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

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

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EDITORIAL

2019 Issue 5 at a Glance:

This issue of our journal includes six original research articles, one review, and four case reports on various topics related to ocular health, objectively investigated by scientists from Turkey and abroad, that offer valuable contributions to our knowledge base.

The first original article in our journal presents initial 6-month outcomes of Descemet membrane endothelial keratoplasty (DMEK) in 100 eyes diagnosed with pseudophakic bullous keratopathy (PBK) and Fuchs endothelial dystrophy (FED). Based on changes in best corrected visual acuity (BCVA) and donor corneal endothelial cell density (ECD) values, the study showed that different donor tissue preparation techniques for DMEK were equally effective and that a staged or combined approach could be used in eyes with FED and cataract with comparable results. The authors emphasized that the results are promising for both FED and PBK patients and expressed pride in reporting the first results from Turkey (see pages 235-242).

The second article of this issue examines the effect of phacoemulsification surgery and intraocular lens implantation on functional balance in adults. The authors report that the significant improvement in visual acuity following cataract surgery enhances patients' functional balance and enables them to move more comfortably and confidently, thereby increasing their quality of life (see pages 243-249).

A study by Hasanreisoğlu et al. evaluating the long-term results of intravitreal dexamethasone implant (DEX) in eyes with noninfectious uveitis demonstrated that this treatment can facilitate overall disease control by suppressing ocular inflammation locally without modifying patients' systemic immunomodulatory therapy. The authors also highlight the importance of monitoring patients receiving multiple injections for IOP increase and cataract progression (see pages 250-257).

In another original study, Karaçorlu et al. retrospectively evaluated neovascular age-related macular degeneration (nAMD) patients treated with a newly described "risk-based algorithm-guided treatment protocol" that is individualized according to the patient's lesion characteristics and visual acuity of the fellow eye, and reported achieving similar visual outcomes with fewer injections compared to other established treatment regimens (see pages 258-269).

In patients with conditions affecting the anterior and posterior segments secondary to ocular traumas, problems such as edema, distortion, and scarring may reduce corneal transparency and interfere with visualization of the posterior segment during pars plana vitrectomy (PPV). While such cases were considered inoperable in the past, favorable outcomes can now be attained using temporary keratoprostheses. Mayalı et al. evaluated the efficacy of combined PPV and penetrating keratoplasty (PK) surgery with the Landers wide-angle temporary keratoprosthesis, and concluded that the combined procedure performed using this device provides a good opportunity to preserve remaining vision and achieve anatomical reconstruction in patients with severe anterior and posterior segment injuries (see pages 270-276).

In patients with dislocated crystalline lens or intraocular lens (IOL) due to lack of intraoperative capsule and zonular support, the choice of secondary IOL to be implanted is also important. In addition, previous vitrectomy in the eye also adds a new dimension to the issue. In their study aiming to answer this question, Ersöz et al. determined that simultaneous dislocated IOL extraction and secondary iris-claw IOL implantation is a fast and safe procedure in vitrectomized eyes, as in non-vitrectomized eyes (see pages 277-282).

In this issue's review entitled "The Management of Uveitic Glaucoma in Children", Kalogeropoulos et al. discuss the current literature on the treatment of uveitic glaucoma in pediatric patients. The authors note that the management of uveitic glaucoma in children is extremely challenging due to the underlying uveitis and the different response to surgery shown by pediatric patients, and emphasize that treating uveitic glaucoma requires a comprehensive and individualized approach including both pharmacotherapeutic and surgical methods. The authors also highlight the fact that although the prognosis of pediatric uveitic glaucoma has improved significantly in recent years, further research into the important issues of increasing surgical success rates and reducing complications is still warranted (see pages 283-293).

Shirvani et al. present the case of an immunocompetent woman with endogenous *Candida* endophthalmitis following trans-

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

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EDITORIAL

urethral lithotripsy. They note that while this condition is usually seen in patients with serious underlying risk factors, it can also occur in an immunocompetent patient, and early diagnosis and timely treatment can provide better visual prognosis (see pages 294-296).

Balcı et al. reported a patient with syphilis whose initial and only presenting sign was unilateral intermediate uveitis, with no other dermatological, neurological, or systemic involvement, reminding us that syphilis can have various ocular manifestations and should be considered in patients presenting with ocular inflammatory conditions that cannot be explained with history and systemic evaluation (see pages 297-299).

Optic disc drusen is an important clinical entity that can be confused with true papilledema because it causes disc elevation and blurring of the margins. Biçer and Atilla diagnosed optic disc drusen in a 17-year-old male who presented with headaches and exhibited bilateral optic disc elevation and blurred margins on fundus examination, and report that optical coherence tomography angiography (OCTA) also facilitated diagnosis in addition to B-mode ultrasonography and fundus autofluorescence imaging. They also state that OCTA evaluation may play an important role in the early detection of potential ischemic complications. (See pages 300-304)

In the final case report of this issue of our journal, McElnea et al. describe a 78-year-old white woman who presented with pain and difficult abduction in her right eye. Computed tomography and MRI of her right eye revealed a mass lesion consistent with metastatic melanoma and involving the medial rectus muscle. Following biopsy of the right medial rectus, the lesion was histopathologically diagnosed as metastatic melanoma. The patient had undergone orbital exenteration of her left eye 12 years earlier due to choroidal melanoma, and the authors stated that with this history, atypically located uveal melanoma metastasis may indicate systemic disease and recurrence. (See pages 305-309)

Respectfully on behalf of the Editorial Board,

Tomris Şengör, MD

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Turk J Ophthalmol 2019;49:235-242

Original Article

Six-Month Results of Descemet Membrane Endothelial Keratoplasty in 100 Eyes: First Clinical Results from Turkey

Osman Şevki Arslan, Cezmi Doğan, Burak Mergen

İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract

Objectives: To evaluate the 6-month outcomes of Descemet membrane endothelial keratoplasty (DMEK) in patients with pseudophakic bullous keratopathy (PBK) and Fuchs' endothelial dystrophy (FED) in a single center in Turkey.

Materials and Methods: The medical records of patients who underwent DMEK were reviewed retrospectively. Best corrected visual acuity (BCVA), donor corneal endothelial cell density (ECD), donor age, duration in solution after obtaining the donor tissue, and duration after exitus of the donor were evaluated preoperatively and BCVA, ECD, and ECD loss (%) at postoperative 6 months were evaluated postoperatively. Graft detachment, graft failure, and pupillary block were recorded as surgical complications. Patients with cataract and FED underwent combined or staged procedures. Two different graft preparation techniques were utilized: 8 and 9.5 mm.

Results: One hundred eyes of 74 patients were included in the study. Fifty-two of the eyes had FED and the remaining 48 had PBK. Mean ECD loss in 6 months was 29.2±4.4% in the FED group and 29.7±5% in the PBK group (p=0.415). Mean BCVA at 6 months was 0.06±0.05 in the patients with FED and 0.07±0.05 in the patients with PBK (p=0.378). Mean ECD loss in 6 months was 28.3±5.3% in the 8 mm group vs. 29.7±4.5% in the 9.5 mm group (p=0.255), and 28.5±5.6% in the combined group vs. 29.8±2.9% in the staged group (p=0.279).

Conclusion: Different graft preparation techniques can be utilized with similar efficiency for DMEK surgery. A staged or combined approach can be used efficiently in the management of patients with FED and cataract. Our results are promising both for PBK and FED patients.

Keywords: DMEK, Fuchs' endothelial dystrophy, pseudophakic bullous keratopathy

Introduction

After the introduction of deep lamellar endothelial keratoplasty (DLEK) in 2001 by Terry and Ousley[1], a new concept evolved for patients with corneal endothelial pathologies. But the field of keratoplasty took another big step forward with the description of a new technique called Descemet's stripping endothelial keratoplasty (DSEK) in 2004.[2] Gorovoy[3] modified the DSEK technique using an automated microkeratome to dissect the donor lenticule (Descemet's stripping automated endothelial keratoplasty; [DSAEK]). Later, Melles et al.[4] described the Descemet's membrane endothelial keratoplasty (DMEK) technique, in which the surgeon can manually prepare the donor Descemet's membrane-endothelial layer (DE) complex.

