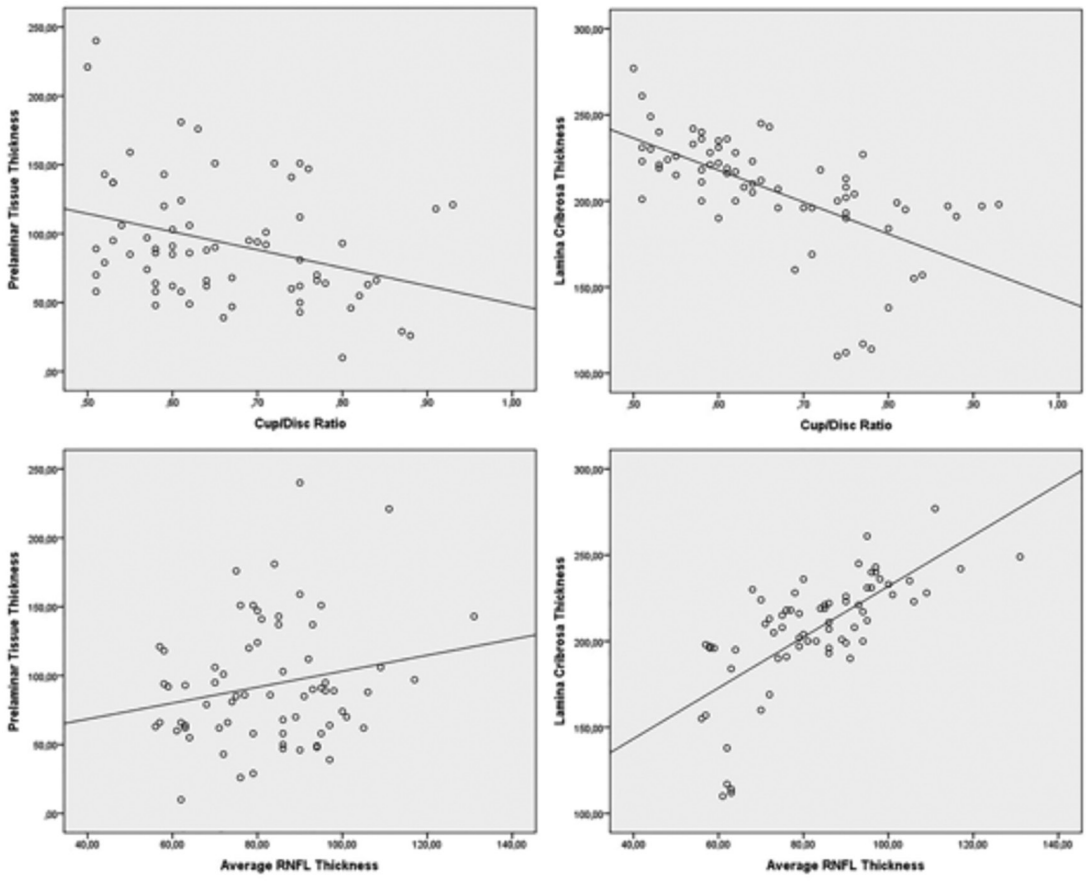

Figure 2. Scatter plots to exhibit correlations between enhanced depth imaging optical coherence tomography measurements vs. vertical cup/disc ratio and average retinal nerve fiber layer (RNFL) thickness

Discussion

The development of EDI in SD-OCT enabled clear visualization of prelaminar and laminar tissues and accelerated investigation of the relationships between these structures and glaucoma.[14,15,16,17,19] Park et al.[16] pointed out a limitation; with EDI OCT, the deeper portion and posterior border of the LC lack the clarity required for precise characterization of the structure. Recently, high-penetration OCT, also known as swept-source-OCT, which uses a center wavelength of approximately 1,050 nm instead of 840 nm (the wavelength used by current SD-OCT instruments), allows the imaging of deeper ocular layers, including the choroid and LC. It has been promised to enable more accurate characterization of the LC.[20,21] In our study, patients whose posterior LC margins were not visualized clearly were excluded from the study. In the studies done using EDI, PTT was shown to decrease with the elevation of IOP and increased again following treatment.[12,13,22,23,24] In addition, Jung et al.[13] reported that prelaminar tissue is thinner in primary open angle glaucoma (POAG) patients compared to normotensive glaucoma patients (NTG). Chung et al.[25] found PTT and LT low in progressing glaucoma patients compared to glaucoma patients who do not show progression. In the study of Chung et al.[25], PTT and LT were found to be related to glaucoma progression; however, only LT was seen to be related to glaucoma progression in multivariate analysis.

To the best of our knowledge, this is the first study to investigate the relationship between PTT and PXG. In our study, PTT was significantly thinner in PXG patients whose IOP was within normal ranges with medical therapy compared to the control group. However, there was no significant difference between stages in the PXG group. In addition, PTT was poorly correlated with vertical cup/disc ratio and a correlation was not found with RNFLav. The standard deviation of PTT is high, which indicates that PTT values are distributed over a wide range in this patient group. The PTT values are also widely distributed in the population and are not homogeneously distributed. Therefore, there is no need to evaluate PTT in follow-up. The results of our study showed that a thinner PTT was correlated with the presence of PXG but not with the severity of glaucoma.

LC is one of the ocular structures where pathologic changes are seen in PEX syndrome.[5,6,7,26,27,28] Insufficient LOXL1 tissue

levels may lead to elastotic changes in affected tissues like LC.[29] Braunsmann et al.[8] reported that LC stiffness significantly decreased in their study done with cadaver eyes with PXG. Since the LC is the primary site of axonal injury in glaucoma, elastotic alteration and decreased LC stiffness may predispose to glaucoma development in patients with PEX.[3] In a study performed with an SD-OCT EDI system, Park et al.[14] found LT was significantly thinner in POAG and NTG patients compared to a control group. In addition, they showed that LT decreased as disease stage increased in glaucoma patients.[14] Kim et al.[30] reported that LC was thinner in PXG patients in similar disease stages compared to POAG patients. In our study, LT was lower in PXG patients compared to the control group. Mean LT was reported to decrease with the increase in disease stage. Park and Park[31] determined that the diagnostic ability of LT is similar to peripapillary RNLF thickness and better than peripapillary RNFL thickness in early stage patients. Lee et al.[32] reported that thin LC was associated with progressive RNLF thinning. In our study, LT was seen to be negatively correlated with vertical cup/disc ratio and positively correlated with RNFLav. In light of these data, it was concluded that LT may be a risk factor for the development of PXG. In addition, the laminar region could be one of the targets of glaucomatous injury. Long-term studies with more patients are needed to support this conclusion.

Study Limitation

A limitation of our study is that patients with PEX were not included; we only compared PXG patients and healthy subjects.

Conclusion

In conclusion, thinning in PTT and LT parameters in SD-OCT EDI systems was correlated with the presence of PXG. In addition, LT has a stronger relationship with disease severity and progression compared to PTT. SD-OCT EDI mode is a recently developed technology and is not available in many centers and LT is not routinely assessed in glaucoma clinics. With advances in OCT systems, LT may be used for diagnosis and follow-up.

Ethics

Ethics Committee Approval: This prospective study was approved by the Medical Ethics Committee of İzmir Tepecik Training and Research Hospital (decision number: 21/12).

Informed Consent: Available.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Giray Ersöz, Duygu Kunak Mart, Emre Ayıntap, İrfan Botan Güneş, Hakkı Özgür Konya, Concept: Mehmet Giray Ersöz, Leyla Hazar, Design: Mehmet Giray Ersöz, Leyla Hazar, Data Collection or Processing: Mehmet Giray Ersöz, Duygu Kunak Mart, Leyla Hazar, Emre Ayıntap, İrfan Botan Güneş, Hakkı Özgür Konya, Analysis or Interpretation: Mehmet Giray Ersöz, Leyla Hazar, Literature Search: Mehmet Giray Ersöz, Leyla Hazar, Writing: Mehmet Giray Ersöz.

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Original Article

Validity and Reliability of the Glaucoma Knowledge Level Questionnaire

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Abstract

Objectives: The present study was conducted to develop an instrument for measuring adults' glaucoma knowledge levels and to establish the instrument's validity and reliability.

Materials and Methods: The study group consisted of 811 persons aged 40-80 years who presented to primary health care institutions and did not have a glaucoma diagnosis. A 27-item questionnaire measuring level of glaucoma knowledge was created by the study team. Following expert consultation, it was structurally evaluated. The difficulty index and discrimination index were calculated for each item. Factor analysis was used to determine construct validity, Cronbach's alpha internal consistency coefficient and item-total correlations were calculated to determine reliability. Confirmatory factor analysis was used to assess the extent to which the factor structure of the scale fit. We analysed correlation with the National Eye Health Education Program (NEHEP) Eye-Q scale in order to evaluate the validity of the scale.

Results: The final glaucoma knowledge level questionnaire comprised 10 items in one dimension. The discrimination index and difficulty index ranged between 0.28 to 0.65 and 33 to 61%, respectively. According to factor analysis, the Kaiser-Meyer-Olkin score was 0.760 and Bartlett's test indicated $p<0.001$. Confirmatory factor analysis showed acceptable scale fit and fit indices. Validity assessment revealed a positive correlation between the total score of the items of the NEHEP scale and glaucoma knowledge level questionnaire score ($r=0.522$; $p<0.001$). Scores were higher in participants who were aged 40-64, living in the city, had education level of high school or above and had previous eye examination or intraocular pressure measurement.

Conclusion: The glaucoma knowledge level questionnaire has the distinction of being the first valid and reliable scale for assessing level of glaucoma knowledge in Turkey.

Keywords: Glaucoma, level of knowledge, scale development

Introduction

Glaucoma is an optic neuropathy characterized by loss of retinal ganglion cells, optic nerve atrophy and visual field loss.[1] This global public health problem is the most common cause of blindness in the world after cataract.[2] It is estimated that glaucoma affects more than 60 million people in the world and that this number will exceed 100 million by the year 2040. Because early glaucoma is usually asymptomatic, many people are unaware of the disease until the onset of vision loss.[3,4] Early diagnosis can prevent glaucoma-related blindness and its adverse effects on quality of life.[5] It is estimated that about 90% of glaucoma-related blindness can be prevented with early and appropriate treatment.[6]

Timely eye examinations and appropriate treatment are critical to reduce visual impairment and blindness caused by glaucoma. However, many people in developing countries do not have regular and timely eye examinations due to a lack of knowledge and awareness about glaucoma-related blindness.[6] As glaucoma does not cause obvious symptoms such as pain,

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many people do not undergo screening for early diagnosis.[2] Glaucoma awareness is especially low in rural areas and poor communities.[6] Some authors have reported that awareness of glaucoma is insufficient even in Western societies.[7,8] In addition to the early recognition of asymptomatic patients, the treatment of diagnosed patients is also an important link in controlling glaucoma. Therefore, knowledge and awareness about glaucoma must be increased among both the general population and glaucoma patients. Patient education has also been shown to improve treatment adherence.[1]

Although tools have been used in studies conducted on various populations to determine the level of knowledge regarding glaucoma and related risk factors, there are no valid and reliable tools for the Turkish population.

This study was conducted to develop a scale that assesses the knowledge level of Turkish adults about glaucoma and to ensure the validity and reliability of this scale.

Materials and Methods

Development and Content Validity of the Glaucoma Knowledge Level Questionnaire

First, we conducted a comprehensive literature review and identified items that measure glaucoma knowledge level. In the preparation of the glaucoma knowledge level questionnaire (GKLQ), 9 items from the glaucoma Eye-Q test[9] developed by the National Eye Health Education Program (NEHEP) were translated into Turkish (one race-related item was excluded). A questionnaire of 27 items in total was created according to expert opinion determined through our review of the literature. Participants were asked to respond to each item as "correct", "incorrect", or "I do not know". Eight of the items were reverse worded.

The appropriateness and comprehensibility of each item was evaluated by 8 specialists (1 ophthalmologist, 6 public health specialists and 1 ophthalmology nurse). The content validity ratio and content validity index of the scale were 0.82 and 0.87, respectively. The specialists were asked to rate each item as "important", "useful but inadequate", or "unnecessary". The expert panel found one item (the reverse-worded "glaucoma is affected by a person's diet") unnecessary according to the content validity criteria and it was removed from the scale. A Turkish language expert (H.Ö.) evaluated the questionnaire and made necessary changes. A pilot study of the questionnaire was conducted with 10 participants, who were asked to add written comments and provide verbal feedback. All of the participants reported that the items were understandable. The Cronbach's alpha coefficient for the pilot study was 0.47.

Ethical Approval

Approval was obtained for the study from the Eskişehir Osmangazi University Ethics Committee (approval number 2016-9/5).

Study Group and Procedure

The study was carried out in Eskişehir, Turkey between June and December 2016. Eskişehir is one of the developed provinces of Turkey and had a population of 844,842 in 2016. Eighty-seven percent of the population lives in the urban center and 13% live in rural areas.

The study included 811 participants aged 40-80 years and a random sampling method was used. The study group consisted of patients who were admitted throughout the duration of the study to primary health care institutions within the Eskişehir Osmangazi University Training and Research Region that was established by the Eskişehir Osmangazi University Faculty of Medicine for the purpose of conducting social research. Patients who were not diagnosed with glaucoma and were not taking any medication for glaucoma were included. Individuals who did not consent to participate in the research, who had communication problems and who did not respond to at least 90% of the questions in the questionnaire were not included in the study. Informed consent was obtained from all participants.

In addition to the questions in the model scale, the participants filled out a questionnaire about sociodemographic characteristics such as age, education level, place of residence and income level. The questionnaire was completed in 10-15 minutes.

Reliability Analysis

Item Discrimination and Difficulty Indices

The item discrimination index and difficulty index were calculated for each item. To do this, the scores were first sorted in numerical order and divided into three groups. The difficulty index was calculated by dividing the number of people who answered the item correctly in the top 27% scoring group and the bottom 27% group by the total number of respondents in the top and bottom groups. If the item difficulty index is lower than 30%, the item is considered difficult. The item discrimination index indicates the degree to which an item discriminates between those who are knowledgeable and those who are not. The item discrimination index was calculated by subtracting the number of correct responders in the lower group from the number of correct responders in the upper group and dividing that figure by the total number of individuals in the lower or upper group (they are equal). Items with item discrimination index lower than 0.19 were considered very weak items that should be removed. Ultimately, 11 items with item difficulty index below 30% and item discrimination index below 0.19 were removed. These items were "Eye pain is common in glaucoma", "Glaucoma occurs due to increased intraocular pressure", "Loss of vision due to glaucoma can improve with treatment", "A complete eye examination is done only by measuring intraocular pressure", "There is more than one type of glaucoma", "The treatment for glaucoma is usually surgery", "Infections of the outer membrane of the eye can cause glaucoma", "Blurred vision and headaches are common in glaucoma", "Vision loss usually develops rapidly in glaucoma", "Men are affected more by glaucoma than women" and "Doing light exercise such as walking lowers ocular pressure".

Internal Consistency (Reliability)

Cronbach's alpha coefficient and item-total correlations were calculated to analyze the scale's reliability. Items with an item-total correlation greater than 0.20 were considered reliable.[10] Five items ("A person cannot understand that he/she has glaucoma", "Individuals at high risk for glaucoma should have their pupils dilated for examination", "Eye drops used for the treatment of glaucoma may cause ocular redness and burning", "Individuals with distant or near vision problems are at risk for glaucoma" and "Overweight individuals are at risk for glaucoma") had item-total correlations lower than 0.20 and were removed from the questionnaire. The reliability levels represented by the Cronbach's alpha coefficient were as follows: 0.40 and below, unreliable; 0.40-0.60, low reliability, 0.60-0.80, very reliable and 0.80-1.00, highly reliable.[11]

Factor Analysis

Factor analysis was used for construct validity. Factor analysis was done using principle components analysis (PCA) with varimax rotation. PCA is often used to reduce the number of items and determine pattern (in other words, the number and relationship of the main dimensions within the structure) when testing the psychometric properties of structured questionnaires.

Confirmatory Factor Analysis

Using Lisrel 8.8 software, confirmatory factor analysis (CFA) was done to assess the consistency of the scale's factor structure. While exploratory factor analysis aims to find a factor or factors based on the relationships between variables, CFA tests a previously determined hypothesis about the relationship between variables.[12] For confirmatory factor analysis, the most commonly used fit indices were calculated to assess the consistency of the model with the data. These indices included the Goodness of Fit Index (GFI), Adjusted Goodness of Fit Index (AGFI), Comparative Fit Index (CFI), Root Mean Square Error of Approximation (RMSEA) and Standardized Root Mean Square Residual (SRMR). Acceptable levels of fit for the indices were >0.90 for GFI, CFI and AGFI, <0.08 for RMSEA and SRMR.[13]

Scoring

The final scale consisted of 10 items and 1 dimension. One of the items was reverse worded. Responses to the statements were scored as 2 if correct, 1 if "I don't know" and 0 if incorrect. The reverse worded item was reverse coded to the other items. The scale had a maximum score of 20 and minimum score of 0.

Validity

To assess the validity of the GKLQ, Spearman's correlation analysis was used to compare total GKLQ scores with total scores of the items of the Eye-Q Test, a widely accepted scale developed by the NEHEP.

Data Analysis

The data were analyzed using the IBM SPSS 15 software package. Descriptive statistics of the study group were reported using frequencies, ratios, means and medians and the distribution measures were reported using standard deviation and minimum and maximum values. The Kolmogorov-Smirnov test was used to assess whether the total scores of the scale were normally distributed. The Mann-Whitney U test, Kruskal-Wallis analysis and Spearman's correlation were used because the data were not normally distributed. The significance level was accepted as $p<0.05$.

Results

Study Group

The mean age of the participants (47.2% male, 52.8% female) was 56.6±10.7 years; 74.8% of the participants were under 65 years of age and 25.2% were aged 65 years and over. Sixty percent of the participants were primary school graduates. The distribution of the study group according to selected sociodemographic and medical history characteristics is shown in Table 1.

Item Discrimination Index and Difficulty Index

Eleven items with an item discrimination index below 0.19 and a difficulty index below 0.29 were removed from the scale. The item discrimination indices ranged from 0.28 to 0.65 and difficulty indices ranged from 33% to 61%.

Factor Analysis

PCA was done with a varimax rotation. In the factor analysis, the Kaiser-Meyer-Olkin index was 0.760 and the Barlett's test result was $p<0.001$. Factor analysis indicated that the single-dimension scale accounted for 26.8% of the total variance. The total correlation values of the items ranged from 24.2% to 42.9%. The factor loadings and reliability values of the GKLQ items are given in Table 2.

Confirmatory Factor Analysis

After the factors were identified through an exploratory factor

Table 1. Distribution of the study group according to selected sociodemographic and medical history characteristics

Variables		n	(%)
Sex	Female	428	52.8
	Male	383	47.2
Age group (years)	40-64	607	74.8
	≥65	204	25.2
Education level	Did not attend school	111	13.7
	Primary school	486	59.9
	High school and higher	214	26.4
Income level	Low	133	16.4
	Middle	537	66.2
	High	141	17.4
Presence of chronic disease	No	381	47.0
	Yes	430	53.0
Previous ophthalmologic examination	No	343	42.3
	Yes	468	57.7
Previous intraocular pressure measurement	No	640	78.9
	Yes	171	21.1

Table 2. Glaucoma knowledge level questionnaire item factor loadings, corrected item-total correlations and Cronbach's alpha coefficients if item deleted

	Factor loading	Corrected item-total correlation	If item deleted Cronbach's alpha coefficient
1. Glaucoma is a common cause of blindness	0.59	0.41	0.65
2. Glaucoma is more common in those who have glaucoma in their family	0.53	0.35	0.66
3. People over the age of 60 years are at higher risk of glaucoma	0.56	0.39	0.65
4. Glaucoma can be controlled	0.57	0.40	0.65
5. The treatment of glaucoma is lifelong	0.38	0.24	0.68
6. People with high blood pressure are at risk for glaucoma	0.44	0.31	0.67
7. Glaucoma results in blindness if not treated	0.59	0.43	0.65
8. In glaucoma, the nerves in the eye may be damaged due to high intraocular pressure	0.56	0.40	0.65
9. People with glaucoma do not need to have regular eye examinations	0.39	0.26	0.68
10. Some medications may cause an increase in eye pressure	0.46	0.30	0.67
Total Cronbach's alpha: 0.69			

Table 3. Glaucoma knowledge level questionnaire confirmatory factor analysis fit indices

Fit index	Glaucoma knowledge level questionnaire
Chi-square/p value	227.70/p=0.0001
Degree of freedom	35
Chi-square value/degree of freedom	227.70/35=6.51
RMSEA	0.082
SRMR	0.058
CFI	0.90
GFI	0.95
AGFI	0.92

RMSEA: Root Mean Square Error of Approximation, SRMR: Standardized Root Mean Square Residual, CFI: Comparative Fit Index, GFI: Goodness of Fit Index, AGFI: Adjusted Goodness of Fit Index

analysis, they were tested with CFA to evaluate their consistency with the identified factor constructs. When the fit indices of the model obtained with the CFA were examined, although the χ^2/df value was not below 3, the GFI, CFI and RMSEA values were 0.95, 0.90 and 0.082, respectively, indicating acceptable model fit. In brief, the resulting index of fit values demonstrated good model fit. The fit values of the scale determined in CFA are given in Table 3 and factor loadings pertaining to the model are given in Figure 1.