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In the 2016 Eye Banking Statistical Report of the Eye Bank Association of America, the results showed that there is an increasing trend toward DMEK surgery starting from 2011, while the use of DSAEK is gradually declining.[5] The results also indicate that penetrating keratoplasty has shown a declining trend relative to endothelial keratoplasty in recent years. While the most common procedure for patients with Fuchs' endothelial dystrophy (FED) and cataract was penetrating keratoplasty in the past, endothelial keratoplasty is now the most preferred technique for surgical management according to the Eye Banking Statistical Report. However, there is no consensus about the optimal management of patients with FED and cataract. Two different approaches have been described for its management: 1) the combined technique, in which the surgeon performs endothelial keratoplasty and cataract surgery in a single session, and 2) the staged technique, in which the surgeon performs the surgeries in two different sessions. Several studies have been conducted showing no difference in the final visual acuity and endothelial cell density between these two approaches.[6,7,8]

Another increasing trend in the use of DMEK surgery has been observed in patients with pseudophakic bullous keratopathy (PBK). Numerous studies have been conducted to show the efficiency of DMEK surgery in this patient group.[9] However, the effect of different donor preparation techniques on surgical success has not been studied.

Although several studies have presented the early and late results of DMEK surgery, no results have been reported from Turkey to date. In this study, we present the initial 6-month results of patients who underwent DMEK surgery in a single tertiary center in Turkey. We share our surgical approach for patients with FED and PBK and compare the outcomes with the current literature in terms of the endothelial cell density (ECD) and best corrected visual acuity (BCVA). In addition, we evaluated the effect of different donor preparation techniques on surgical success and compared the staged and combined techniques.

Materials and Methods

The medical records of patients who underwent DMEK for FED or PBK between 2014 and 2018 were investigated retrospectively. Patients with coexisting ocular pathology (e.g., glaucoma, uveitis) other than FED, PBK, or cataract that may interfere with BCVA and patients who had previous surgeries other than cataract surgery were excluded from the study. In addition, patients who failed to attend regular follow-ups in the first 6 months were excluded from the study (n=12). Approval from the local ethics committee was received. The study adhered to the tenets of the Declaration of Helsinki and informed consent was obtained from all patients before surgery.

BCVA, donor corneal ECD, donor age, duration in solution after obtaining the donor tissue, and duration after exitus of cadaver were evaluated preoperatively and BCVA, ECD, and ECD loss (%) at postoperative 6 months were evaluated postoperatively. Graft detachment, graft failure (development of corneal edema without any detachment), and pupillary block were recorded as surgical complications. For the patients who had cataract and FED, combined or staged procedures were performed.

ECD of the patients was evaluated with a specular microscope (Cellcheck SL Konan, Japan). Donor ECD values and other information about the donor were obtained from the Eye Bank of İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine. Percentage of ECD loss was calculated as the difference between the donor ECD and ECD of the patient at postoperative 6 months. BCVA was measured using the Snellen chart, and the logarithm of the minimal angle of resolution (LogMAR) equivalent was used for statistical analysis.

Patients had complete slit-lamp examination preoperatively and at postoperative 1 day, 3-6 days, 1 month, 3 months, and 6 months, and when needed between these time points.

DMEK Donor Graft Preparation

For dissection of the Descemet membrane graft, cornea-scleral buttons from donor globes were obtained from the cadavers and stored in Optisol GS (Bausch & Lomb Surgical, Irvine, CA, USA) solution (4°C). Endothelial cell morphology and viability were evaluated with specular microscopy in the eye bank for an optimal selection of appropriate cornea for the transplantation. Donor corneas with ECD above 2300 cells/mm^2 were used. Donor age was between 50 and 65 years, and tissue from donors with systemic diseases that can affect graft survival was not used for the surgeries.

For DMEK graft preparation, we preferred two different approaches, one using an 8-mm donor punch for dissection and the other using a 9.5-mm donor punch.

In the first approach, after corneal trephination with the 8-mm donor punch, the endothelial side of the donor cornea was elevated with the help of a sponge and its edges were held with forceps for endothelial stripping.

In the second approach, a 9.5-mm modified donor punch was used for partial corneal trephination in the donor cornea and endothelial stripping was performed with the help of a forceps. Firstly, a corneal stromal area without the endothelial layer was obtained after stripping. Then, after a complete incision was performed with a 2-mm dermal punch over this area, the endothelial layer was returned to its original place. Afterward, an "F" mark was made on this area with a sterile marker and a Sinskey hook. The corneal trephination was then completed with an 8-mm donor punch to yield a DE complex scroll with the "F" mark on its Descemet membrane side (Figure 1).

After corneal trephination with either of these two techniques (8 mm or 9.5 mm technique), the DE complex scroll was used for the surgery immediately after preparation. The DE complex was stored in Optisol GS corneal storage medium during preparation of the recipient bed.

DMEK Surgical Technique

When corneal epithelial edema prevented visualization of the anterior chamber, epithelial stripping was performed for better visualization. After creating side ports with a 20-gauge (G) microvitreoretinal (MVR) blade, a circular 8-mm descemetorhexis was performed under ophthalmic viscoelastic device (OVD) with reverse Sinskey. Cohesive OVD was preferred and the OVD was removed by irrigation and aspiration after descemetorhexis. In some of the patients, peripheral iridectomy was performed with a 23-G vitrector. The donor DE complex was stained with Trypan blue.

The tip of an IOL injector cartridge was combined with a silicone tubing set to create the custom-made injector (Figure 2). The DE complex scroll was loaded by suction into this injector, then injected through the corneal tunnel incision into the anterior chamber. Three 10-0 nylon sutures were used to close the main corneal incision. After forming a shallow anterior chamber with the help of bimanual manipulations on the corneal surface, the donor DE complex was placed with its endothelial side facing the iris and the Descemet membrane side facing the corneal stroma. The "F" mark was checked to ensure correct positioning of donor grafts prepared with the 9.5-mm technique. After complete unrolling, an air bubble was injected through the side port under the graft to facilitate attachment with the recipient corneal stroma. Then the anterior chamber was completely filled with air for 60-120 minutes for complete attachment and an air-fluid exchange was performed after intraocular pressure reached a level that caused the patient to feel deep pain or pressure in his/her globe. A bandage contact lens was applied on eyes that had epithelial stripping. Patients who underwent peripheral iridectomy were observed in the operating room for another hour for the development of pupillary block. The steps of the surgery are depicted in Figure 3.

Postoperative Follow-up

Patients who underwent peripheral iridectomy were ordered to lay in supine position for 1 hour and sit for 15 minutes until 12 am. After 12 am they were ordered to lay in supine position for 2 hours and sit for 15 minutes again. In all of the patients, we observed that the remaining air filled approximately 50% on the second day and no air was observed after 3-5 days. Topical moxifloxacin and dexamethasone drops were prescribed for use every 2 hours on the first day, followed by 6 times daily. The medications were tapered until discontinuation.

Phacoemulsification Technique (Combined and Staged)

Two different approaches were implemented for patients who had FED and cataract. The first approach was combined DMEK with phaco surgery and the second approach was staged procedure in which the patient had cataract surgery and IOL implantation firstly and had another session for DMEK.

When the combined technique was preferred, the main tunnel was kept shorter than usual. The main incision for the tunnel was 2.4 mm in all of the patients. The radius of the capsulorhexis area was 4.5-5 mm to prevent the intraocular lens (IOL) entering the anterior chamber from the capsular bag after implantation. IOL with 6 mm radius of the optic piece was used in all of the patients. Since the capsulorhexis area was small,