Internal Consistency (Reliability)

The internal consistency coefficient (Cronbach's alpha) of the scale was 0.69. Cronbach's alpha values with items removed ranged from 0.65 to 0.68.

Validity

Assessment of validity revealed a positive correlation between the total score of the items in the NEHEP scale and the GKLQ score (r=0.522, p<0.001). The scatter plot of the NEHEP scale and GKLQ scores is presented in Figure 2.

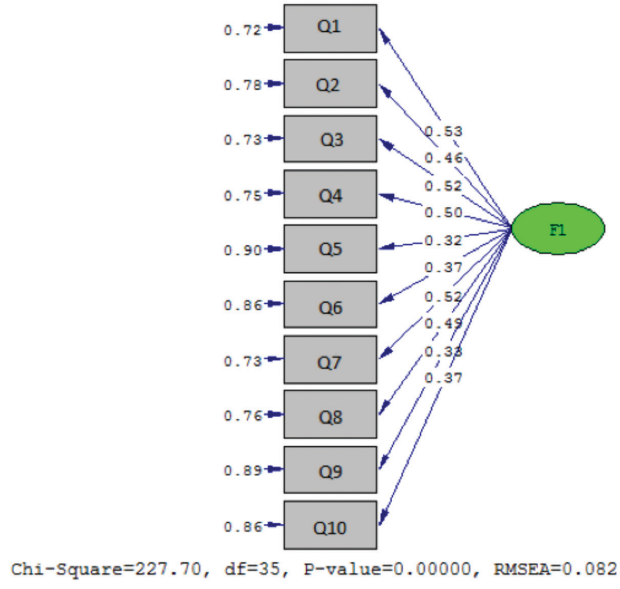

Figure 1. Confirmatory factor analysis diagram for the glaucoma knowledge level questionnaire

In the final version of the scale, the total score possible ranges from 0 to 20 and there is no cut-off score. Higher scores reflect greater knowledge about and awareness of glaucoma. In the study group, the mean (± standard deviation) of the scores obtained from the scale was 13.8±3.3, the median was 14.0 and maximum and minimum scores were 2 and 20. The percentage of correct responses to the GKLQ items varied between 40.2% and 61.0%. The statement with the lowest rate of correct response was "Some medications can cause an increase in eye pressure" and the statement with the highest rate of correct response was "Glaucoma is often the cause of blindness". The percentages of correct responses to the scale items are presented in Figure 3.

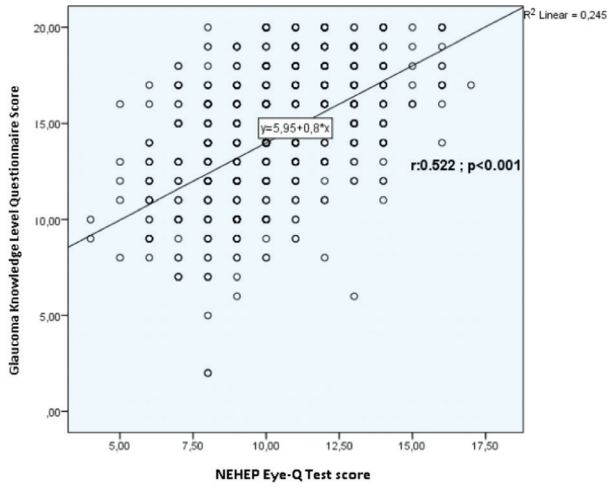

Figure 2. Scatter plot of glaucoma knowledge level questionnaire and National Eye Health Education Program Eye-Q Test scores
NEHEP: National Eye Health Education Program

Table 4. Comparison of median glaucoma knowledge level questionnaire scores of the study group

		Median Score (minimum-maximum)	Test value z; p
Sex	Female	14 (7-20)	87,038; 0.124
	Male	14 (20-20)	
Age group (years)	40-64	14 (2-20)	45,461; 0.000
	≥65	12 (7-20)	
Place of residence	Rural	13 (2-20)	93,667; 0.001
	Urban	14 (5-20)	
Education level	Illiterate	13 (7-20)	44,949; 0.000
	Primary school	14 (2-20)	
	High school and higher	16 (6-20)	
Income level	Low	12 (8-19)	22,109; 0.000
	Middle	14 (2-20)	
	High	15 (5-20)	
Presence of chronic disease	No	14 (2-20)	79,547; 0.473
	Yes	14 (2-20)	
Previous ophthalmologic examination	No	14 (2-20)	90,844; 0.001
	Yes	14 (5-20)	
Previous intraocular pressure measurement	No	14 (2-20)	64,494; 0.000
	Yes	15 (2-20)	

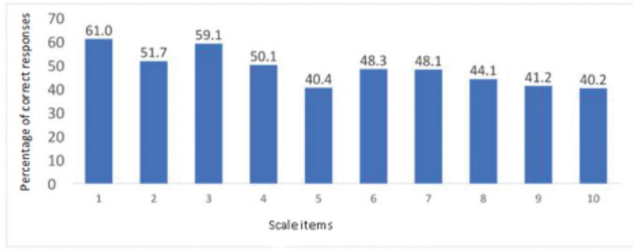

Figure 3. Percentage of participants responding correctly to scale items

There was no gender-based difference in median GKLQ score. Scores were higher among individuals aged 40-64, those with an education level of high school or higher, those with a good income level, those who had previous eye examinations and those who had previous ocular pressure measurements. Table 4 compares the GKLQ scores of the study group obtained from the GKLQ with their sociodemographic and disease-related characteristics.

Discussion

The aim of this study was to develop a scale to measure the level of glaucoma knowledge in a community-based sample and to test the validity and reliability of the scale. In order to determine how effectively scale items assess knowledge, they must be evaluated based on item discrimination and difficulty indices. For this scale, item discrimination index values ranged from 0.28 to 0.65 and difficulty index values ranged from 33% to 61%. An item discrimination index of 0.2 or higher is considered acceptable and indicative that the item can distinguish between the unknowledgeable and the knowledgeable.[14] None of the previously developed glaucoma scales were tested for item discrimination and difficulty indices.

For a reliable scale, the Cronbach's alpha value should be at least 0.70.[15] The Cronbach's alpha value of our scale was 0.69, which was considered adequate. Previously developed glaucoma knowledge scales had lower Cronbach's alpha values. In fact, although the NEHEP scale is the most widely accepted scale for measuring level of glaucoma knowledge, its Cronbach's alpha value is 0.59.[16] Therefore, we believe our scale is reliable. Removal of single items from the scale did not result in a significant increase in the Cronbach's alpha value, indicating good consistency between the scale items.

CFA was done to ascertain whether the model of the 10-item, one-dimensional GKLQ developed with an EFA was confirmed. The first value to be examined in CFA is the p value. This value indicates the significance of the difference between the expected covariance matrix and the observed covariance matrices (χ^2). Naturally, a nonsignificant p value is desired. However, it is also normal for the p value to be significant due to a large sample size. In this study, a significant p value was tolerated and alternative fit indices were evaluated.[17] It is reported that the RMSEA value must be below 0.08 and the GFI and AGFI values must be higher than 0.90 in order for

the model fit to be regarded as acceptable.[13] For this scale, CFA yielded values of 0.082 for RMSEA, 0.95 for GFI and 0.92 for AGFI. These values were evaluated according to fit indices and it was determined that all were at an acceptable level for model fit. Consequently, we consider this evidence that the factor construct resulting from the EFA is strongly confirmed.

We consider the one-dimensional nature of the scale and the small number of items as appropriate for the purpose of the study. There is still no ideal scale for measuring levels of glaucoma knowledge. The NEHEP scale has gained more acceptance compared to other scales. Based on item analyses, three of the items in the NEHEP scale ("Glaucoma is more common among people with glaucoma in their family.", "The risk of having glaucoma is higher among people over 60 years of age.", "Glaucoma can be controlled.") remained in the scale. We believe that the inclusion of items pertaining to the risk factors and treatability of glaucoma in our scale will result in wider acceptance.

Evaluation of GKLQ scores according to sociodemographic characteristics showed that scores were higher among people less than 65 years of age, those living in urban areas, those with education level of high school or higher and those with good income level. These findings are consistent with studies reporting that young age and good socioeconomic and education level are factors that increase knowledge and awareness of glaucoma.[18,19,20] In addition, the participants in our study group who had previously undergone eye examinations and ocular pressure measurement scored higher on the scale. This supports the reliability of the scale.

Conclusion

The scale created in this study is not designed to investigate all aspects of glaucoma knowledge. However, the GKLQ is the first scale for determining glaucoma knowledge in Turkey that has been tested for validity and reliability. While previously published tools assessing glaucoma knowledge generally targeted glaucoma patients, the GKLQ is designed as a simple and quick measurement tool that can also be applied to the general population. The reliability of the scale in specific groups needs to be tested and the scale requires further research and development.

Ethics

Ethics Committee Approval: Approval was obtained for the study from the Eskişehir Osmangazi University Ethics Committee (approval number 2016-9/5).

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Zeynep Demirtaş, Gökçe Dağtekin, Selma Metintaş, Nilgün Yıldırım, Muhammed Fatih Önsüz, Design: Zeynep Demirtaş, Gökçe Dağtekin, Selma Metintaş, Nilgün Yıldırım, Muhammed Fatih Önsüz, Data Collection or Processing: Zeynep Demirtaş, Gökçe Dağtekin, Selma Metintaş, Aziz Soysal, Analysis or Interpretation: Zeynep Demirtaş, Gökçe Dağtekin, Selma Metintaş, Aziz Soysal, Muhammed Fatih Önsüz, Literature Search: Zeynep Demirtaş, Gökçe Dağtekin, Selma Metintaş, Aziz Soysal, Writing: Zeynep Demirtaş, Gökçe Dağtekin, Selma Metintaş.

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Original Article

Does Cataract Surgery Simulation Correlate with Real-life Experience?

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Abstract

Objectives: To evaluate the correlation of cataract surgical simulator and real-life surgical experience and its contribution to surgical training.

Materials and Methods: Sixteen doctors in our department were divided into three groups based on their surgical experience. After being familiarized with the device, the participants were evaluated while performing the navigation, forceps, bimanual practice, anti-tremor and capsulorhexis stages. The capsulorhexis stage was repeated five times. Participants were also assessed while performing capsulorhexis again with their non-dominant hand. The influence of repetition and surgical experience on the recorded points was evaluated. P values below 0.05 were considered statistically significant.

Results: There was correlation between the participants' surgical experience and their scores in the capsulorhexis module. Their dominant hand was more successful than the non-dominant hand in capsulorhexis (p=0.004). Capsulorhexis scores increased with repetition (p=0.001).

Conclusion: Results achieved with the cataract surgery simulation device correlate with surgical experience. The increase in performance upon repeated practice indicates that the simulator supports surgical training.

Keywords: Surgical training, phacoemulsification surgery, virtual reality simulation

Introduction

Surgical training with simulators is utilized in many branches because it allows training in a controlled environment with objective assessment of progress. Surgical simulation also has potential as an important part of the surgical training of ophthalmology residents. Although the number of surgical procedures performed on actual patients is important, it has been proposed that computer-based surgical simulation training will increase success and reduce complication rates in real surgeries.[1]

Cataract surgery is one of the most common surgical procedures in ophthalmology.[2] The procedure requires good hand-eye coordination and has a long learning curve.[3] Numerous studies indicate that simulator and wet-lab training increase surgical performance, shorten residents' learning curve and reduce physician-related complications.[1]

Three simulation devices have been developed for use in cataract surgery: Eyesi® (VRmagic, Mannheim, Germany), PhacoVision® (Melerit Medical, Linkoping, Sweden) and MicrovisTouch® (ImmersiveTouch, Chicago, USA). Most of the studies published in the literature utilized the Eyesi® simulator.[1] This device has been reported to provide systematic, effective and reliable surgical training at a lower cost.[4] There are few studies on the MicrovisTouch® and PhacoVision® simulators.[1] Distinguishing features of the MicrovisTouch® are the advantages of receiving tactile feedback and having an adjustable virtual head. However, this device only has a capsulorhexis stage and not the other modules available in the Eyesi® simulator.[1]

The cataract surgery simulator in our clinic (Eyesi®) is used regularly in surgical training to facilitate the transition to practical application.

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The present study was designed to determine the extent to which simulated procedures contribute to cataract surgery training and correlate with real-life experience.

Materials and Methods

After obtaining approval from the institutional ethics committee, the physicians working as residents in our clinic were informed about the nature of the study and they provided informed consent to use their scores in the study. Sixteen physicians were separated into three groups according to their surgical experience. Group 1 included 7 residents with no experience in cataract surgery who had been working for 2-10 months. Group 2 comprised 6 residents who had performed 20-80 cataract surgeries and been working for 12-24 months. Group 3 included 3 faculty members with experience of 1000-1500 cases. Each physician underwent ophthalmologic examination and those with best corrected visual acuity of 20/20 in both eyes, sufficient stereopsis and normal findings on slit-lamp examination were included in the study.

The study was conducted using the Eyesi® surgical simulation device in our clinic. Only cataract surgery simulation software was installed on our simulator.

All of the simulator sessions in the study were supervised by the same researcher (A.B.O.). The participants were first familiarized with the surgical simulator. They were then asked to perform the navigation application as the first stage, followed by the first steps of the forceps, bimanual application, anti-tremor module and capsulorhexis stages.

Statistical Analysis

In the capsulorhexis module, participants were asked to perform the same procedure twice, first with their dominant hand and then with their nondominant hand. The capsulorhexis procedure was repeated four more times using the dominant hand. Finally, the third stage of the capsulorhexis module, "capsulorhexis in mature cataract", was performed and the participants' scores were noted.

SPSS 15.0 software was used for statistical analysis of the study data. A nonparametric correlation value between surgical experience and the simulator scores was determined (Spearman correlation coefficient). Other data were analysed nonparametrically using Kruskal-Wallis test and p values below 0.05 were considered significant.

Results

Seven of the 16 physicians in the study were female, 9 were male; the mean age was 30.18 years. Simulator scores for the capsulorhexis stage in both dominant and nondominant hands were positively associated with the number of real procedures performed (Figure 1).

Capsulorhexis performed with the dominant hand was more successful than capsulorhexis by the nondominant hand (p=0.004). The success of capsulorhexis increased with repeated attempts (p=0.001) (Figure 1).

The groups of physicians with less experience exhibited sharper increase in success with practice. The "capsulorhexis in mature cataract" stage was completed more successfully by group 3, who had the most practical experience (Figure 1).

When the groups' scores were analyzed in comparison with their experience using the Kruskal-Wallis test, the more experienced group was found to have significantly different scores than the less experienced groups (p=0.009).

According to Spearman correlation analysis, capsulorhexis scores correlated with surgical experience at all stages (Table 1).

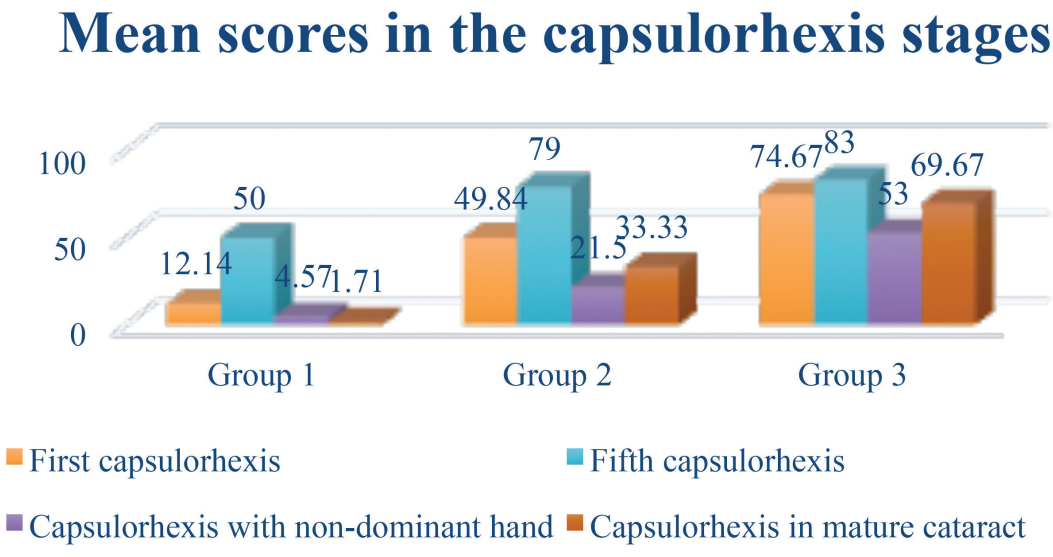

Figure 1. Capsulorhexis stage scores of the groups

Table 1. Comparison of simulator scores according to surgical experience

	Surgical simulation steps	Spearman correlation coefficient	p value
Surgical experience	First capsulorhexis	0.794	0.000
	Fifth capsulorhexis	0.606	0.013
	Capsulorhexis with nondominant hand	0.760	0.001
	Capsulorhexis in mature cataract	0.837	0.000

Discussion

Increasing interest in surgical simulators in recent years has inspired many studies investigating the contribution of these devices to surgical practice and their consistency with real life. In ophthalmology practice, training courses are conducted using these devices. This gives physicians the opportunity to receive theoretical and practical training in cataract surgery or vitreoretinal surgery.

The Eyesi® simulator has been designed with a binocular vision system that enables adjustable depth and magnification with a pedal-controlled imaging. In the model head, the right eye has ports in several axes (at 8, 6, 5 and 3 o'clock positions) to allow the users to handle the probes that simulate surgical instruments (Figure 2).

In the various modules, while performing steps of varying difficulty, the users are scored by the system from 0 to 100 according to the time elapsed, eye deviation, trauma to tissues such as the cornea, lens and iris and whether the stage was completed successfully.

In the navigation stage, the user must use the probe to touch spheres in the anterior chamber and turn them green. In the forceps module, the user is asked to bring triangular targets located at the edges into an area in the anterior chamber. In the bimanual application, the user must touch the spheres with the probes using both hands simultaneously. The anti-tremor module involves using the probe to push the sphere in a certain direction. In the capsulorhexis stage, the user applies viscoelastic material to the anterior chamber, uses a cystotome to create a flap and makes a circular capsulorhexis using forceps. In the 'capsulorhexis in mature cataract' stage of this module, the users can also use tissue dye (Figure 3). The following steps include grasping the lens, cracking and chopping the lens, irrigation and aspiration and inserting the intraocular lens.

A study by Mahr and Hodge[5] demonstrated the validity of the anterior segment anti-tremor and forceps training with the Eyesi® simulator. Fifteen participants were divided into a group of 12 inexperienced surgeons and a group of 3 experienced surgeons. Experienced surgeons scored higher and completed the stages in a shorter time.

Banerjee et al.[6] used the MicrovisTouch® simulator to investigate the concurrent validity of capsulorhexis performance metrics (duration, number of capsular grasps per completed capsulorhexis and roundness of capsulorhexis) and found that simulator results correlated with real-life performance.

Figure 2. The cataract surgery simulator device used in our clinic

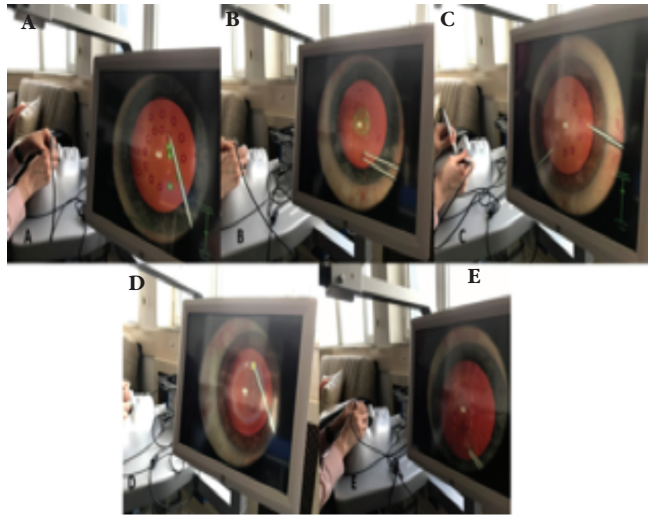

Figure 3. Screen view during the navigation (A), forceps (B), bimanual application (C), anti-tremor module (D) and capsulorhexis (E) stages of the simulator

Selvander and Asman[7] assessed the validity of the capsulorhexis, hydrodissection, phacoemulsification, navigation and forceps training stages in the Eyesi® simulator. There were 24 participants in two groups: 17 medical students and 7 experienced surgeons. The experienced surgeons had statistically better scores in simulated capsulorhexis, navigation and forceps modules, while the difference was less pronounced in the phacoemulsification and cracking and chopping stages. The same researchers asked 35 medical students to repeat the stages in order to determine whether repeated practice and the previous

stages affected the learning curve and they reported a steep learning curve for the first 10 attempts, followed by a plateau. They also reported concurrent validity of the capsulorhexis stage in the latter study.[8]

Privett et al.[9] evaluated the validity of the capsulorhexis stage with Eyesi® in a study including 23 participants, a group of 16 medical students and a group of 7 experienced surgeons. The participants' scores and completion times for capsulorhexis were found to be correlated with real life.

Thomsen et al.[10] tested the Eyesi® cataract surgery simulator in 26 physicians with no cataract surgery experience, 11 experienced cataract surgeons and 5 vitreoretinal surgeons. They determined in this reliability and validity study that experienced cataract surgeons and vitreoretinal surgeons received scores that were adequate or higher. Our data also suggested that the scores obtained in the modules increased with surgical experience.

In another study, 63 participants including 31 medical students and 32 ophthalmologists were randomly divided into 2 groups. All participants were asked to perform capsulorhexis on porcine eyes at two time points. In the interval, one of the groups was trained in the capsulorhexis stage of the Eyesi® simulator. Videos of the procedures were reviewed by an independent team who scored the participants' performance. The group that underwent simulator training showed significant improvement in scores at the second time point and significantly higher scores overall compared to the control group. These findings support the contribution of simulation to surgical training.[11]

Bergqvist et al.[12] also demonstrated that simulator scores increased with repeated practice and emphasized the contribution of this practice to training. We also observed in our study that the participants exhibited better performance when performing capsulorhexis for the fifth time. This finding suggests that repetition may contribute to surgical practice.

In a subjective evaluation based on users' feedback, Dooley and O'Brien[13] reported that capsulorhexis was the most difficult stage in the simulator and stated that allocating more time to this stage during stimulator practice may be beneficial for training.

Belyea et al.[14] investigated the role of simulators in resident training by retrospectively evaluating 592 surgeries by 42 physicians (17 simulator-trained and 25 untrained) with regard to total surgery time and complication rates and found that surgeons with simulator training had a shorter learning curve. Simulator training was associated with lower rate and severity of surgical complications and shorter procedure times.

Pokroy et al.[15] also demonstrated that the simulator is beneficial in surgical training and that practice shortened surgery time. In a study investigating the efficiency of a training program established by the International Ophthalmic Simulation Forum using the Eyesi® simulator, Saleh et al.[16] compared the pre- and post-training simulator scores of 16 inexperienced surgeons. They showed that scores in all stages increased significantly and there was a particularly important impact on the learning curve in the first year of surgery. In our clinic, practicing with the Eyesi® became routine when learning the stages of cataract surgery and preparing for initial real-life procedures and we found that this practice increased surgical safety.

Sachdeva and Traboulsi[17] observed a significant difference in performance when they compared participants with insufficient stereopsis with a control group. This was not taken into consideration in our study because all of the ophthalmology residents had normal stereopsis. Still, the fact that insufficient stereopsis influences performance is evidence of the validity and reliability of simulation.

Besides their role in training, simulators are also ideal to evaluate the effect of surgical environment on surgeon performance. Most of these studies cannot be conducted during real procedures due to ethical concerns related to patient safety. Simulators have been used to evaluate how surgical performance is affected by tiredness, visual acuity, use of the nondominant hand, surgeon distraction and the use of beta-blockers.[18,19,21,22]

During initial surgical experiences, the patient may be an unforgiving teacher. It is predicted that simulators will become more common in daily practice to enhance the learning of residents early in their careers. Although there are foreign publications regarding the role of simulators in virtual reality studies and training, there are no published studies in this area in Turkey. Therefore, our aim was to raise awareness of this topic by sharing our clinical experience.

Conclusion

The scores obtained in the capsulorhexis stage show that the cataract surgery simulator is correlated with real life. The association between repeated practice and improved performance indicates that the device facilitates training.

Simulators may find a place in practice because they allow trainers to explain aspects of the surgical technique to inexperienced trainees without time constraints and the trainee can freely observe the technique in question. Because real patients are not involved in the procedure, simulators provide a less stressful and more convenient environment both for trainees and trainers.

Performing the procedure first in the simulator and then on real patients may be more ethically appropriate. It instills self-confidence in the trainee before operating on actual patients and helps prevent some of the potential medicolegal problems. In short, simulator training is ideal for physicians to foster surgeon confidence prior to real surgical procedures and prevent possible complications.

Ethics

Ethics Committee Approval: Selçuk University Ethics Committee for Non-Interventional Clinical Investigations (decision number: 2017/101).

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: Bengü Ekinci Köktekir, Süleyman Okudan, Design: Bengü Ekinci Köktekir, Süleyman Okudan, Data

Collection or Processing: Ayşe Bozkurt Oflaz, Analysis or Interpretation: Bengü Ekinci Köktekir, Süleyman Okudan, Literature Search: Ayşe Bozkurt Oflaz, Bengü Ekinci Köktekir, Writing: Ayşe Bozkurt Oflaz.

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

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Original Article

Surgical Outcomes in Radiation-induced Cataracts After External-beam Radiotherapy in Retinoblastoma

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Abstract

Objectives: To investigate visual outcomes, surgical complications and tumor recurrence among children with retinoblastoma undergoing phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation for radiation-induced cataract secondary to external beam radiotherapy.

Materials and Methods: The medical records of all patients treated by phacoemulsification and PCIOL implantation for radiation-induced cataract after external beam radiotherapy for retinoblastoma at a single institution between 1980 and 2014 were reviewed retrospectively. The study included 6 eyes of 6 children (4 girls, 2 boys).

Results: Four patients had bilateral and two patients had unilateral retinoblastoma. The median age at diagnosis of retinoblastoma was 28.3 months (range, 12-96 months). All patients received chemoreduction (OPEC protocol) and external beam radiotherapy with or without local ophthalmic therapies and developed radiation-induced cataracts. The median interval from retinoblastoma diagnosis to cataract surgery was 96.3 months (range, 73-122 months). Time interval between surgery and last retinoblastoma treatment was 67.2 months. Postoperative complications included iridocyclitis in 2 eyes and posterior capsule opacification in all eyes. The mean follow-up after surgery was 105.8 months (range, 59-120 months). Final visual acuity was better in all eyes than preoperative visual acuities.

Conclusion: Phacoemulsification and PCIOL implantation is an effective method of managing radiation-induced cataracts in eyes with previously treated retinoblastoma. However, visual acuity was limited by the presence of primary macular tumor.

Keywords: Retinoblastoma, radiotherapy, cataract, phacoemulsification

Introduction

Retinoblastoma is the most common malignant intraocular tumor in childhood, with a prevalence of approximately 1 in 20,000.[1] Treatment methods for retinoblastoma include systemic chemotherapy, local chemotherapy, photocoagulation, cryotherapy, thermotherapy, brachytherapy, external radiotherapy, enucleation and exenteration.[2,3,4] Retinoblastoma is radiosensitive tumor, requiring a dose of 35-45 Gy.[3,5] However, 2 Gy is enough to cause cataracts in the crystalline lens. Therefore, cataract formation is a leading complication, along with retinopathy, orbital hypoplasia and secondary tumor development.[3,4,5] Because cataract both impairs vision and prevents fundus examination, surgery is unavoidable.

Numerous studies have indicated that surgical removal of radiation cataracts in children with retinoblastoma does not generally cause tumor spread or new tumor formation. The aim of this study was to evaluate the visual outcomes, complications and tumor recurrence rates after phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation in children with radiation-induced cataracts.

Materials and Methods

The records of 206 patients who were diagnosed and treated for retinoblastoma in the Tumor Unit of the İstanbul University İstanbul Faculty of Medicine, Department of Ophthalmology between 1980 and 2014 were retrospectively reviewed. Of

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these, 6 eyes of 6 patients who received radiotherapy and later underwent phacoemulsification and PCIOL implantation due to radiation-induced cataract were separately evaluated. The study was approved by the local ethics committee and conducted in accordance with the principles set forth in the Declaration of Helsinki.

The patients' records were screened for demographic data, age at retinoblastoma diagnosis, affected side, hereditary pattern, stage (Reese-Ellsworth and International Classification), macular involvement, treatments received, type and dose of radiotherapy received, time between radiotherapy and cataract development, date of surgery, time between last retinoblastoma treatment and cataract surgery, type of surgery, type of intraocular lens, intra- and postoperative complications, pre- and postoperative best corrected visual acuity (BCVA), postoperative tumor recurrence or spread, postoperative follow-up time and any other postoperative interventions.

All patients were operated due to significant visual impairment and difficulty examining the fundus. Surgeries were performed after a mean period of 67 months with no tumor progression.

Prior to surgery, all patients underwent keratometry and axial length was calculated with ultrasound biometry. For patients with macular involvement, axial length was measured from their fellow eyes. Phacoemulsification (Advanced Medical Optics Sovereign, Santa Ana, California, USA) and PCIOL implantation through a clear corneal incision were performed under general anesthesia. The posterior capsule was left intact in all cases because the patients were at least 90 months old at the time of surgery and Nd:YAG laser could be applied afterwards. This prevented the possibility of retinal detachment, because both tumor spread to the anterior chamber and anterior vitrectomy could result in traction in the retina.

Results

Two hundred seventy-six eyes of 206 patients who were diagnosed and treated for retinoblastoma were retrospectively evaluated. Considering the complications of radiotherapy, external-beam radiotherapy was only applied to 40 eyes of 35 patients; of these, 13 eyes developed cataract. Six eyes with cataract that severely reduced visual acuity and prevented fundus examination underwent phacoemulsification and PCIOL implantation.

Four of the patients were female and 2 were male. Two patients had unilateral retinoblastoma and 4 patients had bilateral retinoblastoma. Only one patient had familial retinoblastoma, while the others were sporadic. The average age at retinoblastoma diagnosis was 28.3 months (12-96 months). According to the Reese-Ellsworth classification, tumor stage was 5B in 1 eye, 3B in 4 eyes and 1B in 1 eye.

All patients received systemic OPEC protocol (vincristine 1.5 mg/m^2 [O], cisplatin 80 mg/m^2 [P], etoposide 200 mg/m^2 [E], cyclophosphamide 600 mg/m^2 [C]) chemotherapy. A radiotherapy dose of 35-40 Gy was delivered over 18-22 sessions. The mean time from last radiotherapy treatment to cataract development was 31.6 months. The mean age at surgery was 124.6 months (90-169). The mean time from last retinoblastoma treatment and surgery was 67.2 months.

Six eyes of 6 patients underwent phacoemulsification and PCIOL implantation via a clear corneal incision under general anesthesia. Foldable acrylic intraocular lenses were implanted. The posterior capsule was left intact in all eyes. None of the patients developed intraoperative complications. Two eyes developed iridocyclitis postoperatively but it responded to topical treatment. When fundus examination became possible postoperatively, radiation retinopathy was detected in one patient.

Posterior capsule opacification was observed in all eyes at a mean of 10.8 months postoperatively and Nd:YAG laser

Table 1. General patient characteristics

Patient	Age (months)	Tumor site	Therapies received	Side	RE	IC	RTCT (months)	Preop BCVA	Postop BCVA
1	12	Macula	RT + CT + TTT	U	4A	C	33	CF 1 mps	CF 2 mps
2	96	Macula	RT + CT	U	3B	C	35	CF 1.5 mps	0.05
3	12	Macula	RT + CT + TTT + RP	B	5B 3B	E C	10	CF 1 mps	CF 3 mps
4	13	Macula	RT + CT	B	5A 2A	E B	23	CF 0.6 mps	CF 2 mps
5	13	Macula	RT + CT + TTT	B	3A 5A	B E	60	CF 4 mps	0.125
6	24	Extra-macular	RT + CT + TTT + Cryo	B	2B 5B	C E	29	0.16	0.6

CT: Chemotherapy (OPEC protocol), RT: Radiotherapy, TTT: Transpupillary thermotherapy, CF: Counting fingers, RP: Radioactive plaque, Cryo: Cryotherapy, RE: Reese-Ellsworth classification, IC: International classification, RTCT: Radiotherapy to cataract time, Preop: Preoperative, Postop: Postoperative, BCVA: Best corrected visual acuity

capsulotomy was performed on 4 eyes at a mean of 70.7 months postoperatively. None of the patients had elevated intraocular pressure or retinal detachment.

Five patients exhibited macular involvement and their preoperative BCVA was counting fingers from an average of 1.6 m. One eye with extramacular involvement had a preoperative BCVA of 0.16. Although visual acuity increased in all eyes postoperatively, improvement was limited due to the macular involvement. The preoperative and postoperative BCVAs and other characteristics of the patients are summarized in Table 1.

The mean postoperative follow-up period was 105.8 months (59-120 months). There was no tumor recurrence or progression in any of the patients during follow-up.

Discussion

Because retinoblastoma is a radiosensitive tumor, external beam radiotherapy was among the first-line treatment options for retinoblastoma for much of the 20th century.[3,4,5] However, due to radiation-induced complications such as cataract, retinopathy, orbital hypoplasia and secondary tumor development, chemotherapy began to take the place of radiotherapy starting in the early 1990s and radiotherapy became a second-line option for chemoresistant tumors with multiple foci and diffuse vitreous and/or subretinal seeding.[3,5,6] Although the lens-protective radiotherapy technique has reduced radiation-induced cataract, eyes treated with radiotherapy still develop cataracts at rates between 22% and 78%.[7,8,9] In our study, of the 276 eyes of 206 patients diagnosed with retinoblastoma in our clinic between 1980 and 2014, only 40 underwent radiotherapy and 13 (32%) of those eyes developed cataracts.

Reese[10] first published surgical outcomes in radiation-induced cataracts in 1939. Reese[10] performed intracapsular cataract extraction and reported mostly inflammation-related complications due to residual cortex fragments. In 1998, Portellos and Buckley[11] evaluated 11 eyes of 8 patients who underwent extracapsular cataract extraction and PCIOL implantation and reported that inflammation and fibrin membrane formation occurred postoperatively in 3 eyes but regressed with treatment. Miller et al.[12] reported in 2005 that postoperative iridocyclitis occurred at a rate of 19% following pars plana lensectomy (PPL), PCIOL implantation and pars plana vitrectomy in 16 eyes of 12 patients. Our patients underwent phacoemulsification and PCIOL implantation with intact posterior capsules. Iridocyclitis was observed postoperatively in 2 eyes but improved with topical treatment. Although there were few patients in our study, we can conclude that postoperative inflammation is less severe after procedures in which the posterior capsule is preserved and the iris plane is avoided, as well as those not using a pars plana approach.

One of the most important points in pediatric cataract surgery is not leaving the posterior capsule intact. Especially with IOL implantation, secondary cataracts are common and can lead to amblyopia due to visual axis obscuration.[13] In eyes treated for retinoblastoma, however, the posterior capsule is believed to possibly serve as a barrier, preventing tumor spread to the anterior segment. For this reason, Hoehn et al.[14] performed lens aspiration and PCIOL implantation and left the posterior capsule intact in their series of 19 patients. Twelve (63.2%) of the eyes developed posterior capsule opacification and underwent Nd:YAG laser capsulotomy. Payne et al.[15] performed extracapsular cataract extraction through a limbal-based scleral tunnel on 12 eyes, choosing to do posterior capsulotomy and anterior vitrectomy in 7 of the eyes because of the dense subcapsular plaque in the posterior capsule, while leaving the posterior capsule intact in the other 5 eyes. They later performed Nd:YAG laser capsulotomy on these 5 eyes. We also left the posterior capsule intact in our patients, both because their age was over 90 months and considering the barrier function of the posterior capsule. Posterior capsule opacification developed in all of our patients, which we treated with Nd:YAG laser with no complications.

Although retinal detachment is among the complications that may develop due to vitreous traction in patients who undergo posterior capsulotomy and anterior vitrectomy, Brooks et al.[16] reported retinal detachment in only 1 patient after PPL and anterior vitrectomy in 42 eyes of 38 patients. We also observed no postoperative retinal detachment in our patients.

One of the most important parameters after surgery for radiation cataract in retinoblastoma patients is the presence or absence of tumor recurrence. Brooks et al.[16] reported 3 tumor recurrences in their series of 42 eyes. They attributed these recurrences to having performed PPL and to the presence of post-radiotherapy haze or vitreous hemorrhage in the vitreous during cataract surgery. In 2005, Hanovar et al.[17] presented the surgical outcomes of 34 eyes of 34 patients. They performed intracapsular cataract extraction on 1 patient, extracapsular cataract extraction on 28 patients and PPL on 5 patients and observed tumor recurrence in 5 cases. They noted that the average time from last retinoblastoma treatment to surgery was 6 months for patients who developed recurrence and 26 months for the other patients. Moshfeghi et al.[18] reported tumor recurrence in 1 of their 4 patients, who had to undergo enucleation. Osman et al.[19] reported tumor recurrence in 3 of 21 patients who underwent lens aspiration, posterior capsulotomy and anterior vitrectomy through a clear corneal incision approach, with 2 requiring enucleation. They believed recurrence in these patients was related to the advanced disease stage and the fact that they performed posterior capsulotomy. They reported that the only difference in these patients was that the time between cataract surgery and last treatment was 12 months. Although the interval is not known clearly, Portellos and Buckley[11] and Miller et al.[12] reported no tumor recurrence in their patients and the time between last retinoblastoma treatment and surgery was at least 16 months.

Hoehn et al.[14] proposed that the lack of tumor recurrence in their study was due to having left the posterior capsule intact. Payne et al.[15] contend that surgery with a scleral tunnel approach is safer and that in this way, there will be no surgical site leakage due to eye scratching, especially in children. Particularly important is definitive tumor control and, according to the literature, the need to wait for at least 9 months prior to surgery. No tumor recurrences were observed in any of our cases despite the very long (mean 105.8 months) postoperative follow-up period, likely due to long interval between the last retinoblastoma treatment and surgery (mean 67.2 months) and the intact posterior capsule.

Even with uncomplicated cataract surgery, final visual acuity is dependent on whether the macula is involved. In a series of 21 cases reported by Osman et al.,[19] postoperative visual acuity was 20/20 in only 4 patients, between 20/20 and 20/200 in 9 patients and lower than 20/200 in the remaining patients. Of the patients with low vision, 3 had macular involvement, 2 had radiation keratopathy, 2 were enucleated due to tumor recurrence and 1 developed neovascular glaucoma. Hoehn et al.[14] reported low vision in 5 patients with macular involvement and in another 4 patients due to radiation keratopathy and retinopathy. Miller et al.[12] reported that cystoid macular edema and postoperative inflammation caused decreased vision but the patients did not completely lose their vision. Portellos and Buckley[11] did not observe low vision in any of their patients but their follow-up was shorter compared to the other studies (mean 20 months). Brooks et al.[16] reported patients with radiation keratopathy and radiation retinopathy but did not explain whether this led to decreased vision. Shanmugen et al.[20] reported vision loss due to radiation maculopathy 3 years after surgery. In our case series, we observed that 2 patients with preoperative BCVA of CF 1 m had a postoperative BCVA of CF 2 and 3 m, while BCVA increased from CF 0.6 m to CF 2 m, from CF 1.5 m to 0.05 and from CF 4 m to 0.125 in 3 other patients. Visual acuity was limited in these 5 patients due to macular involvement. Another patient with no macular involvement and a preoperative BCVA of 0.16 had a postoperative BCVA of 0.6. Ultimately, visual acuity increased in all of our patients.