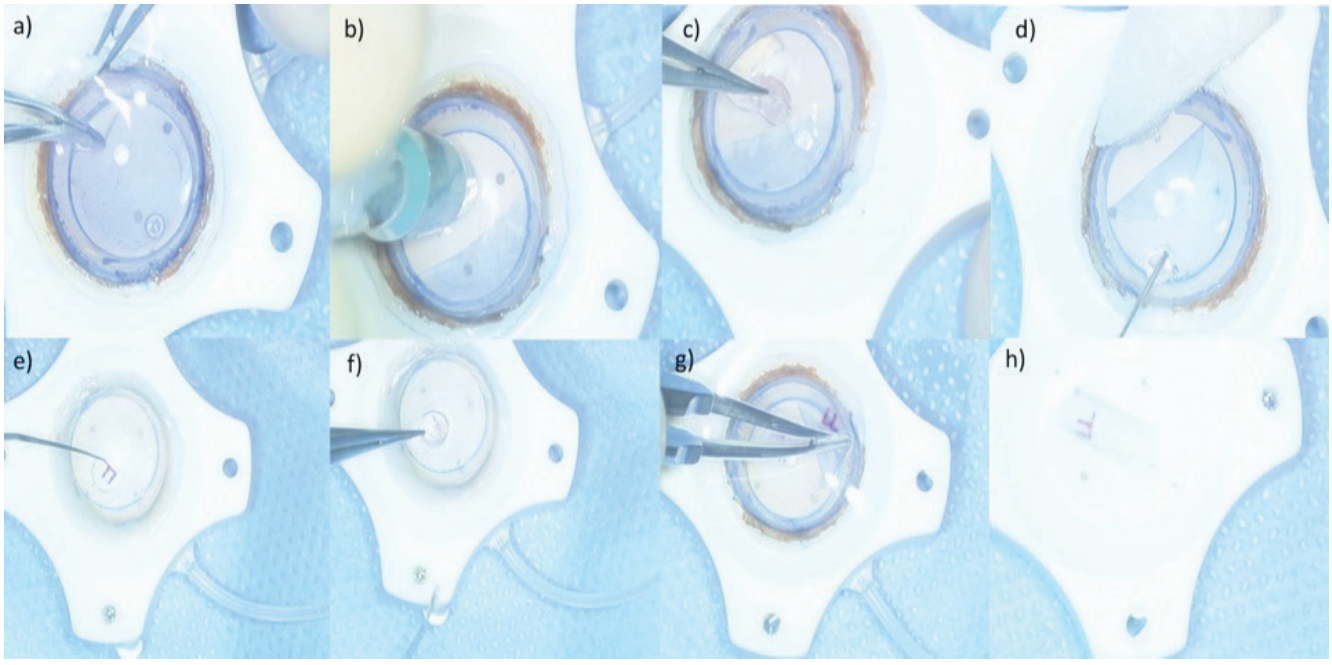

Figure 1. A 9.5-mm modified donor punch was used for partial corneal trephination in the donor cornea and endothelial stripping was performed with the help of a forceps (a). A corneal stromal area without the endothelial layer was obtained after stripping. Then, after a complete incision was performed with a 2-mm dermal punch over this area (b), the endothelial layer was replaced (c-d). An "F" mark was made in this area using a sterile marker and Sinskey hook (e-f). Corneal trephination was then completed with an 8-mm donor punch to yield a Descemet membrane-endothelial layer complex scroll with the "F" mark on the Descemet membrane side (g-h)

a capsular tension ring (CTR) was used in all of the patients before IOL implantation. No dispersive viscoelastic material was used during the cataract surgery to prevent graft dislocation after DMEK. After implanting the IOL and clearing all the viscoelastic material behind the IOL, additional viscoelastic material was applied into the anterior chamber and peripheral iridectomy was performed with a 23-G vitrectomy probe. Then descemetorhexis was performed under viscoelastic material. After descemetorhexis, the main incision was enlarged to 3 mm and DMEK procedures were followed.

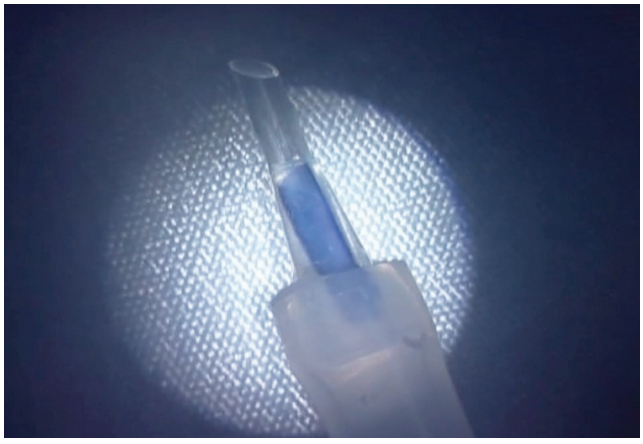

Figure 2. The tip of an IOL injector cartridge was combined with a silicone tubing set to create the custom-made injector

Epithelial scraping was performed in patients with prominent corneal edema preventing visualization of the anterior chamber before combined surgery. A bandage contact lens was applied at the end of the surgeries.

When the staged procedure was preferred, the previously described soft shell technique was utilized for the cataract surgery and DMEK was performed in another session.

Statistical Analysis

Statistical analysis of the data was performed using SPSS software (version 21.0). The Kolmogorov–Smirnov test was used to evaluate the sample distribution. A Student's t-test was used to compare the mean values of two independent groups with normal distribution and the Mann-Whitney U test was used to compare continuous variables with non-normal distributions. Wilcoxon's test was used to compare the mean values of two dependent groups. P values below 0.05 were considered statistically significant.

Results

One hundred eyes of 74 patients were included in the study. The etiology was FED in 52 eyes (52%) of 26 patients and PBK in 48 eyes (48%) of 48 patients. The mean age of the patients with FED was 67.5±5.1 years and it was 62.4±7.5 years in the patients with PBK (p=0.004). While 7 (26.9%) of 26 patients with FED were male and 19 (73.1%) were female, 28 (58.3%) of

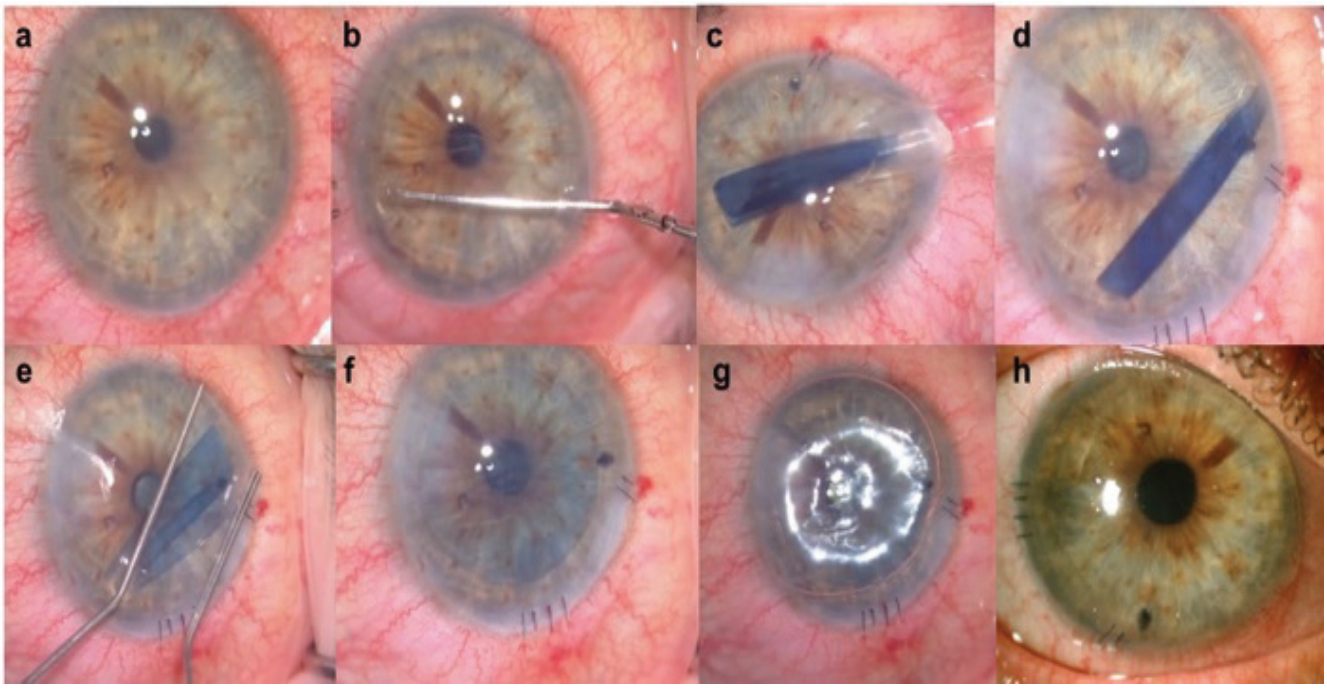

Figure 3. The steps of before Descemet membrane endothelial keratoplasty surgery. Preoperative slit-lamp photograph of a patient with Fuchs' endothelial dystrophy (a). A circular 8-mm descemetorhexis was performed under ophthalmic viscoelastic device (b). The Descemet membrane-endothelial layer (DE) complex scroll was loaded by suction into the custom-made injector and the graft was injected through the corneal tunnel incision into the anterior chamber (c-d). After forming a shallow anterior chamber with the help of bimanual manipulations on the corneal surface, the donor DE complex was positioned with its endothelial side facing the iris and the DM side facing the corneal stroma (e). After complete unfolding (f), an air bubble was injected through the side port under the graft to facilitate attachment with the recipient corneal stroma (g). Slit-lamp photograph of the same patient at postoperative 2 weeks (h)

48 patients were male and 20 (41.7%) were female in the PBK group (p=0.01). The cause of PBK was toxic anterior segment syndrome (TASS) in 4 (8.3%) of 48 eyes.

FED vs. PBK

The baseline conditions for FED and PBK groups before DMEK procedure are summarized in Table 1. The groups were homogenous in terms of donor ECD, donor age, duration of donor tissue in solution, and duration of obtaining the donor tissue after exitus (Table 1).

When ECD loss in 6 months was compared between the two etiologies, the mean ECD of the FED eyes at 6 months after DMEK was 1719.1±152.6 cells/mm^2 and it was 1702.2±145.9 cells/mm^2 for the eyes with PBK (p=0.55). Mean ECD loss in 6 months was 29.2±4.4% in the FED group and 29.7±5% in the PBK group (p=0.415) (Table 2).

In patients with FED, the mean preoperative BCVA was 1.13±0.27 and it changed to 0.06±0.05 at 6 months (p<0.001). In patients with PBK, the mean preoperative BCVA was 2.36±0.69 and it changed to 0.07±0.05 at 6 months (p<0.001). There was no statistically significant difference between the groups in mean BCVA at 6 months (p=0.378) (Table 2).

8 vs. 9.5 mm Donor Preparation Technique

The baseline conditions before DMEK procedure for the patients who underwent different techniques (8 vs. 9.5 mm) are summarized in Table 2. The groups were homogenous in terms of donor ECD, donor age, duration of donor tissue in solution, and duration of obtaining the donor tissue after exitus (Table 3).

When ECD loss in 6 months was compared between the two graft preparation techniques, the mean ECD of the patients for whom the 8-mm technique was preferred was 1733.8±165.9 cells/mm^2 at 6 months after DMEK and it was 1706.7±146.1 cells/mm^2 for the patients for whom the 9.5-mm technique was preferred (p=0.356). The mean ECD loss in 6 months was 28.3±5.3% in the 8-mm group and 29.7±4.5% in the 9.5-mm group (p=0.255) (Table 4).

Triple vs. Staged (Combined) Approach in Patients with FED and Cataract

The baseline conditions before DMEK for the patients who underwent different approaches for the management of FED and cataract (staged vs. triple) are summarized in Table 3. The groups were homogenous in terms of donor ECD, donor age, duration of donor tissue in solution, and duration of obtaining the donor tissue after exitus (Table 5).

Table 1. Comparison of baseline conditions before Descemet membrane endothelial keratoplasty surgery

	FED	PBK	p value
n (%)	52 (52%)	48 (48%)	
Donor ECD (cells/mm^2)	2427.3±137	2423.1±135.9	0.876
Donor age (years)	60.0±2.7	60.5±2.6	0.289
Duration in solution (days)	4.0±2.0	3.8±2.0	0.611
Duration after exitus (days)	4.4±2.2	4.4±2.1	0.925

FED: Fuchs' endothelial dystrophy, PBK: Pseudophakic bullous keratopathy

Table 2. Endothelial cell density (ECD) at 6 months, ECD loss in 6 months, and best corrected visual acuity at 6 months in patients with Fuchs' endothelial dystrophy and pseudophakic bullous keratopathy

	FED	PBK	p value
n (%)	52 (52%)	48 (48%)	
ECD at 6 months (cells/mm^2) (mean ± SD)	1719.1±152.6	1702.2±145.9	0.55
ECD loss (%) (mean ± SD)	29.2±4.4	29.7±5	0.415
BCVA at 6 months (LogMAR) (mean ± SD)	0.06±0.05	0.07±0.05	0.378

ECD: Endothelial cell density, SD: Standard deviation, BCVA: Best corrected visual acuity, FED: Fuchs' endothelial dystrophy, PBK: Pseudophakic bullous keratopathy

Table 3. Comparison of baseline conditions according to different graft techniques before Descemet membrane endothelial keratoplasty surgery

	8 mm	9.5 mm	p value
n (%)	16 (16%)	84 (84%)	
Donor ECD (cells/mm^2)	2415.2±120.1	2427.2±139.2	0.686
Donor age (years)	59.7±2.0	60.3±2.8	0.537
Duration in solution (days)	4.0±1.9	3.9±2.0	0.739
Duration after exitus (days)	4.2±2.3	4.4±2.1	0.609

ECD: Endothelial cell density

When ECD loss in 6 months was compared between the two approaches, the mean ECD of the patients for whom the triple approach was preferred was 1738.8±166.2 cells/mm^2 at 6 months after DMEK and it was 1702.3±140.7 cells/mm^2 for the patients for whom the staged approach was preferred (p=0.149). The mean ECD loss in 6 months was 28.5±5.6% in the triple group and 29.8±2.9% in the staged group (p=0.279) (Table 6).

The mean preoperative BCVA was 1.09±0.28 and it changed to 0.05±0.05 at 6 months in the patients for whom the triple approach was preferred (p<0.001). The mean preoperative BCVA was 1.17±0.26 and it changed to 0.07±0.06 at 6 months in the patients for whom the staged approach was preferred (p<0.001). There was no statistically significant difference in mean BCVA at 6 months between the two groups (p=0.09) (Table 6).

Complications

Peripheral iridectomy was not performed in 15 eyes (15%), and 3 cases of pupillary block were observed among these eyes (3%). However, no pupillary block was observed in the eyes that underwent peripheral iridectomy during surgery.

Graft failure was observed in 10 eyes (10%) and an additional DMEK surgery was performed for all of these cases. TASS was the cause of PBK in 4 of these cases. Penetrating keratoplasty was needed in 5 of these cases. Three eyes had partial graft detachment and 1 had total graft detachment, and air was applied to the anterior chamber to provide reattachment in these eyes. The patient with total graft detachment underwent re-DMEK due to suspicion of upside-down graft application. Complications of DMEK procedures in the study are summarized in Table 7.

Table 4. Endothelial cell density (ECD) at 6 months and ECD loss in 6 months according to the different graft preparation techniques

	8 mm	9.5 mm	p value
n (%)	16 (16%)	84 (84%)	
ECD at 6 months (cells/mm^2) (mean ± SD)	1733.8±165.9	1706.7±146.1	0.356
ECD loss (%) (mean ± SD)	28.3±5.3	29.7±4.5	0.255

ECD: Endothelial cell density, SD: Standard deviation, BCVA: Best corrected visual acuity

Table 5. Comparison of baseline conditions according to the different approaches used in the management of cataract

	Triple (Combined)	Staged	p value
n (% in cases with FED)	24 (46.1%)	28 (53.9%)	
Donor ECD (cells/mm^2)	2432.4±121.1	2423.0±151.5	1.0
Donor age (years)	59.5±2.0	60.3±3.2	0.378
Duration in solution (days)	4.0±1.6	4.1±2.3	0.993
Duration after exitus (days)	4.0±2.1	4.8±2.1	0.19

ECD: Endothelial cell density, FED: Fuchs' endothelial dystrophy

Table 6. Endothelial cell density (ECD) at 6 months, ECD loss in 6 months, and best corrected visual acuity at 6 months according to the different approaches for patients with cataract and Fuchs' endothelial dystrophy

	Combined (Triple)	Staged	p value
n (% in cases with FED)	24 (46.1%)	28 (53.9%)	
ECD at 6 months (cells/mm^2) (mean ± SD)	1738.8±166.2	1702.3±140.7	0.149
ECD loss (%) (mean ± SD)	28.5±5.6	29.8±2.9	0.279
BCVA at 6 months (LogMAR) (mean ± SD)	0.05±0.05	0.07±0.06	0.09