Conclusion

In conclusion, phacoemulsification and PCIOL implantation with clear corneal incision approach and leaving the posterior capsule intact is a reliable method for radiation cataract surgery in retinoblastoma patients. Although this retrospective study did not include a large number of patients, we can conclude that surgical intervention done after ensuring retinoblastoma is controlled with treatment and delayed at least 9 months is safe in terms of tumor recurrence. However, macular involvement limits improvement of visual acuity.

Ethics

Ethics Committee Approval: İstanbul University İstanbul Medical Faculty Clinical Research Ethics Committee (decision no: 2017/1044).

Informed Consent: It was taken.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Şerife Bayraktar, Samuray Tuncer, Design: Şerife Bayraktar, Samuray Tuncer, Data Collection or Processing: Şerife Bayraktar, Analysis or Interpretation: Gönül Peksayar, Rejin Kebudi, Cahit Özgün, Literature Search: Şerife Bayraktar, Writing: Şerife Bayraktar.

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Review

Ocular Drug, Gene and Cellular Delivery Systems and Advanced Therapy Medicinal Products

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Abstract

Due to recent advances in science and technology, when the products used in therapy are examined, ophthalmology has a priority in terms of research and development, preclinical and clinical studies of innovative drugs, medical devices and drug-medical device combination products. Liposomes, micelles, nanoemulsions, nanoparticles with colloidal structures and intraocular implants as sustained-release drug delivery systems have been developed to overcome the barriers to ocular applications, increase absorption, decrease metabolism and elimination and increase the residence time in ocular tissues and compartments. Studies are also ongoing in the area of advanced therapies using gene or cell-based systems which are high-risk products due to their complex structures. In this review, ocular drug, gene and cellular delivery systems and related products and developments in advanced therapy medicinal products are presented in respect to the definition of drug (medicinal product) and current changes in legislation.

Keywords: Ocular delivery systems, ocular gene and cellular delivery systems, colloidal drug and gene delivery systems, advanced therapy medicinal products, national and international legislation

Introduction and Objective

The bioavailability of drugs may be attenuated or inhibited by various factors, including the anatomical structure of the eye, the tear film, the varying permeability of the corneal layers to the drug substances and physiological ocular barriers such as the conjunctiva, blood-aqueous barrier, vitreous and blood-retina barrier. In order to cross these barriers in the anterior and posterior segments of the eye and achieve therapeutic drug concentrations in the targeted region, delivery systems with different structures and compositions that provide controlled or sustained release are being studied and used for treatment.[1,2,3]

In the design, manufacture and application of delivery systems, the properties of the product are determined by the active substance(s) being carried, as well as the system itself, the purpose of treatment, the procedures and devices used and their optimization strategies. Criteria determined in these contexts enable the classification of the product as a drug, medical device, or a drug-medical device combination product and elucidate the path to be followed in the approval process. The objective of this review is to present the developments in ocular drug, gene and cellular delivery systems and related products (including liposomes, nanoparticles, microparticles, implants and advanced therapy medicinal products) which have completed research and development (R&D), preclinical and clinical studies and are being used for the treatment of ocular diseases, within the framework of the definition of drug (medicinal product) and current changes in legislation.

Drug Definition and Legislation

The R&D and manufacturing stages of drugs involve conventional production methods in pharmaceutical technology as well as biotechnological manufacturing processes and advanced technologies in the field of pharmaceutical biotechnology. Delivery systems that can be prepared on a nanometric scale, such

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as liposomes, are currently being produced via nanotechnology. These systems are known in the field of pharmaceutics as colloidal dosage forms and have been used therapeutically for years in accordance with drug licensing processes. In addition to these, nanodelivery systems with different structures and compositions and high-risk drugs, medical devices and combination products that fall into the scope of advanced therapies are being developed.

All previous studies have among their objectives to provide patients with safe and effective drugs and products and to find solutions for untreatable diseases or those with unmet needs. To achieve this goal, it is necessary to demonstrate the quality, efficacy and safety of the drugs or products and ensure quality assurance in their life cycle through a process that begins from pharmaceutical development. For this reason, a risk-based approach with quality risk management, pharmaceutical good manufacturing practices (GMP) and a pharmaceutical quality system must be implemented during registration.[4,5,6,7,8,9]

The European Commission has updated the definition of medicinal product (drug) in the European Union (EU) legislation, taking into account advances in science and technology, the development of innovative drugs and products and their associated risks.[10,11] With the change made to this definition, the classification of biological products, medical devices and combination products has changed. The Regulation on Advanced Therapy Medicinal Products (ATMPs) issued by the EU in 2007 changed the directive that applies to human medicinal products.[12] According to these changes, drug substances with low molecular weight, recombinant proteins having high molecular weight, monoclonal antibodies and the cell itself were classified as medicinal product (drug), biological medicinal product, or biological drug depending on how they are processed.

Products covered by the ATMP Regulation include "somatic cell therapy medicinal products", "gene therapy medicinal products" and "tissue engineered products" that are categorized as drugs and "combined ATMPs," which constitute drug-medical device combination products. Similar products that were approved prior to the publication date of this regulation have been granted time for compliance with the new legislation.[12]

In the United States (US), the Food and Drug Administration (FDA) requires New Drug Applications in the approval process for risky biological and biotechnological products.[13] The FDA has issued a separate guideline for investigational new drugs and biological license applications for preclinical studies of biological products.[14]

During these amendments to the pharmaceutical legislation, the EU changed its directives pertaining to medical devices and *in-vitro* diagnostic products with two new regulations published in the official journal in May 2017 due to the issues observed with medical devices.[15,16] Countries have been granted time to implement these changes, which will affect the international circulation of medical devices and associated products. This necessitates updating the national regulations on medical devices in Turkey, which have been harmonized with those in the EU, within the granted transition period.[17,18,19] In the meantime, the US FDA has issued new regulations on drug-medical device combination products.[20,21]

In a period when international regulation on drugs, medical devices and related products are constantly being amended, regulatory harmonization has been conducted in our country and updates to the legislation are made by the Turkish Medicines and Medical Devices Agency (TMMDA) of the Turkish Ministry of Health. These include regulations involving drugs and medical devices.[22,23,24] Although drug regulations include different definitions of medicine or medicinal product, the Regulation on the Safety of Drugs defines a drug as *"*any substance or combination of substances presented as having properties for treating or preventing disease in human beings, or which may be used in human beings with a view to restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological or metabolic action*"*. Thus, our legislation contains a definition of drug or medicinal product that is consistent with current international regulations.[25] This definition was later referred to in other regulations and a similar definition is included for "human medicinal product" in the Regulation on Manufacturing Plants of Medicinal Products for Human Use published in October 2017. This regulation encompasses the quality assurance system and the GMP included therein.[26] In addition, the GMP guideline states that production requires "the establishment of an effective pharmaceutical quality assurance system and the term pharmaceutical quality system is used for consistency with international terminology".[27] With these updates, the national legislation of Turkey continues to effect change in accordance with internationally accepted criteria in order to harmonize with international regulations.

As in all diseases, the approval process for ocular drugs and delivery systems is based on the structure, properties and intended use of the active substance and the delivery system containing it. In the course of developing safe and effective drugs and products and delivering them to patients, the first step is demonstrating the quality of the drug or product manufactured under GMP conditions.[4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27] Considering the diversity of drugs (medicinal products), medical devices and combination products, this process requires legislation and definitions. Legal definitions are important because they enable the classification of a product and determine the route to be followed in R&D, preclinical and clinical trials. Starting from pharmaceutical development, the basic requirements for transition to clinical research and the critical parameters of the variety of drugs and products within the scope of ocular applications are shown in Figure 1. In these processes, it is important to know and validate the properties of the active substance, delivery system and the resulting drug or product in terms of design, composition, production and stability.

Like other drugs, all ocular drug, gene and cellular delivery systems, associated products and ATMPs that are produced under pharmaceutical GMP conditions within a pharmaceutical quality assurance system or pharmaceutical quality system, that are of proven quality and that have been tested for

safety and efficacy in preclinical studies must be applied in clinical trials to evaluate their safety and efficacy in humans.[4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27]

Liposomes

Liposomes are nanovesicular or microvesicular drug or gene delivery systems which range in size from 0.025 to 10 µm and contain a single lipid bilayer or multiple interwoven lipid bilayers. With structures consisting primarily of phospholipids and cholesterol, liposomes can carry hydrophobic drugs within their lipid layers and hydrophilic drugs in the interior aqueous compartment enclosed by the lipid bilayer. Conventional liposomes contain only phospholipids and cholesterol in their structure and polymer-coated liposomes are produced by adding PEGylated phospholipids (phospholipids chemically modified with polyethylene glycol) to this composition. Targeted liposomes can also be prepared by chemically modifying the surface of liposomes with targeting molecules. Cationic liposomes containing positively charged components are used as non-viral gene delivery systems. Cationic liposomes form complexes with and transport negatively charged antisense oligonucleotides, plasmids, nucleic acids, or small interfering ribonucleic acids. Liposomes are prepared using sterile production processes at laboratory or industrial scale.[3,28,29,30,31,32] Numerous R&D and clinical trials have been conducted in which cationic liposomes were used as non-viral gene delivery systems but none of these products have completed clinical phase studies.[33,34] Conventional, polymer-coated and targeted liposomes being used therapeutically were licensed through existing pharmaceutical legislation.[3]

The liposomal products commercially manufactured to date have included doxorubicin, daunorubicin, cytarabine, vincristine sulfate, irinotecan, amphotericin B, morphine sulfate, verteporfin, bupivacaine as active substances. In addition, hepatitis B and influenza vaccines having targeted liposome structures have been developed.[30] The assessment reports and short product and labeling information of these liposomal drugs and vaccines are published by the legal authorities of the countries in which they are approved. Targeted liposomal vaccines that are part of liposomal systems have also been referred to in the literature as virosomes.[35,36] In 2017, a product containing daunorubicin and cytarabine was approved by the US FDA as the first liposomal combination drug.[37]

Among the liposomal drugs, Visudyne®, a conventional liposome containing vertoporfin, is the first liposomal drug developed for the treatment of subfoveal choroidal neovascularization due to macular degeneration, pathological myopia, chronic central serous chorioretinopathy and choroidal hemangioma. Visudyne® is administered by intravenous infusion, then the active substance is activated by laser application to the eye.[38]

Although liposomes developed for parenteral administration have been used therapeutically for many years, the number of liposomal drugs for ocular and intraocular administration have passed from R&D to clinical trial for ocular and intraocular applications is rather limited. Liposomal delivery systems containing different active substances have been examined in preclinical studies with experimental applications in the anterior and posterior segments of the eye and there are numerous studies and patents in the literature.[39,40,41] Examples include conventional liposomes containing amphotericin B,[42,43] gentamicin,[44] clindamycin,[45] 5-fluorouracil,[46,47] cyclosporine

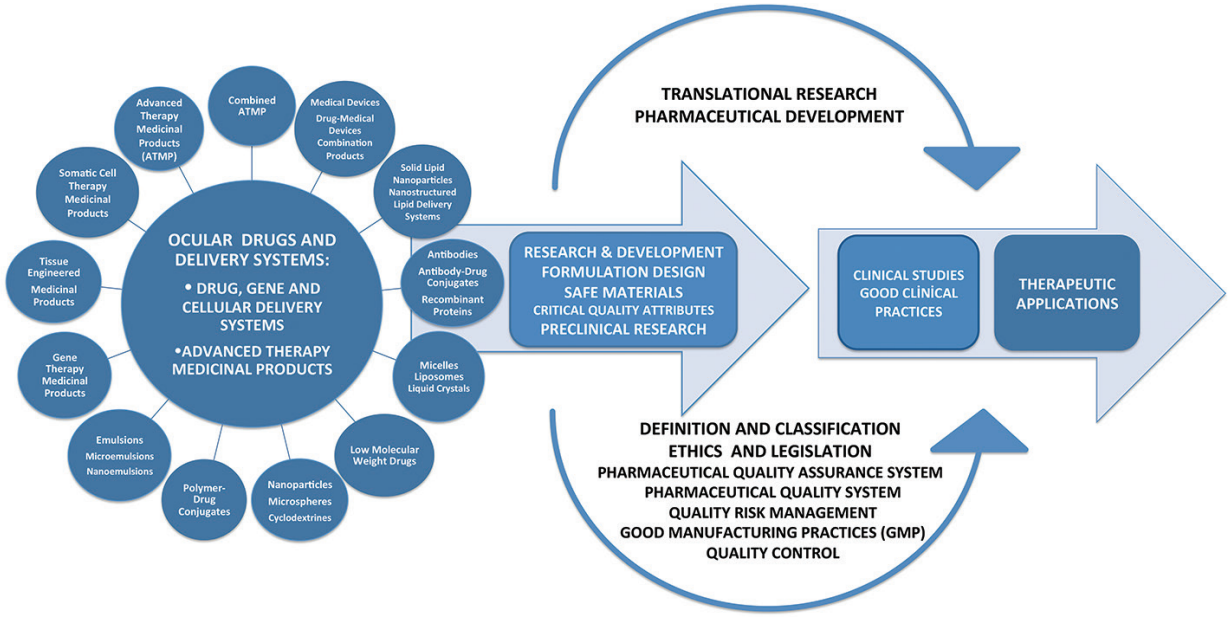

Figure 1. Basic requirements for the translation of ocular drug, gene and cellular delivery systems and advanced therapy medicinal products from the research and development and preclinal research stages to clinical investigations

A,[40,48,49] tobramycin,[50] norfloxacin,[51] acyclovir,[52] tacrolimus (FK506),[53] indocyanine green,[54] and timolol,[55] and polymer-coated liposomes[40] containing cyclosporine A.

Liposomal drugs that have transitioned from preclinical research to clinical phase trials include latanoprost-loaded conventional liposomes developed for subconjunctival administration. A study on the subconjunctival administration of liposomal latanoprost to rabbits demonstrated reduction in intraocular pressure for 3 months.[56] Phase 1 and 2 trials on the safety and efficacy of latanoprost-loaded liposomes in the treatment of ocular hypertension and primary open-angle glaucoma have been completed.[57,58] The liposomal latanoprost developed through these studies has been patented.[59]

Liposomes are known to present challenges in terms of their structures, properties and stability compared to other colloidal delivery systems. In 2002, the US FDA issued a draft guideline on the manufacturing, controls, pharmacokinetic properties and bioavailability of liposomal drugs having complex structures. This guideline was updated and reissued as a draft in 2015.[60] In addition, the EU European Medicines Agency (EMA) has published its views on data requirements for the production of liposomal drugs and on surface coating of nanodrugs.[61,62] These documents explained that specifications vary depending on the formulation and manufacturing conditions of liposomal drugs and that critical quality attributes should include particle size, size distribution and morphology of the vesicular structure of a liposomal drug. They state that quality attributes will impact *in-vivo* pharmacokinetic and pharmacodynamic properties of liposomes, which will affect the efficacy and safety of the drug and the need for comparability studies was noted.[60,61,62] The US FDA draft guideline and the EMA opinions contain important criteria that should be considered and met when liposomal drugs are manufactured by other companies after patent expiry. Therefore, comparability studies to demonstrate the quality, efficacy and safety of liposomal drugs and manufacturing liposomal drugs as nanosimilar drugs have gained priority. The aforementioned guideline and reflections also elucidate how to proceed for liposomal systems in the R&D stage.

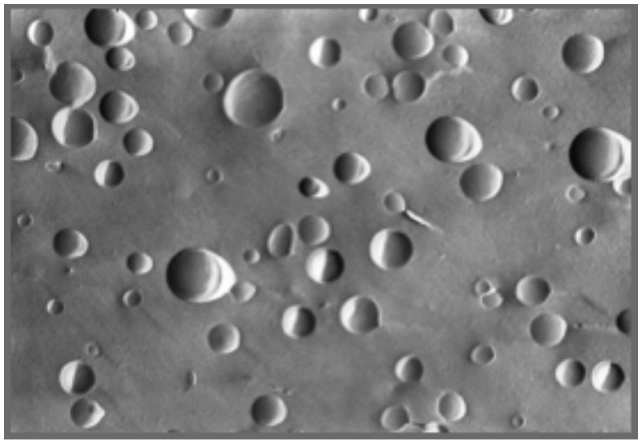

Figure 2. Morphological structure of polymer-coated liposomal cyclosporine A by freeze-fracture scanning electron microscope

Liposome particle size, vesicular structure and number of bilayers in the liposome membrane are among the analyses which are known to be critical and are evaluated in studies in the field of liposome technology. An example of this is a patent for liposomal cyclosporine A containing different phospholipids and phosphatidylethanolamine-PEG conjugates and prepared for ocular use with thin-film hydration followed by extrusion. According to this, polymer-coated liposomal formulations of cyclosporine A were developed and compared with conventional liposomal formulations.[40] It was found that the aggregation observed shortly after preparation of conventional liposomal cyclosporine A did not occur with polymer-coated liposomal cyclosporine A formulations. The colloidal stability of liposomal cyclosporine A was provided by the steric coating formed on the liposome surface by the PEG component of the liposomes. An example of the unilamellar vesicular structure achieved with polymer-coated liposomal cyclosporine A is illustrated in Figure 2. It has been shown that polymer-coated liposomal cyclosporine A formulations have a z-average particle size (measured with laser light scattering) of 140-190 nanometers depending on the amount of drug present in the liposome composition and the structure, ratio and phase transition temperatures of the phospholipids and phosphatidylethanolamine-PEG conjugates and their polydispersity index varies between 0.08 and 0.20.

Nanoparticles and Microparticles

Nanoparticles and microparticles are solid colloidal particulate systems that enable the controlled release of active substances which are adsorbed to the structure or dispersed or dissolved within the lipids or polymers forming the matrix. These delivery systems can be made with very different methods based on microencapsulation and polymerization technologies. Based on the size and structure of the resulting particle depending on the method used in the preparation or production and the solubility of components, they have been described as nanospheres, nanocapsules, microspheres, microcapsules, or micropellets.[63,64,65,66,67,68,69,70,71] Matrix materials included in the composition of nanoparticles include albumin,[72] chitosan,[73,34] alginate,[75] polylactic-glycolic acid,[76] polyalkylcyanoacrylates,[77,78] polymers such as hyaluronic acid coated poly-epsilon-caprolactone,[71] lipids,[68,69,79,80,81,82] and cyclodextrins.[83,84] As a result of the studies carried out with nanoparticle and microparticle ocular delivery systems, there is no drug having particulate structure that is used in therapy.

Of the nanoparticulate drug delivery systems, Abraxane® became the first to be approved by the FDA in 2005 after completion of clinical phase trials. This drug has colloidal dimensions, contains nanoparticle albumin-bound paclitaxel and is used parenterally for the treatment of metastatic breast cancer.[85]

Abraxane® has been used in a phase 2 clinical trial for the treatment of inoperable intraocular melanoma.[86] In addition, clinical phase trials have been started to evaluate the use of sulfur

hexafluoride-lipid type A microspheres (Lumason®) for contrast in ultrasonography to diagnose cancer and evaluate brain perfusion.[87,88] In another clinical trial in the EU, a phase 2 safety and efficacy study of ophthalmic dexamethasone nanoparticles in diabetic macular edema was launched in 2017.[89]

During the course of legislative changes, the US FDA issued another guideline in 2014 for applications classified as nanotechnology products within its jurisdiction. This guideline highlighted the need to consider how the properties of nanosized products (between 1-100 nanometers), their aggregates and surface-coated structures affect human health. Products in this guideline include drugs, biological products and medical devices.[90]

In addition, the EMA issued its position on the use of cyclodextrins as excipients. Although the document does not address cyclodextrin nanoparticles, it states that cyclodextrins enhance the ocular penetration of drugs and that 4% concentrations of α-cyclodextrin and 5% concentrations of randomly methylated β-cyclodextrin can be toxic in the corneal epithelium of rabbits. It also reported that a 10% solution of β-cyclodextrin sulfobutyl ether derivative and a 12.5% solution of β-cyclodextrin hydroxypropyl derivative had no toxic or irritant effect on rabbit eyes.[91] Therefore, it is important to analyze the side effects and toxicity of cyclodextrin used in nanoparticles developed for ocular applications based on its structure, proportion and properties.