ECD: Endothelial cell density, SD: Standard deviation, BCVA: Best corrected visual acuity, FED: Fuchs' endothelial dystrophy, PBK: Pseudophakic bullous keratopathy

Table 7. Complications of before Descemet membrane endothelial keratoplasty and their management

Complication	n (%)	1st Management	2nd Management	n (%)
Graft failure	10 (10%)	Re-DMEK	Penetrating keratoplasty	5 (5%)
Partial graft detachment	3 (3%)	Rebubbling	-	-
Total graft detachment	1 (1%)	Re-DMEK	-	-
Pupillary block	3 (3%)	Removal of air	-	-

DMEK: Descemet membrane endothelial keratoplasty

Discussion

In recent years, endothelial keratoplasty techniques (DMEK and DSAEK) have been the major surgical approach for the management of FED and PBK. Although penetrating keratoplasty is still in use, it has the disadvantages of complications, lower patient satisfaction, and lower BCVA. However, endothelial keratoplasty techniques, especially DMEK, require more surgical experience. Despite this drawback, after enough surgeries, it can be performed in any center because special surgical equipment is not necessary for this surgical approach, unlike DSAEK. In DMEK, the surgeon has the advantage of preferring the best approach for the patient in each step of donor tissue preparation. Furthermore, in a recent meta-analysis, DMEK was found to show better postoperative results regarding BCVA, patient satisfaction, and graft-related issues.[10] In this study, we presented our results of the increasingly popular DMEK surgery in 100 eyes with FED or PBK.

In clinical studies, the success of DMEK surgery is usually evaluated based on both ECD loss and change in BCVA. While Droutsas et al.[11] showed 31.6% ECD loss at 6 months after DMEK surgery for the treatment of patients with FED, Ham et al.[12] showed 28.4% ECD loss. Consistent with these previous studies, we observed mean ECD loss at 6 months of 29.2±4.4% in the FED group and 29.7±5% in the PBK group. Our study also showed that there was no difference between the FED and PBK patients in terms of ECD loss at 6 months. This indicates that DMEK surgery might be equally successful in terms of ECD in patients with FED and PBK.

In general practice, the 9.5 mm technique is preferred for donor graft preparation.[13] In our study, we evaluated whether there is a difference between the 9.5 mm and 8 mm techniques. Although contact with the endothelial layer during the 8 mm preparation technique might cause concern about increased ECD loss, we did not observe any significant increase in loss. Our results showed that both techniques can be used effectively with comparable endothelial cell loss.

Although penetrating keratoplasty was the main approach in the past, recent advances in endothelial keratoplasty techniques have made it the main approach for patients with FED. However, there is controversy regarding the best approach to patients with FED and cataract. This issue is important because the rate of cataract formation within 1 year after any endothelial keratoplasty was reported to be as high as 40%.[14] Two different approaches have been described in the literature. In the combined technique, the surgeon can perform the DMEK surgery together with phacoemulsification in the same session, whereas in the staged technique, DMEK is performed in another session after phacoemulsification. Previous studies offered conflicting results about the success of both approaches. Most of the studies suggested that the two techniques were similar in terms of final BCVA and ECD.[6,7] Schoenberg et al.[8] reported the results of 108 triple DMEK procedures and found that triple DMEK safely achieved excellent BCVA. Sykakis et al.[6] reported increased graft dislocation rate in the combined technique. However, this increase was attributed to the use of Healon-GV rather than Healon. Similar to the previous studies, we did not observe any difference between the techniques in terms of ECD loss or BCVA at 6 months in our study.

Graft failure is one of the complications of DMEK surgery. Re-DMEK, back-up DSEK, or penetrating keratoplasty can be used for the management of graft failure.[15] Heinzelmann et al.[16] showed that pre-cut donor graft was linked to increased graft failure rate. Thus, donor tissue preparation should be performed immediately before surgery. In our study, graft failure was observed in 10 eyes (10%) and an additional DMEK procedure was performed for all of these cases. TASS was the cause of PBK in 4 of these cases. Penetrating keratoplasty was needed in 5 of these cases. Although previously we showed that DSAEK was successful in cases of chronic TASS in terms of visual and anatomical outcomes,[17] our study suggests that DMEK might not be a good approach for patients with PBK secondary to TASS. However, further studies with a larger number of patients should be conducted to compare the success of DMEK and DSAEK for the treatment of PBK secondary to TASS.

Another complication of the DMEK surgery is graft detachment. This complication can be managed with re-bubbling. Although the rates of total and partial graft detachment were 30% and 62-63% in initial reports,[18,19,20,21,22] the detachment rate decreased to as low as 4-34.6% in recent years due to increased surgical experience.[19] In our study, 3 eyes (3%) with partial graft detachment and 1 eye (1%) with total graft detachment were observed and air was applied to the anterior chamber to provide reattachment. Suspecting upside down graft application, we performed re-DMEK in the patient with total graft detachment.

Study Limitations

The relatively short follow-up time, small number of patients with PBK secondary to TASS, and the retrospective, non-randomized, and descriptive design of the study are limitations of our study. Due to the non-randomized and descriptive nature of the study, some of our findings may lack generalizability. In addition, central corneal thickness data were not included in the study.

Conclusion

DMEK was found to be a safe and effective method for patients with FED and PBK. In patients with FED together with cataract, we did not observe any difference in final BCVA or ECD between the staged or combined procedures, which indicates that both approaches can be used efficiently in these patients. Furthermore, no difference in 6-month ECD was found between graft preparation using the 8 mm or 9.5 mm techniques. Further studies including central corneal thickness data should be performed to investigate the results of the increasingly popular DMEK procedure.

Ethics

Ethics Committee Approval: İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethic Committe-41341.

Informed Consent: Received.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Osman Şevki Arslan, Cezmi Doğan, Concept: Osman Şevki Arslan, Cezmi Doğan, Burak Mergen, Design: Osman Şevki Arslan, Cezmi Doğan, Data Collection or Processing: Burak Mergen, Cezmi Doğan Analysis or Interpretation: Burak Mergen, Osman Şevki Arslan, Cezmi Doğan, Literature Search: Cezmi Doğan, Burak Mergen, Writing: Cezmi Doğan, Burak Mergen, Osman Şevki Arslan.

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

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Original Article

Impact of Cataract Surgery on Functional Balance Skills of Adults

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Abstract

Objectives: To investigate the impact of phacoemulsification surgery and intraocular lens implantation on the functional balance skills of adults.

Materials and Methods: This prospective study included patients with cataract who were recommended phacoemulsification surgery and intraocular lens implantation between May and October 2016. The Berg Balance Scale and Tinetti Gait and Balance Test were performed by a physical therapy specialist before and 1 month after surgery. Patients were analyzed in terms of age, visual acuity, and balance. Balance scores before and after cataract surgery were compared. We also compared patients with high (≤2 LogMAR) and low (>2 LogMAR) visual acuity. P values below 0.05 were accepted as statistically significant.

Results: Fifty-one patients (27 female and 24 male, mean age 66.96 years) were included in the study. One month after surgery, the patients' Berg Balance scores and Tinetti Gait and Balance scores were increased by 3.60±5.00% and 4.14±6.55%, respectively. Postoperative increase in visual acuity was significantly greater in the 16 patients with visual acuity less than 0.05 (>2 LogMAR) (p=0.036), but balance scores were not significantly different.

Conclusion: Visual acuity is significantly improved one month after cataract surgery, which also leads to significant increases in low functional balance scores among patients with poorer vision. The rapid increase in vision after cataract surgery enhances balance skills, resulting in safer mobility and increased quality of life.