Implants

In ocular implants, the active substance is contained in a reservoir and coated with polymeric membranes having different permeability. Release of the active substance from the implant at the desired rate and duration is designed according to the properties of the active substance and the polymers used. These systems were first developed as non-eroding implants; later, the use of biodegradable polymers enabled the design of eroding implants for treatment.[2,3]

The implants currently in use are delivery systems that contain low molecular weight drugs and can provide extended release of the active ingredient. The first of these, Vitrasert®, was developed as an intravitreal implant and contains ganciclovir.[92] Later, Retisert® and Iluvien®, which contain fluocinolone acetonide, were introduced.[93,94] These implants are non-eroding and are surgically implanted and removed when necessary. In addition, the biodegradable implant Ozurdex® is an intravitreal implant that provides sustained release of dexamethasone.[95]

Some systems reported in the literature are the subject of ongoing clinical studies. These include another delivery system containing live cells which enable the release of ciliary neurotrophic factor (CNTF) from genetically modified retinal pigment epithelium (RPE) cells.[96,97,98,99] The release of protein drugs has been demonstrated from implants incorporating this system, which the manufacturer named "Encapsulated Cell Technology®" (ECT). The composition of ECT has live cells and an implant portion considered a medical device which allows the passage of proteins released from these cells into the biological fluids. Information about clinical trials being conducted with ECT is summarized in Table 1.[96,97,98,99,100,101,102,103,104,105,106]

In clinical trials evaluating ECT products in the treatment of retinitis pigmentosa, geographic atrophy and macular degeneration involving recurrent choroidal neovascularization, genetically modified RPE cells encapsulated in the NT-501 implant were applied to patients with different study protocols (Table 1).[96,97,98,99,100,101,102,103,104,105,106] Results of studies conducted

Table 1. Information about the clinical studies related to the Encapsulated Cell Technology® products providing ciliary neurotrophic factor release from genetically modified retinal pigment epithelium cells

Diseases	Encapsulated Cell Technology®	Low dose (LD): 5 ng/day High dose (HD): 20 ng/day	Clinical trial information	References
Retinitis pigmentosa	Drug: Ciliary neurotrophic factor 1 NT-501 implant	Duration: 6 months Patient Nr: 5 HD, 5 LD	Phase 1 (completed) NCT00063765	96, 100
Geografic atropy	Drug: Ciliary neurotrophic factor 2 NT-501 implant	Duration: 12 months Patient Nr: 27 HD, 12 LD Control patient: 12	Phase 2 (completed) NCT00447954	96, 97, 101
Retinitis pigmentosa (late stage)	Drug: Ciliary neurotrophic factor 3 NT-501 implant	Duration: 12 months Patient Nr: 43 HD, 22 LD	Phase 2 (completed) NCT00447993	96, 102
Retinitis pigmentosa (early stage)	Drug: Ciliary neurotrophic factor 4 NT-501 implant	Duration: 24 months Patient Nr: 48 HD, 20 LD	Phase 2/3 (completed) NCT00447980	98, 103
Retinitis pigmentosa (early stage or Usher syndrome type 2-3)	Drug: Ciliary neurotrophic factor 3 NT-501 implant	Duration: 36 months Patient Nr: 30	Phase 2/3 (ongoing) NCT01530659	99, 104
Macular degeration (recurrent choroidal neovascularization)	Drug: Ciliary neurotrophic factor 3 NT-503-3 implant	Duration: 36 months Patient Nr: 42	Phase 1 (terminated) NCT02228304 Comparator drug: Eylea	105
Glaucoma	Drug: Ciliary neurotrophic factor 1 NT-501 implant	Duration: 24 months Patient Nr: 60	Phase 2 (completed) NCT02862938	106

indicate that the rate of CNTF release can be controlled, the pharmacokinetic profile is appropriate, there is no passage into systemic circulation, the cells in the implant maintain their viability for the specified duration and there is no antibody formation against CNTF or the cells. However, it was reported that patients with geographic atrophy did not show statistically significant improvements in visual acuity and vision was only preserved in the group that received a high dose.[96,97,98,99] The clinical research registry shows that another trial regarding the treatment of macular degeneration has been discontinued, while a phase 2 clinical trial initiated for the treatment of glaucoma continues.[105,106] An article on the long-term (60-96 months) follow-up of retinitis pigmentosa patients who received ECT implants reported no signs of efficacy resulting from treatment.[107]

Because it encapsulates genetically modified cells in an implant and releases human neurotrophic factor into the eye via a semipermeable membrane, the EMA considered this ECT product a "cell-based drug delivery system". The EMA legally classified the product based on EU regulations on medicines and ATMPs.[11,12,108] According to this, it was stated that the CNTF released from the genetically modified live cells has the properties of a drug active substance and the capsule with the semipermeable membrane that enables drug release and the polymeric scaffold on which the cells grow are medical devices integrated into the product. As a result of this evaluation, the product contained both drug and medical device components and was classified as an ATMP and "combined gene therapy medicinal product". This classification was made based on the fact that the release of the active ingredient CNTF from the implanted system was enabled by genetically engineering RPE cells through biotechnological methods.[11,12,108] Genetically altered RPE cells that release CNTF have received "orphan drug" status.[109]

Advanced Therapy Medicinal Products

ATMPs include gene- and cell-based drugs and their combinations with medical devices.[12] As stated in the legislations section, when human tissue and cell-containing gene and cell-based products for which the US FDA requires new drug applications and the ATMPs defined by the EU are considered in terms of their characteristics, it is observed that the same principles and criteria apply for ensuring their quality, efficacy and safety.

In order to enable the therapeutic use of safe and effective cell-containing drugs, the US introduced the "Regenerative Medicine Advanced Therapy" (RMAT) designation in the 21st Century Cures Act enacted in 2016. The act describes these as a drug that is *"a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products"*. According to the definition in the 21st Century Cures Act, a drug is eligible for RMAT designation if it is *"intended to treat, modify, reverse, or cure a life-threatening disease or condition"*. The final requisite is that *"preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs"*.[110] The cellular drugs defined by this act do not include human cell-tissue products that have been used with minimal manipulation in routine treatment for many years through transplantation or transfusion.[110] Drugs defined as RMAT or with RMAT designation according to this act are ATMPs and orphan drugs classified by the EU as ATMPs.

The four classes of biological medicinal products according to the EU ATMP Regulation have recently been listed on the EMA website as "somatic-cell therapy medicines", "gene therapy medicines", "tissue-engineered medicines" and "combined ATMPs" (http://www.ema.europa.eu). With developments in advanced therapies, efforts are ongoing to ensure international harmonization of the content and terminology used for drugs or medicinal products in the legislation of the EU and USA.

In the ATMP regulation, gene therapy medicinal products are described as biological medicinal products that *"contain recombinant nucleic acids or genes administered to humans for treatment, diagnosis and prevention"*. Somatic-cell therapy medicinal products are defined as *"products obtained from cells or tissues that are substantially manipulated to alter their biological characteristics, physiological functions, or structural properties and are not used for the same essential functions"*. *"Products that contain engineered cells or tissues and that are administered to humans for the purpose of repairing, regenerating, or replacing human tissue"* are designated as tissue-engineered medicinal products. *"ATMP that contain one or more medical devices as an integral part"* are called combined ATMP.[12]

In Turkey, ATMP are included in the "*Regulation on Registration of Medicinal Products for Human Use*".[22] In a guideline on the clinical research of ATMP, ATMP are defined as *"tissue- and cell-based human medicinal products classified as gene therapy medicinal products, somatic-cell therapy medicinal products, tissue-engineered medicinal products and combined advanced therapy medicinal products"*.[111] In brief, ATMPs, which are defined as high-risk products in international regulations, are included within the scope of medicines in Turkish legislation in accordance with international principles. In addition, information on the manufacturing conditions of ATMP obtained from human tissues and cells is included in the *"Good Manufacturing Practices (GMP) Guide for Manufacturing Plants of Human Medicinal Products"* updated by the Ministry of Health TMMDA, in accordance with the change in legislation.

In the EU, the multidisciplinary Committee for Advanced Therapies has been established within the EMA for ATMP and the committee considers applications, presents opinions and performs classification and certification procedures.[12] The ATMP approved in the EU to date include a drug with the trade name Holoclar® which was developed for ocular administration. Holoclar® uses the patient's own limbal stem cells, which are expanded and differentiated in culture to yield corneal epithelial cells. It has been reported that this biological medicine, which was conditionally licensed in the EU in 2015 within the framework of legislation, is the first stem cell-based ATMP. Holoclar® is classified as a tissue-engineered medicinal product within the ATMP category.

It has been stated that although the active substance in the

composition of Holoclar® is human corneal epithelial cells, there are also stem cells in its structure. Holoclar® is used in adults for corneal regeneration in cases of severe limbal stem cell deficiency and burns, including chemical burns and has orphan drug status. Administered by implantation, Holoclar® is the equivalent of a transparent, circular live tissue containing 79,000-316,000 cells/cm^2; the cells presented to treatment are found on a support layer of fibrin in transport medium.[112]

In addition, clinical research is being done with gene therapy medicinal products within the scope of ATMP. In one of these clinical trials, recombinant adeno-associated viral vector carrying human mitochondrial ND4 gene was classified as a gene therapy medicinal product (rAAV2/2-ND4). This orphan gene therapy medicine is administered intravitreally as a single dose to patients with Leber's hereditary optic neuropathy and a clinical trial investigating of its efficacy is in progress.[113]

Clinical studies of gene therapy medicinal products initiated in the EU and USA include trials of retinal gene therapy providing AAV2 viral vector-mediated Rab escort protein-1 expression developed for the treatment of choroideremia. This research investigates the efficacy and safety of this gene therapy medicine, which is administered to patients subretinally as a single dose.[114,115]

In addition to this, the EMA in the EU classifies a large number of products within the scope of ATMP. These also include RPE cells obtained as a result of manipulating induced pluripotent stem cells. In the EU, RPE cells obtained through the differentiation of induced pluripotent stem cells have been classified as tissue-engineered products and medicines, based on their administration for regeneration, repair, or replacement in retinal degenerative diseases.[116] RPE cells classified as drugs in the ATMP group are among the most studied and important cells in R&D in the development of retinal drug and gene delivery systems.[117]

In 2017, results were published of a clinical trial launched in 2013 in collaboration with Japan's National Research Institute (RIKEN) for the use of RPE cells obtained from stimulated pluripotent stem cells for the treatment of age-related macular degeneration. The report stated that six patients were initially recruited for the study but a mutation was detected in the cell property analyses of the second patient and the trial was discontinued without performing the procedure in the second patient. In previous animal studies conducted with RPE cells obtained for this trial, the cells passed the tests related to tumorigenic properties but the procedure was not performed in the second patient due to the potential risks.[118] Another document on the RIKEN website stated that after the trial launched in 2013, the Regenerative Drug Safety Act was enacted in Japan in 2014 and that the trial was discontinued due to insufficient time to complete the study (http://www.riken-ibri.jp/AMD/img/20151125en.pdf).

Conclusion

From studies of drug delivery systems starting with liposomes, which are known to have an extended development and approval process, we have reached far more advanced stages today, where the cell itself is a drug, biological medicinal product, or advanced therapy product, or is given advanced therapy medicinal status in regenerative medicine and defined as a regenerative medicine. In this process, dosage forms such as liposomes and nanoparticles, known as colloidal delivery systems, are now referred to as "nanodrugs" or "nanopharmaceuticals" and fall within the field of nanotechnology. Studies are ongoing in the development of new nanodrugs for the treatment of eye diseases with different products and ocular implants are being used in therapy. Studies on ATMP and systems containing cells that enable the release of drugs with high molecular weight continue and the treatment of ocular diseases remains the priority.

This process in which various nanodrugs, gene and cellular delivery systems and ATMPs all involving their own risks are developed and in ongoing clinical research, involves a period of change and harmonization among national and international legislation. Compliance with national and international regulations is of utmost importance in the development of high-risk drugs obtained from engineered cells that are promising for the treatment of chronic diseases or untreatable eye diseases. Manufacturing these products within a pharmaceutical quality assurance system during development stages is a critical step toward faster transition from R&D to the clinic. This requires multidisciplinary research teams and the establishment of infrastructure with GMP conditions that meet the legal requirements of pharmaceutical quality systems.

Ethic

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Türkan Eldem, Design: Türkan Eldem, Data Collection or Processing: Türkan Eldem, Analysis or Interpretation: Türkan Eldem, Bora Eldem, Literature Search: Türkan Eldem, Writing: Türkan Eldem, Bora Eldem.

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Case Report

Candida parapsilosis Infection After Crescentic Lamellar Wedge Resection in Pellucid Marginal Degeneration

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Abstract

Infectious keratitis after corneal lamellar surgery is a rare complication. In this report, we present unexpected complications after crescentic lamellar wedge resection (CLWR) and their treatment in a patient with pellucid marginal degeneration. A 42-year-old male patient developed fungal keratitis due to *Candida parapsilosis* in the late postoperative period after CLWR. Infection was controlled with medical treatment. However, recurrent intraocular infections and cataract formation occurred, probably due to capsular damage and inoculation of microorganisms into the crystalline lens during antifungal drug injection. Lensectomy was performed due to cataract progression and recurrence of the infection when treatment was discontinued. Amphotericin B was administered to the anterior chamber at the end of the operation. Four months later, an intraocular lens was implanted and corneal cross-linking treatment was performed. At the last visit, visual acuity reached 9/10. This case shows that good visual acuity can be achieved with appropriate treatment of fungal keratitis and all associated complications after CLWR.

Keywords: Pellucid marginal degeneration, crescentic lamellar wedge resection, *Candida parapsilosis*, fungal keratitis, iatrogenic trauma

Introduction

Pellucid marginal degeneration (PMD) is a bilateral, asymmetric, noninflammatory ectatic disorder of the cornea. Cornea thinning typically occurs in a 1-2 mm band parallel to the limbus between 4 and 8 o'clock.[1,2]

Glasses and contact lenses are sufficient for visual rehabilitation in the early stages but surgical treatment is necessary in advanced stages. In crescentic lamellar wedge resection (CLWR), the abnormally thin corneal stroma is removed while sparing the central cornea and the margins of normal-thickness stroma are reapposed.[3,4,5,6]

Infectious keratitis after keratoplasty procedures is a rare but serious complication. The incidence is reported as 1.5-12.6% after full-thickness techniques.[7,8] There are few publications in the literature regarding lamellar surgeries.[7,8,9] There are no previous reports of keratitis after CLWR for PMD.

In this article, we present a case of unilateral *Candida parapsilosis* infection after bilateral CLWR for PMD and the unexpected complications that occurred during its treatment.

Case Report

A 42-year-old male refugee under follow-up for PMD had an uncorrected visual acuity (UCVA) in the right eye of counting fingers from 4 m and best corrected visual acuity (BCVA) of 2/10 with refraction values of -5.00, -12.00 α 35, topographic astigmatism (TA) of 21.2 dioptri (D) α 95. In the left eye, UCVA was counting fingers from 2 m, BCVA was 1/10 with refraction of -6.00, -14.00 α 45 and TA of 23.8 D α 93.5 (Figure 1, Figure 2 a1-b1). Bilateral CLWR was planned for both eyes due to insufficient visual improvement with spectacles and contact lens incompatibility.

The borders of the area to be excised were mapped onto the cornea preoperatively under the biomicroscope light using a 27-gauge needle. Under general anesthesia, a crescent blade was used to make a crescent-shaped incision in the cornea including the area of thinning between 4-8 o'clock, 1-2 mm from the limbus. Stromal dissection from the incision to just above the Descemet's membrane was done and the thinned corneal stroma was resected using a crescent blade and scissors. After

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ensuring the Descemet's membrane was intact, the upper and lower normal-thickness corneal tissue was reapposed using five 10/0 sutures, followed by paracentesis through the limbus to reduce intraocular pressure. The five previously placed sutures were knotted and eight 10/0 polypropylene sutures were added. Topical antibiotic (0.5% moxifloxacin, 4 times daily), topical corticosteroid (1% prednisolone acetate, 4 times daily) and artificial tear drops were prescribed postoperatively. Topography was performed at each postoperative visit. Loose sutures were replaced. The same surgical procedure was performed in the right eye 3 months after the left eye.

On postoperative day 15, UCVA was 5/10, BCVA of 7/10 with refraction of +1,00, -4.50 α 55 and TA was 15.3 D α 167 in the right eye and UCVA was 6/10, BCVA was 9/10 with refraction of +2.00, -4.00 α 70 and TA was 9.4 D α 10 in the left eye (Figure 2 a2-b2).

Slit-lamp examination at postoperative 5 months revealed a single loose suture at 5 o'clock on the resection line in the left eye, a 1x2 mm area of stromal infiltrate, mild edema surrounding the infiltrate and inflammatory reaction in the anterior chamber (+2 cells) (Figure 3a). After taking samples for direct microscopy and culture, treatment with topical fortified vancomycin 50 mg/mL 8 times daily, ceftazidime 50 mg/mL 8 times daily and 2% fluconazole 6 times daily was initiated. Direct microscopy of corneal scraping showed yeast and culture produced *Candida parapsilosis*. Antibiogram results indicated sensitivity to fluconazole, voriconazole and amphotericin B. Based on these findings, the fortified vancomycin and ceftazidime were discontinued and treatment was continued with 2% fluconazole drops hourly and oral fluconazole 200 mg daily. Initial response to this therapy was good. However, after 5 weeks the patient exhibited enlargement of the lesion, extensive keratic precipitates throughout the cornea and hypopyon in the anterior chamber. UCVA was 2/10 and fundus examination and ultrasonography revealed no signs of endophthalmitis. Suspecting resistance to the antifungal therapy, the agent was changed to topical 0.15% amphotericin B (amph B) hourly. After taking a sample from the anterior chamber under local anesthesia, 3 injections of 7.5 µg/0.1 mL amph B were administered at 72-hour intervals. Four days after the procedure, the hypopyon disappeared, the anterior chamber reaction regressed and the lesion was diminished in size. However, after the third injection, the patient developed hyphema nearly filling the anterior chamber. The hyphema regressed on day 7, revealing lens opacification and posterior synechia at 5 o'clock, just opposite the incision (Figure 3b). During follow-up, the patient experienced three infectious episodes with hypopyon at intervals of five to seven weeks after discontinuing antifungal therapy. Infection was controlled by resuming antifungal therapy. Lensectomy and synechotomy were performed without intraocular lens implantation while the patient continued antifungal therapy due to cataract progression

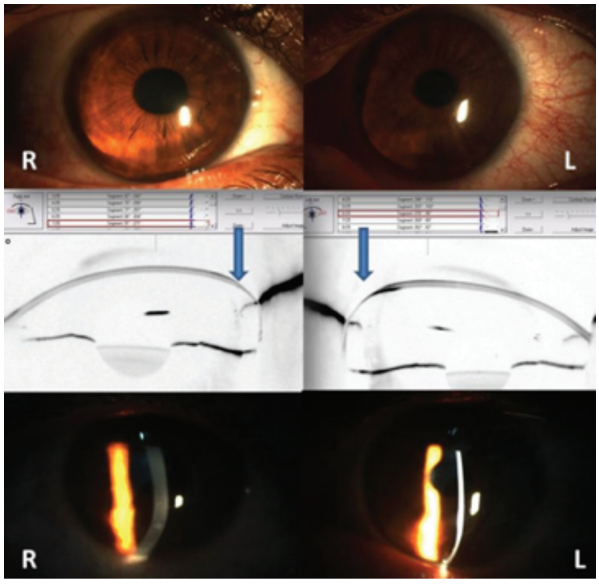

Figure 1. Preoperatively, both eyes show inferior corneal steepening and stromal thinning, while perilimbal stromal thickness is normal
R: Right eye, L: Left eye

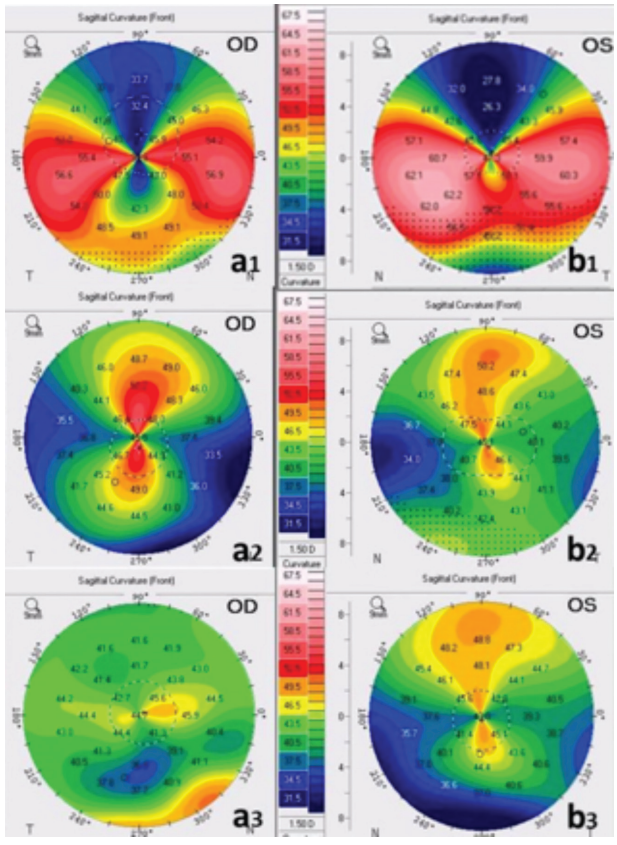

Figure 2. a1,b1) Topography in initial examination revealed typical crab claw pattern and topographic astigmatism was 21.2 dioptri (D) in the right eye and 23.8 D in the left eye; a2,b2) At postoperative day 15, astigmatism was markedly reduced at 15.3 D and 9.8 D in the right and left eyes, respectively; a3,b3) At postoperative 23 months, astigmatism was 6.1 D in the right and 1.4 D in the left eye
OD: Right eye, OS: Left eye

and recurrence of the infection after treatment was discontinued (Figure 3c). At the end of the procedure, 7.5 µg/0.1 mL amph B was administered to the anterior chamber and topical antifungal therapy was continued for another month. Four months after cataract surgery, an intraocular lens was implanted in the sulcus in a second procedure (Figure 3d). Two months later, corneal stability was achieved in the left eye by performing corneal cross-linking therapy (Figures 3e-3f).

There were no intraoperative or early postoperative complications in the right eye (Figure 4).

At 23 months after the first operation, the right eye had BCVA of 8/10 with refraction of -1.00, +2.00 α 135 and TA of 6.1 D α 104, while the left eye had BCVA of 9/10 with refraction of +1.50, -4.00 α 65 and TA of 1.4 D α 50 (Figure 2 a3-b3).

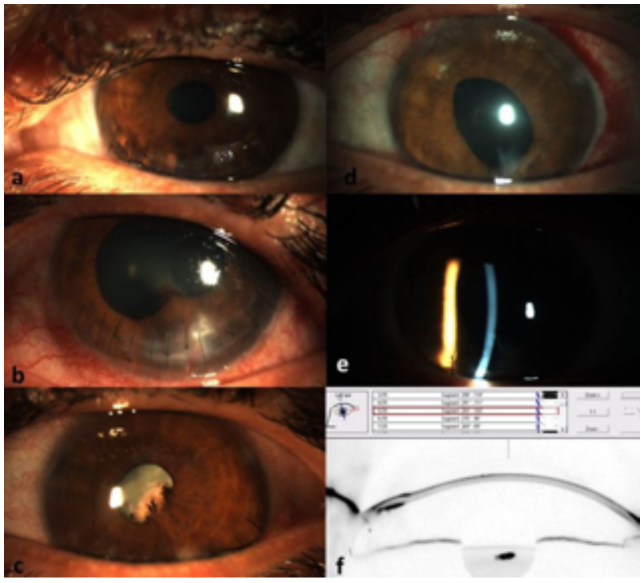

Figure 3. Images of the left eye. a) At 5 months, a single slack suture and a keratitis focus at 5 o'clock; b) At 7 months, localized lens opacity and posterior synechia; c) Cataract progression and capillaries extending from the iris margin onto the lens; d,e) pseudophakia; f) Scheimpflug section after corneal cross-linking

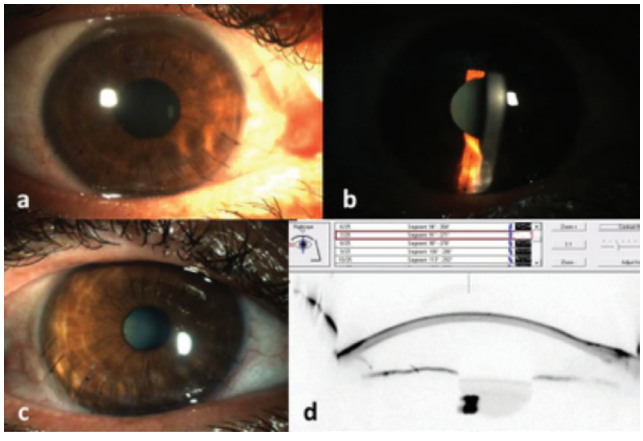

Figure 4. Postoperative images of the right eye, a,b) day 15; c) 21 months; d) Scheimpflug section

Discussion

PMD typically usually shows bilateral involvement of the inferior cornea 1-2 mm from the limbus. Surgical treatment is difficult due to the peripheral location of the ectasia.[5,6] Some surgical techniques that can be used include large-diameter penetrating keratoplasty (PK), crescentic lamellar keratoplasty, crescentic lamellar keratoplasty combined with PK, CLWR, tuck-in keratoplasty, lower-quadrant eccentric PK and corneoscleroplasty.[3,4,5,6,10,11]

In CLWR, a narrow crescent of peripheral tissue is excised to remove the thinned corneal stroma and reduce astigmatism.[11] Advantages of this technique are that the normal central cornea is preserved and there is no risk of graft rejection, primary graft failure, or interface haze because donor tissue is not used. As steroids are used for a shorter time, there is also low risk of developing steroid-related complications. The deeper corneal layers remain intact, thus providing a stronger incision site and shorter visual recovery time. In addition, risk of retinal detachment, choroidal detachment and endophthalmitis is low because the only invasive procedure performed to the anterior chamber is a small paracentesis.[2] CLWR was performed in our patient to avoid graft-related complications and provide rapid visual rehabilitation. There was significant early visual improvement in both eyes and excellent outcomes were achieved at 2-year follow-up. At 23 months after resection, TA decreased to 21.2 D to 6.1 D in the right eye and 23.8 D to 1.4 D in the left eye.

There are many predisposing factors for the development of keratitis after corneal surgeries. Suture-related problems (43-60%), persistent epithelial defects (38-74%), topical medication use (40-81%), low socioeconomic status (60%), soft contact lens use (9-45%) and lid anomalies (23%) are the most commonly reported.[7,8,12,13] In developed countries, *Candida albicans* is the most frequently isolated fungus in corneal infections; however, the prevalence of *Candida parapsilosis* is increasing.[9,14] New keratoplasty techniques may reduce the rate of postoperative infectious keratitis but retrospective data regarding the rate of keratitis following lamellar surgeries are still limited.[9]

There are few publications related to surgical treatments used in PMD and the present case is the first report of keratitis after CLWR. Our patient exhibited infection in the late postoperative period. He had predisposing risk factors such as a loose suture and low socioeconomic level. Despite a good initial response to topical and systemic antifungal therapy, the patient was later treated with anterior chamber injections of antifungal drug because the infection penetrated to the deeper layers. The infectious episodes accompanied by recurrent hypopyon were attributed to anterior lens capsule injury and introduction of microorganisms to the lens during antifungal administration to the anterior chamber. After the infection was controlled, lensectomy was performed while showing extreme care to protect the posterior capsule barrier to prevent spread of infection to the vitreous and the intraocular lens was not implanted in the same session due to the possibility of microorganisms remaining in the

capsular bag. Intraocular lens implantation was performed four months after lensectomy, when there was no further recurrence of infection and the fungus was believed to be eradicated. Finally, two months later, corneal cross-linking treatment was done both for antimicrobial purposes and to reinforce the resection area. After an extended follow-up period, both patients had good visual acuity without undergoing keratoplasty.

Although CLWR is effective and reliable for the treatment of PMD and less invasive than full-thickness techniques, unexpected complications may occur at each stage of treatment due to various factors. Treating these complications patiently and appropriately is important to achieve good visual outcomes.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ayşe Burcu, Selma Özbek-Uzman, Concept: Selma Özbek-Uzman, Ayşe Burcu, Design: Selma Özbek-Uzman, Ayşe Burcu, Züleyha Yalnız-Akkaya,

Data Collection or Processing: Selma Özbek-Uzman, Züleyha Yalnız-Akkaya, Evin Şingar-Özdemir, Firdevs Örnek, Analysis or Interpretation: Selma Özbek-Uzman, Züleyha Yalnız-Akkaya, Literature Search: Selma Özbek-Uzman, Writing: Selma Özbek-Uzman, Züleyha Yalnız-Akkaya.

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Case Report

A Case of Allergic Urticaria After Ophthalmic Nepafenac Use

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Abstract
A 21-year-old male patient with no history of systemic disease or drug use presented to our clinic with redness and pain in the right eye. Best corrected visual acuity was 20/20 in both eyes. Inflamed pinguecula was observed on slit-lamp examination and the patient was prescribed ophthalmic nepafenac eye drops. After instilling the drops that day and the next day, the patient presented again due to pruritus and rash. Upon consultation with the dermatology department, the patient was diagnosed with drug-induced allergic urticaria and the nepafenac drops were discontinued. Although urticaria has been reported as a side effect after systemic non-steroidal anti-inflammatory drug (NSAID) use, such a reaction has not been reported with an ophthalmic NSAID and ours is the first reported case of urticaria following ophthalmic nepafenac use. This unique case highlights the fact that ophthalmologists must also keep urticaria in mind as a potential side effect when prescribing this drug.
Keywords: Nepafenac, allergic, urticaria

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in oral, intramuscular and topical (skin and ophthalmic) forms for a variety of indications. Ophthalmic NSAIDs currently in use include nepafenac, ketorolac tromethamine, diclofenac sodium, bromfenac and flurbiprofen. A study performed in rabbit eyes demonstrated the distribution of ophthalmic nepafenac in the cornea, aqueous humor, iris, ciliary body and choroid.[1] These ophthalmic drugs are used in the management of inflammatory ocular diseases, allergic conjunctivitis and postoperative pain following refractive and cataract surgery and in the treatment of cystoid macular edema after cataract surgery.[2,3,4,5,6]

Adverse effects of ophthalmic NSAIDs include corneal melting,[7,8,9,10] ocular tissue hemorrhage,[7] blurred vision, photophobia, posterior capsule opacity, foreign body sensation, dry eye and increased intraocular pressure.[11] Adverse effects involving the pulmonary, gastrointestinal, dermatologic, renal, cardiovascular, hematologic, pulmonary and central nervous systems have been reported after topical, intramuscular and oral administration.[12,13,14,15,16,17,18,19] Here we present urticaria as a previously unreported adverse effect of an ophthalmic NSAID.

Case Report

A 21-year-old male patient presented to our clinic with pain and redness in his right eye. On physical examination, visual acuity using Snellen chart was 20/20 in both eyes and intraocular pressures were 14 and 15 mmHg in the right and left eyes, respectively. On slit-lamp biomicroscopic examination, minimally inflamed pinguecula was noted on the nasal conjunctiva of the right eye. No pathology was observed in the left eye except pinguecula (Figure 1a, b). Fundus examination revealed no pathology in either eye. The patient reported no disease or drug use in his systemic medical history. Treatment was initiated with ophthalmic nepafenac (Nevanac 0.1%, Alcon) four times daily and the patient was scheduled for follow-up one week later. The next day, the patient returned to the outpatient clinic due to redness and itching on his body.

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He stated that an itchy rash had formed on his trunk and arms the previous day, approximately 1-2 hours after instilling the nepafenac eye drop and he had been treated for allergy that night in the emergency department. A similar reaction had occurred 1-2 hours after instilling the drop that morning and the dermatology department was consulted. Erythematous, edematous plaque lesions were observed on the arms, neck and abdomen on dermatologic examination and the patient was diagnosed with allergic urticaria by the dermatologist (Figure 2a, b, c). The dermatologist instructed the patient to discontinue the nepafenac drops and prescribed oral antihistamines to treat the urticaria. The ophthalmology department recommended preservative-free lubricating drops and scheduled the patient for follow-up. At follow-up three days later, the patient's skin lesions and symptoms had completely regressed and his ocular complaints had also improved.

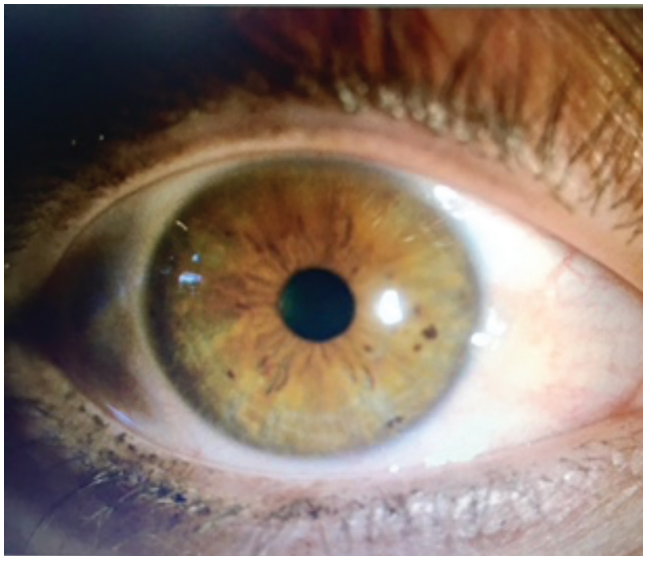

Figure 1a. Inflamed pinguecula in the right eye

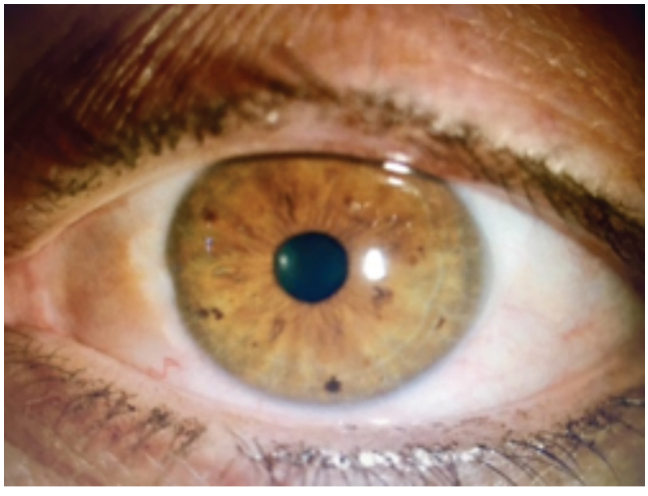

Figure 1b. Pinguecula in the left eye

Discussion

NSAIDs act by inhibiting the enzyme cyclooxygenase (COX), thus reducing the synthesis of prostaglandin, prostacyclin and leukotriene from arachidonic acid. There are two forms of COX. COX-1 is generally found in all tissues and plays a protective role by regulating the action of prostaglandins. COX-2 increases inflammation by stimulating immune system cells and other tissues in the presence of various stimuli such as mitogens, inflammatory cytokines and tumor promoters.[20]

Ophthalmic NSAIDs currently in use include nepafenac, ketorolac tromethamine, diclofenac sodium, bromfenac and flurbiprofen. The chemical designation of nepafenac is 2-amino-3-benzoylbenzeneacetamine and it is available as a 0.1% suspension. Ophthalmic nepafenac is the only prodrug among the NSAIDs. It is deaminated to form amfenac, a potent COX inhibitor. Ophthalmic nepafenac targets the anterior segment and intraocular vascular tissues. An *in vivo* study in humans showed nepafenac had a significantly shorter time to peak anterior chamber concentration after instillation on the cornea, followed by amfenac, ketorolac and bromfenac.[21] Ophthalmic nepafenac takes effect approximately 15 minutes after topical application and lasts more than 8 hours.[22] Quantitative plasma

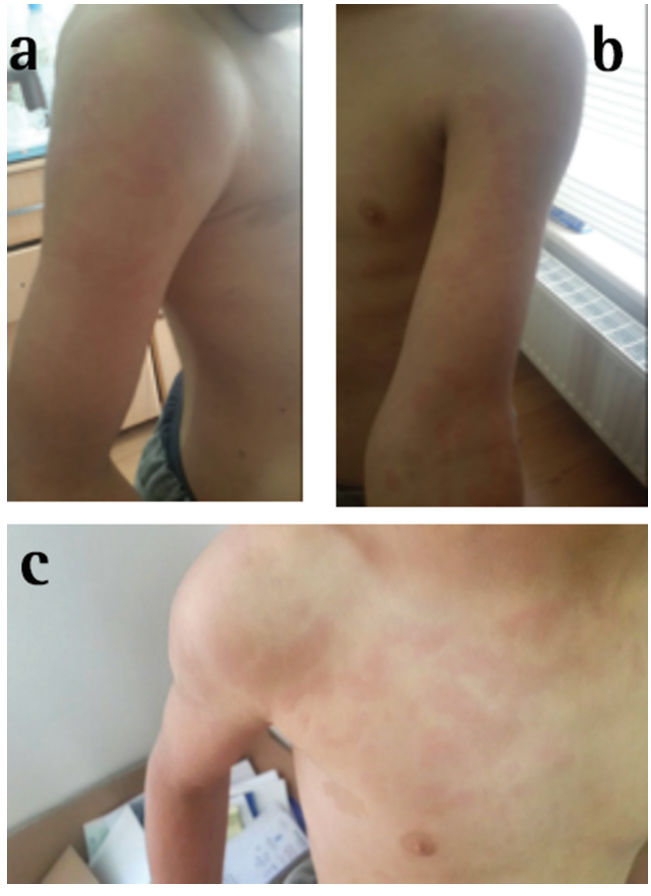

Figure 2. Erythematous and edematous plaques on the patient's right arm (a), left arm (b), and upper trunk (c)

concentrations of nepafenac and amfenac were measured in subjects 2-3 hours after ocular administration and mean steady-state C-max values of the drugs were 0.310±0.104 ng/mL and 0.422±0.121 ng/mL, respectively. Ophthalmic diclofenac has been associated with corneal melting in studies of the ophthalmic side effects of topical NSAIDs.[7] In another study, topical ketorolac and bromfenac were associated with severe corneal damage and the authors suggested that patients with corneal damage should be asked about their use of these agents.[8,9] Topical nepafenac has also been associated with corneal melting.[10] Ophthalmic NSAIDs may prolong bleeding time by impairing platelet aggregation, thus leading to hemorrhage in ocular tissues.[7] Therefore, caution is warranted when using ophthalmic NSAIDs long-term in patients using systemic NSAIDs, patients who smoke or use alcohol and in elderly and pediatric populations. In a study of the ocular side effects of nepafenac, ocular adverse events that occurred at rates of at least 1% included blurred vision, photophobia, posterior capsular opacity, foreign body sensation, dry eye and increased intraocular pressure.[11]

Adverse effects have also been reported after using topical and intramuscular NSAIDs. In one of these reports, a patient with asthma history experienced an asthma attack after using piroxicam topical gel (NSAID) for knee pain.[15] Another patient with no history of gastric ulcer developed gastric ulcer perforation four days after starting intramuscular ketorolac (NSAID) treatment for traumatic humerus and femur fracture.[16] The systemic side effects of oral NSAIDs on the gastrointestinal, renal, cardiovascular, hematological, pulmonary and central nervous systems have been demonstrated in various studies.[17,18,19,20] Dermatologic side effects include urticaria, morbilliform and vesiculobullous eruptions, exfoliative erythroderma, erythema multiforme, Steven Johnson syndrome and toxic epidermal necrosis.[21,22] Urticaria occurs as the result of mediator release from mast cells or basophils after contact with a triggering stimulus. These mediators induce vasodilation and transudation from small vessels, which causes the development of the characteristic erythematous, edematous, itchy papules and plaques. Many factors are implicated in the etiology of urticaria. The main etiological causes of acute urticaria are drugs, food and infections. It is usually possible to determine the etiology based on only a detailed history. Nearly all drugs can cause urticaria but the most common are antimicrobials (penicillin, sulfonamides), analgesics and antiinflammatory drugs (acetylsalicylic acid, NSAIDs, opiates), angiotensin converting enzyme (ACE) inhibitors and blood products.[23,24] In a study conducted in rabbits, it was determined that ocular instillation of 0.5% (50 µL) diclofenac resulted in a peak plasma concentration of 185 ng/mL after 15 minutes at the earliest.[25] In addition, it has been shown in rabbits that 7-10% of ophthalmic flurbiprofen enters the ocular circulation, while 74% passed to the systemic circulation.[26] Urticaria is a known adverse effect of systemic NSAID use and we believe that our patient developed it after the ophthalmic NSAID entered the systemic circulation via the conjunctival vessels and nasolacrimal duct. Although there are previous reports of allergic urticaria after oral NSAID use,[23,24] our case is novel as the first reported case in the literature of allergic urticaria as an adverse event after ophthalmic NSAID use.