Keywords: Vision, cataract, balance, phacoemulsification, falls

Introduction

Cataract is a treatable condition that generally emerges in old age and is a leading cause of vision loss. Today, increases in education level and the average human lifespan are increasing the demand for cataract surgery. In addition to reduced vision, cataracts also cause visual problems such as glare, defects in color vision, and loss of contrast sensitivity and depth perception. These symptoms lead to problems such as loss of balance, less independent mobility, falls, injuries, and increased mortality risk in individuals with visual impairment.[1] Every year, approximately 646,000 people worldwide lose their lives due to falls, and according to a report from the World Health Organization, falls are the second most common cause of injury-related deaths.[2] Furthermore, the daily activities of elderly patients are affected and patient's quality of life is impaired.[3] Cataract surgery is now performed not only to treat blindness, but to improve quality of life. Atasavun and Akı[4] reported that studies in different age groups have shown that the incidence of falls is higher among the visually impaired than among individuals with auditory

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impairment or with no visual impairment. According to 2016 data from the Australian Institute of Health and Welfare, falls become a common problem over the age of 65 and are one of the leading causes of accidental deaths (40% for men and 66% for women).[5] Other studies have shown that an average of 30% of older adults fall once a year and 20% of them are hospitalized as a result of these falls.[6,7]

Although there are various studies in the literature evaluating the relationship between vision and balance, some of these studies have not demonstrated functional balance, while vision was not evaluated objectively in others.[8] The relationship between vision and balance cannot be fully elucidated without an objective assessment of vision level, especially for patients with low vision.[9] Some studies involved retrospective evaluations of surveys conducted in patients who had history of falls. However, various factors may be overlooked in these studies due to inaccurate recollection of events. In addition, because balance is affected by many parameters such as age, sex, muscle strength, vestibular function, medication use, and comorbidities, it is difficult to form a well-matched control group and establish a direct relationship between vision and balance.[10] Therefore, in the present study, we prospectively enrolled a group of patients whose characteristics did not differ except for vision. By evaluating these patients before and after cataract surgery, the relationship between vision and balance was revealed more clearly, without confounding by other variables.

In this study, we investigated the effect of vision increase in adult cataract patients after phacoemulsification surgery and intraocular lens implantation on functional balance skills.

Materials and Methods

Adult patients with cataract who were recommended phacoemulsification and intraocular lens implantation in our center between May and October 2016 were enrolled in the study. The study was designed in accordance with Declaration of Helsinki criteria and each participant signed an informed consent form before the study. The study was approved by the Antalya Training and Research Hospital ethics committee.

Exclusion criteria for the study were presence of chronic diseases such as rheumatoid arthritis or osteoarthritis, immobility with or without assistive devices or severe lower extremity deformities that might affect mobility, vestibular problems, history of stroke, and presence of dementia or memory problems.

Demographic data such as age, sex, marital status, education level, and occupation were determined for the individuals who met the study criteria and agreed to participate in the study. The patients' corrected visual acuity was assessed using Snellen E chart before and after cataract surgery. Functional balance was evaluated by the same physical therapist before and one month after surgery using the Berg Balance Scale (BBS) and Tinetti Gait Test (TGT) and Tinetti Balance Test (TBT).[11,12]

Berg Balance Scale: Designed primarily to assess balance and determine risk of falls in older adults, the BBS consists of 14 items for direct observation of performance. A ruler, stopwatch, chair, step, an area that allows 360 degrees of rotation, and 15-20 minutes are needed to perform the BBS. Each item is scored 0-4 according to the patient's ability to meet the time and distance requirements of the test. A score of 4 indicates ability to complete the task independently. The maximum score is 56. A score of 0-20 is interpreted as poor balance, 21-40 as acceptable balance, and 41-56 as good balance (Figure 1).

Tinetti Gait and Balance Tests: This test is preferred for determining the risk of falls, especially in the elderly, and consists of 13 items for balance and 9 items for gait. Items are scored binarily (0 or 1) or on a 3-point scale (0-2). Scores are calculated over a maximum of 16 for balance and 12 for gate, for a maximum total score (gait + balance) of 28 (Figure 2).

Statistical Analysis

The research data were entered into a spreadsheet file and evaluated with Microsoft® Excel® for Mac 2011 version 14.5.9 (151119) and Statistical Package for the Social Sciences version 20 (SPSS 20) (IBM, New York, USA) software. Female and male patients were compared in terms of age, visual acuity, and balance using Mann-Whitney U test. Relationships between the parameters of age, visual acuity, and balance were evaluated with Pearson correlation analysis. Balance scores before and after cataract surgery were compared using dependent-samples t-test. Patients with high (<2 LogMAR) and low (>2 LogMAR) preoperative visual acuity were compared using independent-samples t-test. Values associated with balance were analyzed with one-way ANOVA. P values less than 0.05 were considered statistically significant.

Results

This prospective study included a total of 51 patients, 27 (52%) women and 24 (48%) men, who met the inclusion criteria. Their mean age was 66.96 (33-87 years). There were no significant differences between the male and female patients in terms of age or preoperative and postoperative visual acuity (Table 1). Mean preoperative visual acuity was 1.32±0.75 (0.3-2.5) LogMAR. Visual acuity increased significantly in both groups postoperatively ($p<0.001$).

Both male and female patients also showed significant postoperative improvements in balance. At postoperative 1 month, BBS scores were increased by 3.60±5.00% (0-20%), while TGT and TBT were increased by 4.14±6.55% (0-38.46%). The increase in TGT and TBT scores was found to be statistically significant (Table 2).

Comparison based on preoperative visual acuity revealed a significantly greater increase in postoperative 1-month visual acuity among the 16 patients in the >2 LogMAR (<0.05) group compared to the 35 patients in the ≤2 LogMAR (≥0.05) group ($p=0.036$). However, there was no significant difference between these two groups in terms of increase in balance and gait scores (Table 3).

1. SITTING TO STANDING
INSTRUCTIONS: Please stand up. Try not to use your hands for support.
( ) 4 able to stand without using hands and stabilize independently
( ) 3 able to stand independently using hands
( ) 2 able to stand using hands after several tries
( ) 1 needs minimal aid to stand or to stabilize
( ) 0 needs moderate or maximal assist to stand
2. STANDING UNSUPPORTED
INSTRUCTIONS: Please stand for two minutes without holding.
( ) 4 able to stand safely 2 minutes
( ) 3 able to stand 2 minutes with supervision
( ) 2 able to stand 30 seconds unsupported
( ) 1 needs several tries to stand 30 seconds unsupported
( ) 0 unable to stand 30 seconds unassiste
If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported.
Proceed to item #4.
3. SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A
STOOL
INSTRUCTIONS: Please sit with arms folded for 2 minutes.
( ) 4 able to sit safely and securely 2 minutes
( ) 3 able to sit 2 minutes under supervision
( ) 2 able to sit 30 seconds
( ) 1 able to sit 10 seconds
( ) 0 unable to sit without support 10 seconds
4. STANDING TO SITTING
INSTRUCTIONS: Please sit down.
( ) 4 sits safely with minimal use of hands
( ) 3 controls descent by using hands
( ) 2 uses back of legs against chair to control descent
( ) 1 sits independently but has uncontrolled descent
( ) 0 needs assistance to sit
5. TRANSFERS
INSTRUCTIONS: Arrange chairs for a pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
( ) 4 able to transfer safely with minor use of hands
( ) 3 able to transfer safely definite need of hands
( ) 2 able to transfer with verbal cueing and/or supervision
( ) 1 needs one person to assist
( ) 0 needs two people to assiste to be safe
6. STANDING UNSUPPORTED WITH EYES CLOSED
INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.
( ) 4 able to stand 10 seconds safely
( ) 3 able to stand 10 seconds with supervision
( ) 2 able to stand 3 seconds
( ) 1 unable to keep eyes closed 3 seconds but stays steady
( ) 0 needs help to keep from falling

7. STANDING UNSUPPORTED WITH FEET TOGETHER
INSTRUCTIONS: Place your feet together and stand without holding.
( ) 4 able to place feet together independently and stand 1 minute safely
( ) 3 able to place feet together independently and stand for 1 minute with supervision
( ) 2 able to place feet together independently but unable to hold for 30 seconds
( ) 1 needs help to attain position but able to stand 15 seconds with feet together
( ) 0 needs help to attain position and unable to hold for 15 second
8. REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING
INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the finger reaches while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)
( ) 4 can reach forward confidently >25 cm (10 inches)
( ) 3 can reach forward >12 cm safely (5 inches)
( ) 2 can reach forward >5 cm safely (2 inches)
( ) 1 reaches forward but needs supervision
( ) 0 loses balance while trying/requires external support
9. PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION
INSTRUCTIONS: Pick up the shoe/slipper which is placed in front of your feet.
( ) 4 able to pick up slipper safely and easily
( ) 3 able to pick up slipper but needs supervision
( ) 2 unable to pick up but reaches 2-5cm (1-2 inches) from slipper and keeps balance
independently
( ) 1 unable to pick up and needs supervision while trying
( ) 0 unable to try/needs assist to keep from losing balance or falling
10. TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING
INSTRUCTIONS: Turn to look directly behind you over toward left shoulder. Repeat to the right.
Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.
( ) 4 looks behind from both sides and weight shifts well
( ) 3 looks behind one side only other side shows less weight shift
( ) 2 turns sideways only but maintains balance
( ) 1 needs supervision when turning
( ) 0 needs assist to keep from losing balance or falling