Ethics

Informed Consent: Patient-confirmed approval was obtained. In addition, written approval has been received for the presentation of the patient as a case report.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Erdoğan Yaşar, Concept: Nilgün Yıldırım, Design: Deniz Öztürk Kara, Data Collection or Processing: Erdoğan Yaşar, Analysis or Interpretation: Nilgün Yıldırım, Literature Search: Deniz Öztürk Kara, Writing: Erdoğan Yaşar.

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

Financial Disclosure: The authors declared that this study received no financial µsupport.

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Case Report

Optical Coherence Tomography Angiography in Branch Retinal Artery Occlusion

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Abstract

Optical coherence tomography angiography (OCTA) is a non-invasive alternative method used in the diagnosis and follow-up of acute branch retinal artery occlusion to show changes secondary to ischemia. We report a case with acute branch retinal artery occlusion. A 52-year-old man presented with a complaint of sudden-onset visual loss in the right lower quadrant of the left eye for the previous three days. Best-corrected visual acuity was 0.4 temporally. Inferonasal visual field deficit was detected with confrontation. Pupillary light reactions were normal in both eyes and there was no relative afferent pupillary defect. Dilated fundus examination revealed retinal lesion suggesting superior temporal branch retinal artery occlusion. He was treated with dextran 40 and pentoxifylline. Follow-up fundus fluorescein angiography could not performed because of chronic renal failure; OCTA demonstrated superficial and deep capillary non-perfusion areas and telangiectases in areas corresponding to the artery occlusion.

Keywords: Acute vision loss, optical coherence tomography angiography, retinal artery occlusion, branch retinal artery occlusion

Introduction

Acute retinal artery occlusion is an ocular emergency with painless, sudden-onset, unilateral loss of vision or visual field.[1] Occlusion may occur at the level of the ophthalmic artery, the central retinal artery, a branch thereof, or the cilioretinal artery. It is more common in older men with cardiovascular disease.[2,3] It is frequently associated with embolic or thrombotic diseases. Medical history and ophthalmologic examination are often sufficient for diagnosis but additional imaging methods may also be needed for diagnosis and follow-up.

Fundus fluorescein angiography (FFA) is an invasive method requiring intravenous administration of dye that can cause side effects. In recent years, optic coherence tomography angiography (OCTA) has become widely available as an alternative to FFA in various ophthalmologic diseases. OCTA is a new non-invasive method for the detection and quantification of the retinal microcirculation without the use of dye but motion contrast. It senses erythrocyte movement in the vascular lumen by comparing the OCT signal amplitude between consecutive B-scans using the split-spectrum amplitude-decorrelation angiography algorithm, thereby providing high-quality vascular images with shorter acquisition times. Retinal tissue can be examined in layers via segmentation. Images from 3x3, 6x6 and 8x8 mm areas are used for the macula and 4.5x4.5 mm for the optic disc.[4,5] It can quickly and non-invasively provide three-dimensional images of the retinal microvasculature.

Case Report

A 52-year-old male patient presented with the complaint of sudden vision loss in his left eye 3 days earlier. Past medical history was significant for chronic kidney disease, secondary hypertension, chronic hepatitis C virus infection and arrhythmia. Ophthalmologic examination revealed best corrected visual acuity of 10/10 in the right eye and 4/10 in the left eye from the temporal field. Confrontation test revealed inferonasal visual field loss in the left eye. Direct and indirect light reflexes were normal in both eyes and there was no relative afferent pupillary defect. Anterior segment examination was normal and intraocular pressure was 13 mmHg in both eyes. Dilated fundus exam demonstrated soft exudates consistent with hypertensive

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retinopathy in the right eye. Fundoscopy of the left eye revealed an area of pallor in the superotemporal quadrant and the macula with macular cherry red spot, which were consistent with occlusion of the superotemporal branch of the left retinal artery (Figure 1). On OCT, peripapillary retinal nerve fiber layer (RNFL) thickness was within normal limits (Figure 2). In the patient's visual field, there was an inferonasal defect in the left eye corresponding to the occluded region (Figure 3). The patient was treated with a single dose of 500 cc intravenous dextran-40 and 200 mg intravenous pentoxifylline. In etiologic studies, Doppler ultrasonography revealed an atherosclerotic stenosis in the right and left main carotid arteries and a calcified plaque causing luminal narrowing in the left internal carotid artery. Transthoracic echocardiography revealed second- to third-degree aortic valve regurgitation and first-degree tricuspid valve regurgitation. There was no improvement in visual acuity or visual field despite treatment. At follow-up 7 months later, OCT showed thinning of the superior, inferior and temporal peripapillary RNFL (Figure 4). On the thickness map, ganglion cell layer was thinner in the superior and temporal areas (Figure 5). Decreased vascular density in the superficial and deep capillary plexus consistent with ischemia in

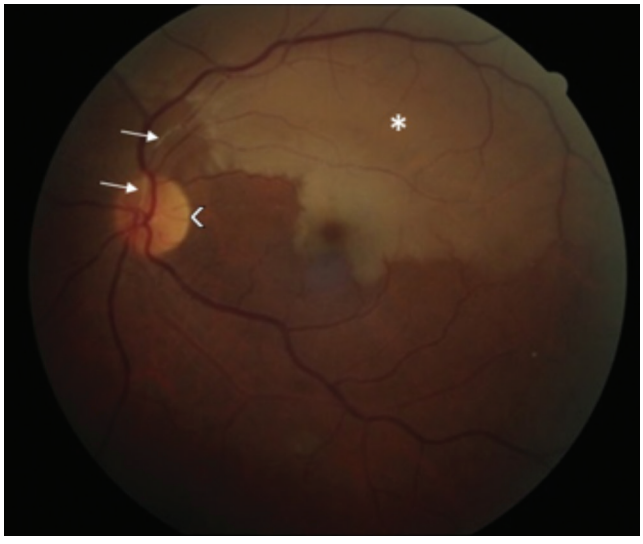


Figure 1. Color fundus photograph in the left eye shows sclerotic plaque in the proximal superotemporal artery and pallor of the superotemporal quadrant, macula and temporal optic disc

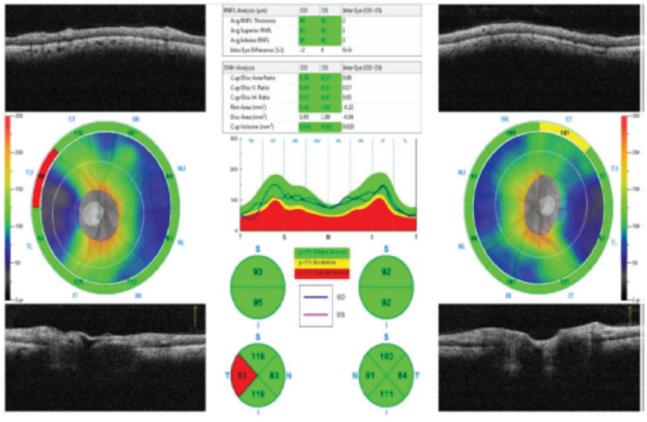


Figure 2. In optical coherence tomography images, the peripapillary retinal nerve fiber layer is within normal limits in both eyes
OD: Right eye, OS: Left eye

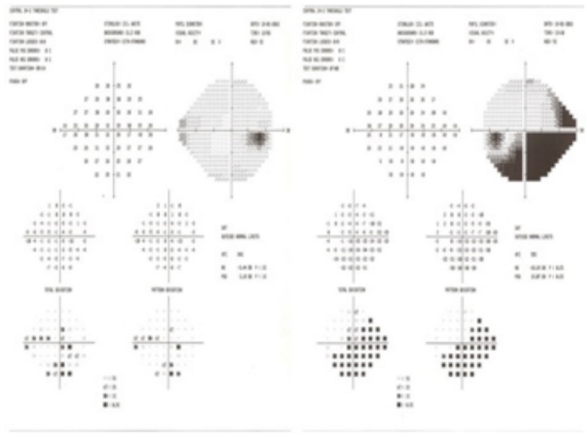


Figure 3. Threshold perimetry test shows loss of visual field in the inferior half of the left eye in accordance with superotemporal artery branch occlusion

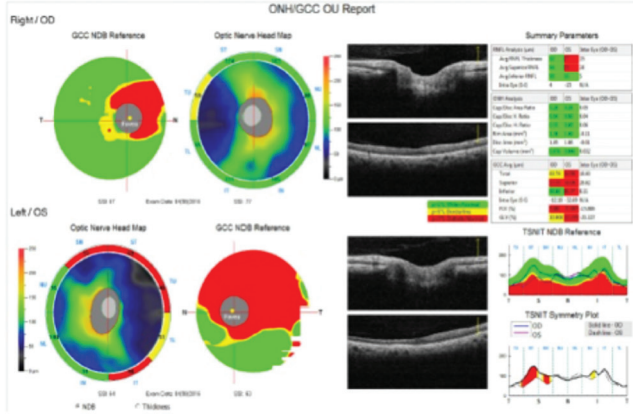


Figure 4. Peripapillary retinal nerve fiber layer thinning is apparent in the superior, inferior and temporal quadrants on optical coherence tomography
OD: Right eye, OS: Left eye

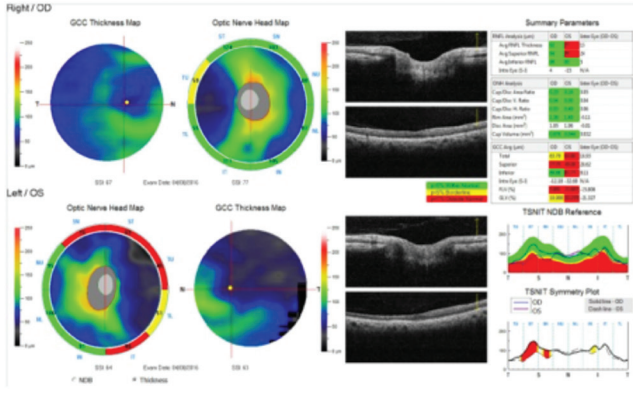


Figure 5. Optical coherence tomography thickness map indicated ganglion cell layer thinning in the superior and temporal quadrants
OD: Right eye, OS: Left eye

the regions supplied by the superotemporal branch of the retinal artery was observed in a 6x6 mm macular field on OCTA (Figure 6). The borders of the ischemic area were more clearly seen in en face images (Figures 6b, d). In optic disc OCTA, capillary density was reduced in the superotemporal region and collateral vessels were present in the area (Figure 7). When compared to the fellow eye, there was a decrease in the macular deep and superficial capillary density in the superior and temporal quadrants (Table 1) and a decrease in peripapillary capillary density in the superior quadrant (Table 2). Visual field loss persisted in post-treatment threshold perimetry (Figure 8).

Discussion

Acute branch retinal artery occlusion causes sudden, painless, unilateral, localized visual field loss in the retinal regions supplied by the affected artery.[6] Although characteristic symptoms and fundus findings are sufficient for diagnosis of retinal artery occlusions, FFA can demonstrate lack of filling or slow filling of affected arteries along with completely normal choroidal perfusion. FFA has been utilized for approximately 50 years to visualize retinal vascular structures by injecting intravenous contrast agent. In the presented case, FFA could not be performed due to kidney disease. OCTA was recently introduced into clinical practice and is used in various retinal vascular diseases. An important advantage of OCTA is that it does not require the use of contrast agents. It can be safely used

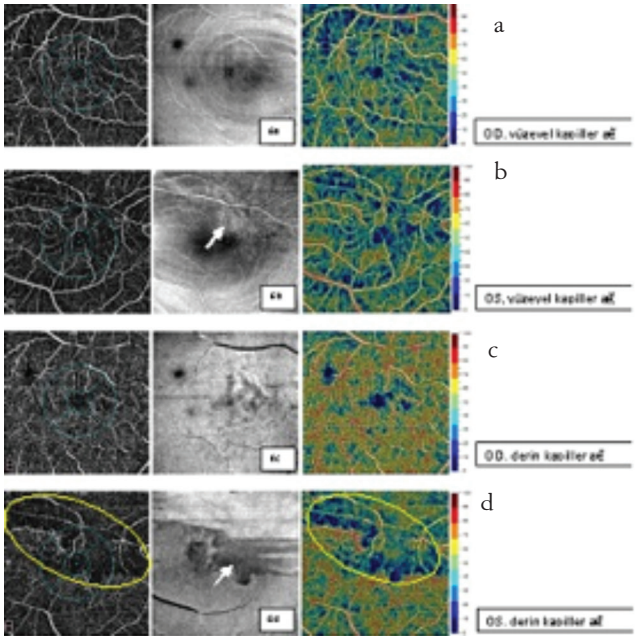


Figure 6. Macular optical coherence tomography angiography shows superficial capillary plexus loss and disruption of the deep capillary plexus in the left eye compared to the fellow eye. Ischemic areas are more clearly seen in en face images (b, d)
OD: Right eye, OS: Left eye

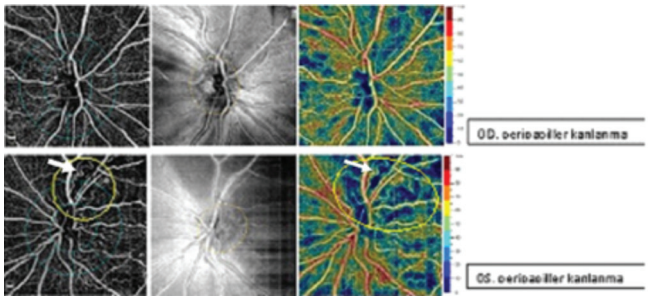


Figure 7. Optic disc optical coherence tomography angiography shows reduced papillary vascular density in the superotemporal optic disc and telangiectatic vessels (circles) in the left eye compared to the fellow eye
OD: Right eye, OS: Left eye

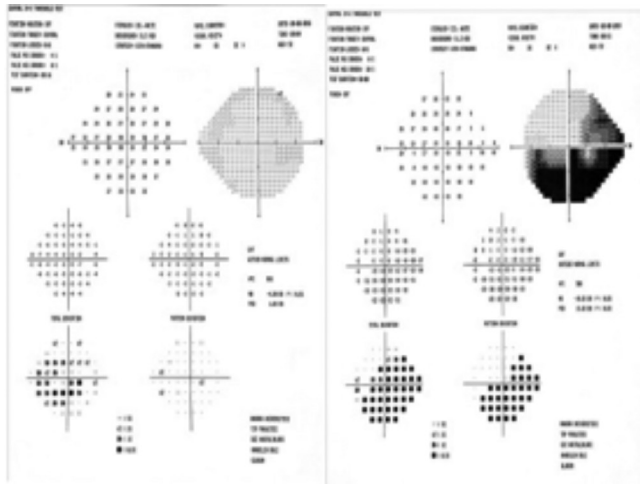


Figure 8. Visual field loss in the left inferior hemisphere persists in threshold perimetry after treatment

Table 1. Comparison of superficial and deep vascular density in macular optical coherence tomography angiography images between the eyes showed a decrease in the superior and temporal quadrants of the left eye

	7 months post-treatment			
	Right eye		Left eye	
	Thickness	Density	Thickness	Density
Temporal	279	57.83	198	38.67
Superior	243	57.47	189	47.30
Nasal	248	47.57	281	46.70
Inferior	278	57.32	282	58.21

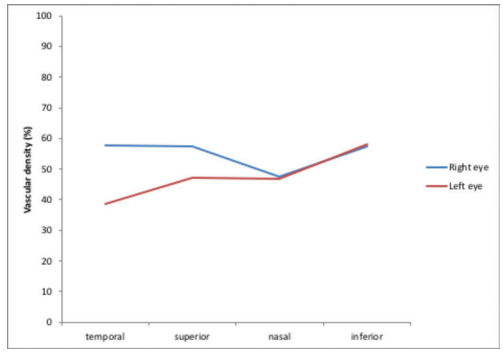
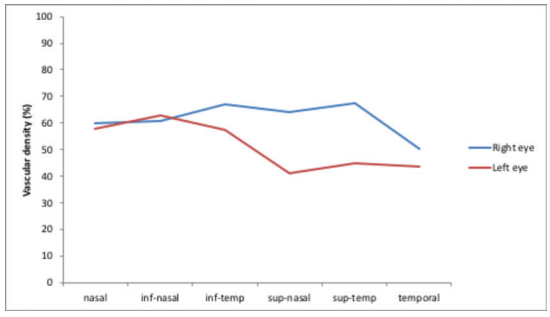


Table 2. Comparison of peripapillary vascular density in optic disc OCTA images between the eyes showed a decrease in the superior quadrant of the left eye		
	7 months post-treatment	
	Right eye	Left eye
Nasal	60.00	57.68
Inferonasal	60.56	62.81
Inferotemporal	66.89	57.52
Superonasal	63.99	40.88
Superotemporal	67.53	44.79
Temporal	50.47	43.55



in patients with diseases limiting the use of contrast agents, such as kidney disease and those who require frequent follow-up. In retinal artery occlusion, edema resolves within weeks due to recanalization and reperfusion but vascular changes and atrophy of the inner retinal layers persist.[7] Therefore, in cases where FFA is contraindicated, retinal morphology of the superficial and deep capillary plexus and the inner retinal layers can be visualized using OCTA with the help of its multilayer analysis. The ischemic area appears hyporeflective in en face OCTA imaging. We observed that in the superficial vascular plexus, not all collaterals were affected but some had disappeared, while there were areas of capillary drop-out and patchy areas of nonperfusion in the deep capillary plexus. In the literature it's said that in branch retinal artery occlusion some capillaries may be dilated while others collapse.[8] Our patient exhibited more pronounced ischemic areas and reduced capillary perfusion in the deep capillary plexus, consistent with the literature.[8,9] The development of telangiectatic vessels was also observed in ischemic areas. Radial peripapillary capillaries were not detected in full-thickness analyses. OCTA images can be acquired in sizes of 3x3, 6x6, or 8x8 mm. Therefore, peripheral vascular lesions may not always be detectable in OCTA. When images are acquired in peripheral gaze position, the macula and optic disc are not included in the image area, thus limiting the use of the eye-tracking feature in the OCTA software and reducing image quality, thereby limiting vascular perfusion analyses. These limitations can be eliminated by using a montage technique or additional lenses for wide-angle imaging.[10,11] There is no consensus regarding the timing and method of retinal artery treatment.[12,13,14] Our patient presented 72 hours after the onset of symptoms and considering his initial visual acuity, we administered pentoxifylline and dextran therapy with the aim of increasing retinal tissue oxygenation via vasodilatation and hemodilution. Anticoagulant and antiaggregant drugs were used because of the patient's comorbid conditions. Although clinical findings can be adequate for the diagnosis of branch retinal artery occlusion, imaging techniques such as FFA can be useful in differential diagnosis. In cases that have contraindication for FFA or other invasive techniques, new imaging modalities such as OCTA will be an effective and safe alternative in diagnosis and follow-up.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Huban Atilla, Concept: Tuna Çelik, Huban Atilla, Design: Tuna Çelik, Huban Atilla, Data Collection or Processing: Tuna Çelik, Feyza Bilen, Analysis or Interpretation: Tuna Çelik, Feyza Bilen, Fatime Nilüfer Yalçındağ, Huban Atilla, Literature Search: Tuna Çelik, Feyza Bilen, Writing: Tuna Çelik, Feyza Bilen, Fatime Nilüfer Yalçındağ, Huban Atilla.