11. TURN 360 DEGREES
INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other
direction.
( ) 4 able to turn 360 degrees safely in 4 seconds or less
( ) 3 able to turn 360 degrees safely one side only in 4 seconds or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cueing
( ) 0 needs assistance while turning
12. PLACING ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED
INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has
touched the step/stool four times.
( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds
( ) 3 able to stand independently and complete 8 steps in >20 seconds
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete >2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try
13. STANDING UNSUPPORTED ONE FOOT IN FRONT
INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If
you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel
of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step
should exceed the length of the other foot and the width of the stance should approximate the
subject's normal stride width)
( ) 4 able to place foot tandem independently and hold 30 seconds
( ) 3 able to place foot ahead of other independently and hold 30 seconds
( ) 2 able to take small step independently and hold 30 seconds
( ) 1 needs help to step but can hold 15 seconds
( ) 0 loses balance while stepping or standing
14. STANDING ON ONE LEG
INSTRUCTIONS: Stand on one leg as long as you can without holding.
( ) 4 able to lift leg independently and hold >10 seconds
( ) 3 able to lift leg independently and hold 5-10 seconds
( ) 2 able to lift leg independently and hold = or >3 seconds
( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently
( ) 0 unable to try or needs assist to prevent fall
TOTAL SCORE (Maximum = 56:)_____

Figure 1. Berg Balance Scale

Discussion

Vision is one of the most important factors in maintaining balance and preventing falls. Kulmala et al.[13] demonstrated in their study of elderly women that visual impairment had the greatest impact on falls when compared with other sensory impairments. This finding was attributed to the fact that other senses can somewhat compensate for deficiencies by filling in gaps regarding posture and balance. In a study performed in Turkey, it was shown that individuals with visual impairments accounted for a significantly higher proportion of a group of adults with fall-related extremity fractures (78.6%) compared to the control group (38.1%).[14] This led the authors to conclude that first assessing vision and treating any detected impairments is imperative for the prevention of falls and accidents. These studies demonstrate that the incidence of fall-related fractures can be reduced through regular eye examination in adults, regular use of eyeglasses among patients with refractive error, and timely interventions for treatable eye disorders, primarily cataracts. A study of 1361 individuals in China also indicated that corrected visual acuity lower than 0.5 in the better-seeing eye significantly increased the incidence of falls.[15]

In the present study, all patients exhibited significant visual improvement at 1-month follow-up after cataract surgery, consistent with the literature.[16] In addition to postoperative increase in vision, our patients also had higher balance scores on the BBS and TBT. This suggests that the risk of falls will decrease as a result of higher balance scores associated with improved vision.

According to the results obtained from all of the balance tests used, we observed that the women had lower balance scores than the men in our study. To et al.[17] also reported that the incidence of falls was three times higher in females than males in their 2014 study. However, when we analyzed postoperative changes in balance scores, we found that balance scores increased more among the women in our study. The increase in TBT scores was statistically significantly in females ($p=0.003$) but not in males.

		Response	
Maneuver	Normal	Adaptive	Abnormal
Sitting balance	Steady, stable	Holds onto chair to keep upright	Leans, slides down in chair
Arising from chair	Able to arise in a single movement without using arms	Uses arms (on chair or walking aid) to pull or push up; and or moves push up; andlor moves attempting to arise	Multiple attempts required or unable without human assistance
Immediate standing balance (first 3-5s)	Steady without holding onto walking aid or other object for support	Steady, but uses walking aid or other object for support	Any sign of unsteadinesst
Standing balance	Steady, able to stand with feet together without holding object for support	Steady, but cannot put feet together	Any sign of unsteadiness regardless of stance or holds onto object
Balance with eyes closed (with feet as close together as possible)	Steady without holding onto any object with feet together	Steady with feet apart	Any sign of unsteadiness or needs to hold onto an object
Turning balance (360")	No grabbing or staggering; no need to hold onto any objects; steps are continuous (turn is a flowing movement)	Steps are discontinuous (patient puts one foot completely on floor before raising other foot)	Any sign of unsteadiness or holds onto an object
Nudge on sternum (patient standing with feet as close together as possible, examiner pushes with light even pressure over sternum 3 times; reflects ability to withstand displacement)	Steady, able to withstand pressure	Needs to move feet, but able to maintain balance	Begins to fall, or examinerhas to help maintain Begins to fall, or examiner balance
Neck turning (patient asked to turn head side to side and look up while standing with feet as close together as possible)	Able to turn head a t least half way side to side and be able to bend head back to look at ceiling; no staggering, grabbing, or Symptoms of lightheadedness, unsteadiness, or pain	Decreased ability to turn side to side to extend neck, but no staggering, grabbing, or symptoms of lightheadedness, unsteadiness, or pain	Any sign of unsteadiness or symptoms whenq turning head or extending neck
One leg standing balance	Able to stand on one leg for 5 s without holding object for support		Unable
Back extension (ask patient to lean back as far as possible, without holding onto object if possible)	Good extension without holding object or staggering	Tries to extend, but decreased ROM (compared with other patients of same age) or needs to hold object to attempt extension	Will not attempt or no extension seen or staggers
Reaching up (have patient attempt to remove an object from a shelf high enough to require stretching or standing on toes)	Able to take down object without needing to hold onto other object for support and without becoming unsteady	Able to get object but needs to steady self by holding on to something for support	Unable or unsteady
Bending down (patient is asked to pick up small objects, such as pen, from the floor)	Able to bend down and pick up the object and is able to get up easily in single attempt without needing to pull self up with arms	Able to get object and get upright in single attempt but needs to pull self up with arms or hold onto something for support	Unable to bend down or unable to get upright after bending down or takes multiple attempts to upright
Sitting down	Able to sit down in one smooth movement	Needs to use arms to guide self into chair'or not a smooth movement	Falls into chair, misjudges distances (lands off center)

ROM = range of motion.
'The patient begins this assessment seated in a hard, straight-backed, armless chair.
tunsteadiness defined as grabbing at objects for support, staggering, moving feet, or more than minimal trunk sway.

Componentst	Normal	Abnormal
Initiation of gait (patient asked to begin walking down hallway)	Begins walking immediately without observable hesitation; initiation of gait is single, smooth motion	Hesitates; multiple attempts; initiation of gait not a smooth motion
Step height (begin observing after first few steps: observe one foot, then the other; observe from side)	Swing foot completely clears floor but by no more than 1-2 in	Swing foot is not completely raised off floor (may hear scraping) or is raised too high (> 1-2 in)
Step length (observe distance between toe of stance foot and heel of swing foot; observe from side; do not judge first few or last few steps; observe one side at a time)	At least the length of individual's foot between the stance toe and swing heel (step length usually longer but foot length provides basis for observation)	Step length less than described under normal
Step symmetry (observe the middle part of the patch not the first or last steps; observe from side; observe distance between heel of each swing foot and toe of each stance foot)	Step length same or nearly same on both sides for most step cycles	Step length varies between sides or patient advances with same foot with every step
Step continuity	Begins raising heel of one foot (toe off) as heel of other foot touches the floor (heel strike); no breaks or stops in stride; step lengths equal over most cycles	Places entire foot (heel and toe) on floor before beginning to raise other foot; or stops completely between steps; or step length varies over cycles
Path deviation (observe from behind; observe one foot over several strides; observe in relation to line on floor (eg, tiles) if possible; difficult to assess if patient uses a walker)	Foot follows close to straight line as patient advances	Foot deviates from side to side or toward one direction§
Trunk stability (observe from behind; side to side motion of trunk may be a normal gait pattern, need to differentiate this from instability)	Trunk does not sway; knees or back ate not flexed; arms are not abducted in effort to maintain stability	Any of preceding features present§
Walk stance (observe from behind)	Feet should almost touch as one passes other	Feet apart with steppingll
Turning while walking	No staggering; turning continuous with walking; and steps are continuous while turning	Staggers; stops before initiating turti; or steps are discontinuous

*The patient stands with examiner at end of obstacle-free hallway. Patient uses usual walking aid. Examiner asks patient to walk down hallway at his or her usual pace. Examiner observes one component of gait at a time (analogous to heart examination). For some components the examiner walks behind the patient; for other components, the examiner walks next to patient. May require several trips to complete.
tAlso ask patient to walk at a "more rapid than usual" pace and observe whether any walking aid is used correctly (see text for discussion). tAbnormal gait finding may reflect a primary neurologic or musculoskeletal problem directly related to the finding or reflect a compensatory maneuver for other, more remote problem.
§Abnormality may be corrected by walking aid such as cane, observe with and without walking aid if possible. IIAbnormal finding is a usually compensatory maneuver rather than a primary problem.