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Case Report

Intravitreal Fluocinolone Acetonide (ILUVIEN) Implant for the Treatment of Refractory Cystoid Macular Oedema After Retinal Detachment Repair

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Abstract
Cystoid macular oedema (CMO) is one of the most frequent postoperative macular complications to cause partial visual recovery after successful retinal detachment (RD) repair. Refractory CMO is difficult to treat and many strategies have been employed with varying degrees of success. We report for the first time the use of ILUVIEN implant to treat refractory CMO after successful RD repair. A 65-year-old female presented with right eye full-thickness macular hole and underwent pars plana vitrectomy, internal limiting membrane peeling and cryotherapy with gas tamponade with 12% C3F8. She subsequently developed right eye macula-on RD and proliferative vitreoretinopathy and required multiple procedures for successful retinal reattachment. Later, she developed CMO that responded to intravitreal triamcinolone injections and intravitreal dexamethasone 0.7-mg implants but recurrence of CMO continued to be a problem. After receiving ILUVIEN intravitreal implant, her visual acuity improved and CMO resolved without recurrence for 13 months. Refractory CMO after RD repair is difficult to treat and in a quarter of cases will not improve without treatment. Our case shows that a single ILUVIEN implant maintained anatomical dry fovea and improved vision. This also demonstrates that ILUVIEN is an effective management strategy to reduce the need for repeated treatments.
Keywords: Cystoid macular oedema, retinal detachment repair, ILUVIEN

Introduction

There are several pre- and postoperative factors that may influence visual outcome after successful retinal detachment (RD) repair. The most important preoperative factors are visual acuity (VA) and the duration of the RD. Cystoid macular oedema (CMO) and epiretinal membranes are the main postoperative factors and CMO appears to be the most frequent postoperative macular complication to cause partial visual recovery after successful RD repair.[1]

The exact aetiology of CMO after RD repair is unclear but inflammation is thought to be an important mechanism.[2,3] Spontaneous resolution of CMO within 2 years postoperatively has been reported in up to 76% of cases.[4] Many strategies have been employed to manage CMO after RD surgery, with varying degrees of success. Different anti-inflammatory medications have been used, including non-steroidal anti-inflammatory medications and topical, periocular and intravitreal corticosteroids.[3,5,6]

ILUVIEN implant (non-biodegradable 0.2 µg/d fluocinolone acetonide; Alimera Sciences, Inc.) is a sustained-release intravitreal steroid lasting up to 36 months that has been approved in the UK to treat chronic refractory CMO in pseudophakic eyes unresponsive to available therapies.[7]

We report for the first time the use of ILUVIEN implant to treat highly refractory CMO after successful RD repair and the outcomes of 20-month follow-up period after ILUVIEN implant.

Case Report

A 65-year-old female presented to our tertiary eye centre

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with 6 weeks' history of painless right eye vision distortion and no history of eye injury or trauma. On examination, VA was 6/24 in the right eye and 6/5 in the left eye. Following slit-lamp biomicroscopy and fundoscopy a diagnosis of right eye full-thickness macular hole was made and optical coherence tomography showed right eye cuff of subretinal fluid, left eye epiretinal membrane and posterior vitreous detachment. Ten years before presentation she had uneventful bilateral phacoemulsification and intraocular lens implantation with no other significant past ocular or medical history.

Eight weeks later, she underwent right eye pars plana vitrectomy, internal limiting membrane peeling and cryotherapy with C3F8 12% gas tamponade. Two weeks postoperatively, she exhibited a flat retina, closed macular hole and her VA had improved to 6/18 with normal intraocular pressure (IOP). Unfortunately, 7 weeks postoperatively, she developed right eye macula-on RD due to proliferative vitreoretinopathy (PVR) in the inferior retina. RD repair was done within 3 days with silicone oil (Densiron 68) tamponade and retinectomy to release the PVR. After 4 months, VA of the right eye after removal of silicone oil was 6/12 with flat retina and closed macular hole.

Four months later, her VA declined to 6/36 in the right eye and remained 6/5 in the left eye and fundus fluorescein angiogram confirmed severe right eye CMO. She underwent right eye posterior sub-Tenon's triamcinolone injection and was started on ketorolac trometamol eye drops (Acular) 3 times/day and oral acetazolamide 250 mg slow-release 2 times/day. Treatment of the CMO during the follow-up period is summarised in Table 1. She received 3 posterior sub-Tenon's triamcinolone injections and 2 intravitreal triamcinolone injections within 14 months with no complications. The CMO initially responded to each triamcinolone injection but later recurred (Figure 1A).

The patient then received 4 intravitreal dexamethasone 0.7-mg implants (Ozurdex; Allergan, Inc.) uneventfully within 15 months, which maintained a dry fovea for a longer period but the CMO recurred again (Figure 1B, C, D, E). She also received a trial of anti-vascular endothelial growth factor (Avastin) but there was no response. At that point, the patient decided that she no longer wanted repeated injections and decided to wait until her fund application to receive ILUVIEN implant as special case was approved.

Table 1. Summary of treatments for cystoid macular oedema during the follow-up period

Time after successful RD repair	Treatment
9 months	1st sub-Tenon's triamcinolone injection
10 months	2nd sub-Tenon's triamcinolone injection
11 months	3rd sub-Tenon's triamcinolone injection
17.5 months	1st IVTA
23 months	2nd IVTA
39.5 months	1st Ozurdex implant
47 months	2nd Ozurdex implant
52 months	3rd Ozurdex implant
54.5 months	4th Ozurdex implant
64 months	Intravitreal Avastin injection
88 months	ILUVIEN implant

RD: Retinal detachment, IVTA: Intravitreal triamcinolone

Her refractory CMO persisted after 2 years without treatment. Finally, she received ILUVIEN intravitreal implant. In the first week she developed mild right eye anterior uveitis; IOP was 27 mmHg in the right eye and 18 mmHg in the left eye. These markedly regressed within a week on dexamethasone drops and latanoprost drops and topical medications were stopped within 4 weeks. At the time of this report, it is 20 months since receiving the ILUVIEN implant and she still has a dry fovea with right eye VA of 6/18 (Figure 2).

Discussion

Refractory CMO after RD repair is difficult to treat and in a quarter of cases it will not improve without treatment. Intravitreal corticosteroid injections have shown to be an effective treatment option. We are not aware of any published literature in which ILUVIEN was used to treat this condition. This approach not only maintained an anatomical dry fovea but also provided visual improvement with a single ILUVIEN implant. This also demonstrates that ILUVIEN is an effective management strategy to reduce the need for repeated treatments. There is a risk of IOP

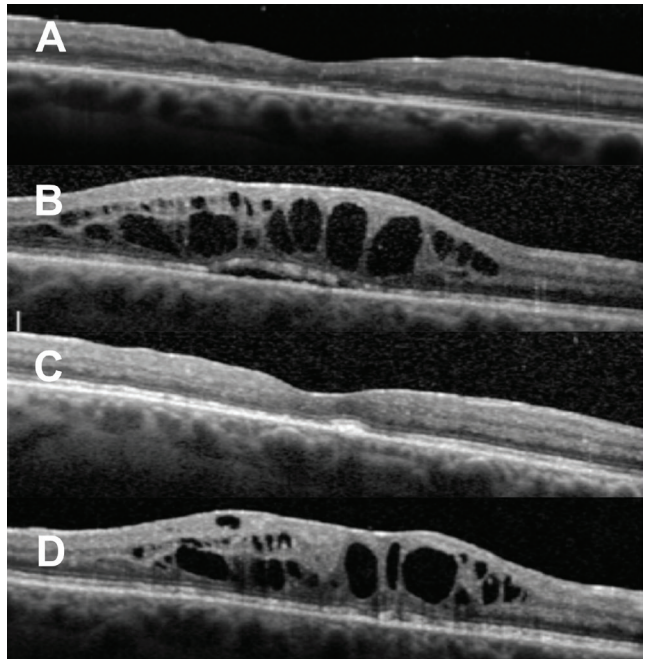

Figure 1. Optical coherence tomography images. A) One month after the first intravitreal triamcinolone injection. B) One month before the first Ozurdex implant, C, D) One month and 5 months after the first Ozurdex implant, respectively

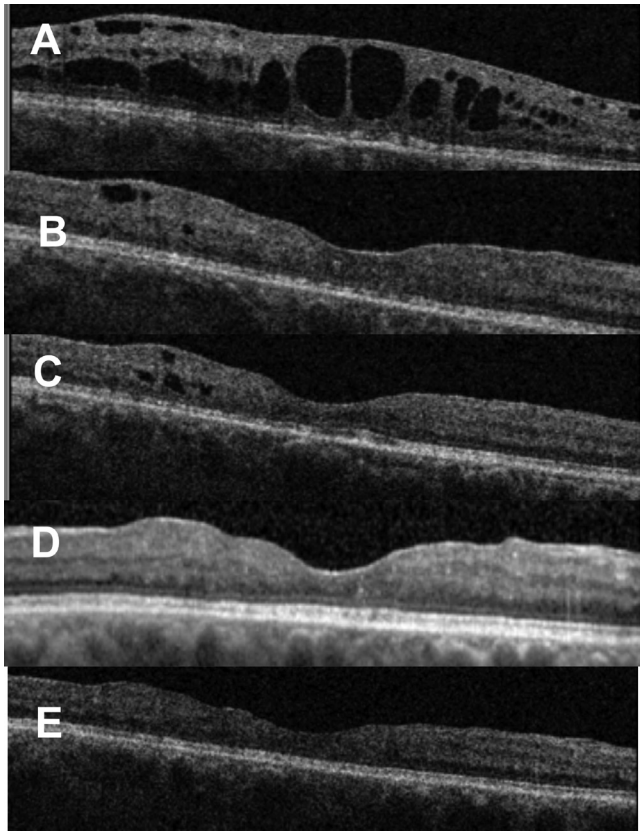

Figure 2. Optical coherence tomography images. A) Five months before ILUVIEN implant. B, C, D, E) Images taken 1, 6, 13, 20 months after ILUVIEN implant, respectively

elevation after receiving ILUVIEN intravitreal implant but in our case IOP was well controlled with short-term treatment. Further investigation of more cases with longer follow-up is needed. Better understanding of the exact aetiology of CMO after RD repair will lead to the development of more targeted treatment options.

Ethics

Informed Consent: It was taken.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Fadi Alfaqawi, Arijit Mitra, Ash Sharma, Concept: Fadi Alfaqawi, Ambreen Sarmad, Arijit Mitra, Ash Sharma, Design: Fadi Alfaqawi, Data Collection or Processing: Fadi Alfaqawi, Ambreen Sarmad, Analysis or Interpretation: Fadi Alfaqawi, Ambreen Sarmad, Literature Search: Fadi Alfaqawi, Ambreen Sarmad, Kholoud Ayesh, Writing: Fadi Alfaqawi, Ambreen Sarmad, Kholoud Ayesh.

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

Financial Disclosure: The authors declared that this study received no financial support.

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Letter to the Editor

Kajal-induced Artefact Simulating a Ciliary Body Tumor on Magnetic Resonance Imaging

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**VK Clinic, Ophthalmology Clinic, Chennai, India

Dear Editor,

It is well known that magnetic resonance imaging (MRI) is a boon to the field of neurological and orbital imaging but it is equally important to be aware of the various artefacts and practical issues associated with them. Here we report such an instance where we encountered an eyeball lesion in the region of the ciliary body which disappeared on more detailed evaluation. Awareness of the possibility of such pseudolesions and the reasons for their occurrence is essential to avoid misinterpretation as true pathological lesions.

A 34-year-old female presenting with history of headache was found to have a small nodular T2 hypointense lesion with a thin hyperintense border in the medial aspect of the left eyeball in the retrolental region (Figure 1). There was blooming on the gradient images but the lesion was not seen clearly on other images. The postgraduate resident raised the possibility of a ciliary body tumor.

However, as the lesion appearance was not characteristic of any condition, I wished to see the patient in person to see if she had applied any cosmetic products. She had applied kajal (an eye cosmetic) before the MRI scan and had not removed it. We thought the observed lesion could be due to susceptibility artefact arising from the applied kajal. We rescanned the patient after asking her to wash her face and making sure that there was no kajal around her eyes. Repeat MRI scan with routine T2 and thin heavily T2-weighted sections showed no lesion in the eyeball (Figure 2). A careful ophthalmological examination with dilated pupils also ruled out a solid ciliary body mass.

Patients having MRI scans as outpatients may present for examination after applying cosmetics including eye makeup, face lotions, nail polish and hair loss concealers. Eye and face makeup products may cause artefactual distortion of the orbital contents due to the iron oxide in the pigments used to produce dark shades of makeup. Though these artefacts do not interfere with brain imaging, it precludes imaging of orbital contents if they are of clinical concern. This susceptibility artefact is usually propagated along the frequency-encoding axis of the images.[1] Susceptibility artefacts caused by eye makeup may mimic ocular disease such as ciliary body melanoma or cyst.[2] The susceptibility artefacts are expectedly more prominent in association with 3-Tesla MR systems than lower field strengths. Escher and Shellock[3] in their study involving 38 different types of cosmetics on 3-Tesla MRI found that all 5 of the eyeliners, all 3 of the mascaras, 3 of the 10

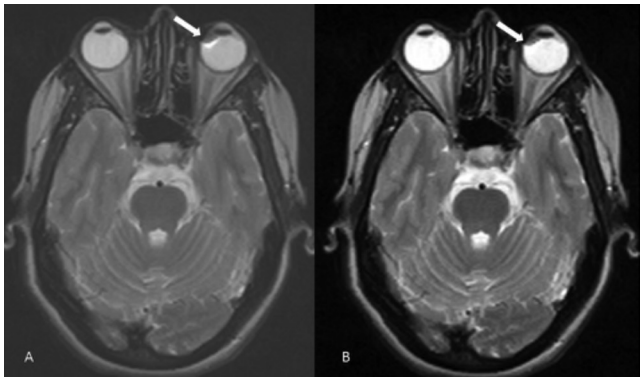

Figure 1. Axial T2-weighted images (A, B) show small nodular T2 hypointense lesion with a thin hyperintense border in the medial aspect of the left eyeball in the retrolental region (arrows)

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Received: 13.12.2017 **Accepted:** 17.01.2018

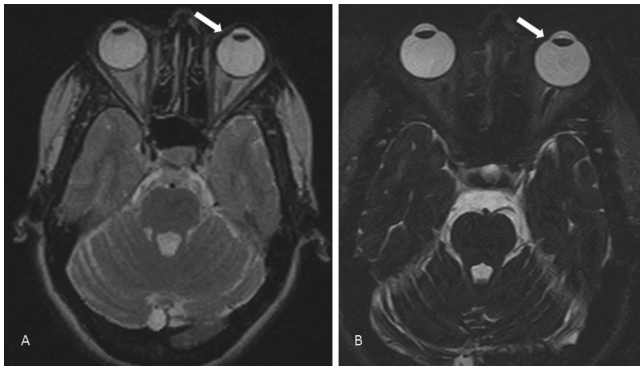

Figure 2. Axial 5 mm-thickness T2-weighted image (A) and thin heavily T2-weighted 1 mm section (B) showed no lesion in the eyeball (arrows)

eye shadows and the 1 hair concealer created small to very large artefacts which were related to the presence of iron oxide or other metal-based ingredient.

As it is prudent to prevent these artefacts, it would be very wise to advise patients to thoroughly remove all cosmetics before they arrive for MRI exams. According to American College of Radiology guidelines, all individuals undergoing an MR procedure must remove all readily removable metallic personal belongings and devices, body piercings (if removable), cosmetics containing metallic particles (such as eye make-up) and clothing items with metallic fasteners, hooks and zippers.[4] Though ferromagnetic detection systems have been used in screening MRI patients primarily to prevent accidents related to external ferromagnetic objects like pocket knives, a pillar-type ferromagnetic detection system may be a useful adjunct to screen patients for biomedical implants and embedded foreign bodies.[5]

We would like to emphasize the importance of removing cosmetic products from the parts of the body to be scanned by the MRI to avoid wrong diagnosis and loss of diagnostic information.

Keywords: Artifact, magnetic resonance imaging, susceptibility

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Venkatraman Indiran, L. Raguram Subha, Jagannathan Kokilavani, Concept: Venkatraman Indiran, L. Raguram Subha, Jagannathan Kokilavani, Design: Venkatraman Indiran, L. Raguram Subha, Jagannathan Kokilavani, Data Collection or Processing: Venkatraman Indiran, L. Raguram Subha, Analysis or Interpretation: Venkatraman Indiran, L. Raguram Subha, Literature Search: Venkatraman Indiran, L. Raguram Subha, Jagannathan Kokilavani, Writing: Venkatraman Indiran, Jagannathan Kokilavani.

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

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http://www.isot2018.si/

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Distance Visual Acuity Measurements Equivalency Table

						Spatial Frequency
ETDRS Standard Line Number	**Qualitative Measurements**	**Decimal**	**Snellen**	**LogMAR**	**Angle of Resolution**	**Cycle per Degree**
-3		2.00	20/10	-0.30	0.5	60.00
-2		1.60	20/12.5	-0.20	0.625	48.00
-1		1.25	20/16	-0.10	0.8	37.50
0		1.00	20/20	0.00	1	30.00
		0.90		0.05		27.00
1		0.80	20/25	0.10	1.25	24.00
		0.70		0.15		21.00
2		0.63	20/32	0.20	1.6	18.75
		0.60		0.22		18.00
3		0.50	20/40	0.30	2	15.00
4		0.40	20/50	0.40	2.5	12.00
		0.30		0.52		9.00
5		0.32	20/63	0.50	3.15	9.52
6		0.25	20/80	0.60	4	7.50
7		0.20	20/100	0.70	5	6.00
8		0.16	20/125	0.80	6.25	4.80
9		0.13	20/160	0.90	8	3.75
10	CF from 6 m	0.10	20/200	1.00	10	3.00
11	CF from 5 m	0.08	20/250	1.10	12.5	2.40
12	CF from 4 m	0.06	20/320	1.20	16	1.88
13	CF from 3 m	0.05	20/400	1.30	20	1.50
14		0.04	20/500	1.40	25	1.20
15	CF from 2 m	0.03	20/640	1.51	32	0.94
16		0.025	20/800	1.60	40	0.75
17		0.020	20/1000	1.70	50	0.60
18	CF from 1 m	0.016	20/1250	1.80	62.5	0.48
21	CF from 50 cm	0.008	20/2500	2.10	125	0.24
31	HM from 50 cm	0.0008	20/25000	3.10	1250	0.02

Abbreviations:
CF: Counting fingers, HM: Perception of hand motions, m= meter, cm= centimeter

Equations of conversions for Microsoft Excel:
- Log10 (Decimal Acuity)= LogMAR Equivalent
Power (10; -Logmar Equivalent)= Decimal Acuity (for English version of Microsoft Excel)
Kuvvet (10; -Logmar Equivalent)= Decimal Acutiy (for Turkish version of Microsoft Excel)

Reference
Eğrilmez S, Akkın C, Erakgün T, Yağcı A. Standardization in evaluation of visual acuity and a comprehensive table of equivalent. Turk J Ophthalmol. 2002;32:132-136.

Near Visual Acuity Measurements Related Equivalency Table*														
Snellen	**20/400**	**20/320**	**20/250**	**20/200**	**20/160**	**20/125**	**20/100**	**20/80**	**20/63**	**20/50**	**20/40**	**20/32**	**20/25**	**20/20**
Decimal	0.05	0.063	0.08	0.10	0.125	0.16	0.20	0.25	0.32	0.40	0.50	0.63	0.80	1.00
Jaeger	J19	J18	J17	J16	J15	J14	J13	J11	J9	J7	J5	J3	J2	J1
Times New Roman Point	60	48	36	30	24	18	14	12	10	8	6	5	4	3
LogMAR	1.3	1.2	1.1	1.0	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.0

*Adapted from Rabbets RB: Visual acuity and contrast sensitivity. In: Rabbets RB, editor. Clinical visual optics. Edinburgh: Butterworth-Heinemann, 1998:19-61.