Figure 2. Tinetti Balance and Gait Tests

Table 1. Demographic characteristics of the study patients and their visual acuity levels before and after cataract surgery					
	Age (years)	Visual acuity (LogMAR)			
		Preoperative	Preoperative	p	Fellow eye
Female (n=27) (mean)	43-79 (66.59±10.02)	0.3-3.0 (1.31±0.80)	0.0-0.1 (0.27±0.04)	**0.001**	0.0-2.5 (0.48±0.67)
Male (n=24) (mean)	33-87 (67.38±13.53)	0.3-2.5 (1.33±0.71)	0.0-0.15 (0.01±0.03)	**<0.001**	0.0-1.9 (0.51±0.74)
Total (n=51) (mean)	33-87 (66.96±11.69)	0.3-3.0 (1.32±0.75)	0.0-0.15 (0.20±0.04)	**<0.001**	0.0-2.5 (0.48±0.69)

Table 2. Balance scores of the study patients before and after cataract surgery									
	Female			Male			Total		
	Preoperative	Preoperative	p	Preoperative	Preoperative	p	Preoperative	Preoperative	p
Berg Balance Scale (mean)	23-56 (48.67±8.69)	27-56 (50.78±8.43)	0.369	45-56 (52.75±3.44)	46-56 (53.88±2.95)	0.230	23-56 (50.59±7.00)	27-56 (52.24±6.59)	0.224
Tinetti Gait Test (mean)	5-12 (9.89±1.74)	7-12 (10.37±0.82)	**0.009**	8-12 (10.29±1.04)	10-12 (10.63±0.40)	**0.043**	5-12 (10.08±1.45)	7-12 (10.49±1.07)	**0.001**
Tinetti Balance Test (mean)	6-16 (14.11±3.17)	7-16 (14.78±2.64)	**0.003**	12-16 (15.21±1.38)	12-16 (15.58±1.02)	0.095	6-16 (14.63±2.53)	7-16 (15.16±2.06)	**0.001**
Tinetti total (mean)	11-28 (24.00±4.70)	14-28 (26.48±0.71)	0.072	20-28 (25.08±1.41)	22-28 (24.00±1.41)	0.101	11-28 (25.00±1.41)	17-28 (25.50±0.70)	**0.020**

Table 3. Changes in balance scores according to visual acuity before cataract surgery (Mean values are given in parentheses)			
	Visual acuity (Snellen)		
	≥0.05 (n=35)	<0.05 (n=16)	p
Age (years)	33-84 (66.91±11.35)	43-83 (67.06±12.78)	0.967
Increase in visual acuity (%)	97.17±5.66	99.38±1.41	**0.036**
Preoperative Berg Balance Test	23-56 (50.54±7.00)	28-56 (50.69±7.22)	0.946
Preoperative Berg Balance Test	27-56 (52.40±6.45)	29-56 (51.88±7.09)	0.795
Preoperative Tinetti Balance Test	6-16 (14.57±2.66)	8-16 (14.75±2.30)	0.818
Preoperative Tinetti Balance Test	7-16 (15.09±2.20)	9-16 (15.31±1.78)	0.720
Preoperative Tinetti Gait Test	5-12 (10.00±1.53)	7-12 (10.25±1.29)	0.574
Preoperative Tinetti Gait Test	7-12 (10.43±1.45)	9-12 (10.63±0.89)	0.547

This may indicate a stronger association between balance and vision in women.

Preoperative vision level also affects the benefit of cataract surgery on visual outcome.[18] When we compared our patients' results in two groups based on preoperative visual acuity level, the group with preoperative visual acuity worse than 0.05 showed a significantly larger increase in postoperative 1-month visual acuity than the other group (p=0.036). However, we detected no significant differences between these two groups in terms of increases in balance or gait scores. Although studies evaluating the effect of vision on balance and falls have yielded very different results, most authors agree that increased vision has a positive impact on the ability to maintain balance.[15,17,19,20] In contrast to these data, the authors of a study published in 2015 argued that visual impairment in elderly cataract patients was not associated with balance disorders or falls.[21] Furthermore, Cumming et al.[22] found that improving older adults' vision through treatment actually increased the incidence of falls, but they attributed this discrepant result to the fact that the patients became more mobile and active when their vision was restored. In their study of 413 patients over 50 years old, To et al.[17] observed a 78% reduction in risk of falls after surgery on the first eye and 83% after surgery of the second eye. Foss et al.[23] reported that the incidence of falls decreased by 32% after surgery on the second eye. Desapriya et al.[19] showed that early cataract surgery substantially improved visual acuity but had no significant effect on falls. However, Supuk et al.[24] emphasized that after cataract surgery, there was a significant decrease in vertigo rather than in the incidence of falls.

Most of the published studies on this topic have been retrospective, with patients' visual acuities analyzed after examining the patients' records or conducting surveys regarding

their falls history.[4,14,15,16,17,24,25,27] Compared to objective tests, these surveys both provide inadequate information and may give rise to misleading data due to patients' inaccurate recollection of past events. Moreover, as visual acuity is measured at the time of the study, accurate information cannot be obtained about the patients' visual acuity at the time of falling. The scientific significance of our study lies in the fact that it was planned as a prospective study and the patients were tested and evaluated at the same time by an ophtalmologist and a physical therapist. Most previous studies focused on vision and falls incidence, but there are few studies that have tested and compared patients' pre- and postoperative balance.

Like many other studies, the current study demonstrates that, by referring individuals to eye examinations at regular intervals, quality of life can be increased and a substantial proportion of falls can be prevented in older adults.[3,14,15,17,20,28,29]

Study Limitations

One limitation of our study is that vision level varied in the patients' fellow eyes. While the fellow eye also had cataract in some patients, others had near perfect vision (mean LogMAR=0.48). This might have affected their balance scores. The visual benefit of cataract surgery might also vary depending on the status of the fellow eye.[18] Moreover, sudden increase in vision in one eye while the other eye still has cataract may cause imbalanced vision and consequently impaired balance rather than improved balance. In fact, Meuleners et al.[25] found that the incidence of falls requiring hospitalization doubled in the interval between first and second cataract surgeries compared with the preoperative period, and argued that ophthalmologists must warn patients to be more careful regarding falls after the first surgery.

Another limitation of the study is that we did not assess any other vision functions such as visual field, contrast sensitivity, depth perception, or color vision, factors that may also play a role in increasing the risk of falls. However, it is known that most of these parameters also improve after cataract surgery.[3,26] Therefore, we believe that the cataract surgery we performed corrected these parameters to some degree along with visual acuity.

Conclusion

This study demonstrates that phacoemulsification and intraocular lens implantation significantly increases visual acuity within the first postoperative month. As a result, the low functional balance scores of individuals with severe visual impairment increased significantly. This significant postoperative improvement in vision functions may contribute to better balance and enhance patients' quality of life.

Ethics

Ethics Committee Approval: Antalya Training and Research Hospital Clinical Research Ethics Committee, 2016-129.

Informed Consent: Received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Fulya Duman, Zeynep Kılıç, Concept: Fulya Duman, Design: Fulya Duman, Data Collection or Processing: Fulya Duman, Zeynep Kılıç, Analysis or Interpretation: Fulya Duman, Emel Ece Özcan Ekşi, Literature Search: Fulya Duman, Writing: Fulya Duman.

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

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Original Article

Intravitreal Dexamethasone Implant in the Treatment of Non-infectious Uveitis

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Abstract

Objectives: To evaluate the long-term results of intravitreal dexamethasone implant (DEX) for noninfectious uveitis.

Materials and Methods: The study included 62 eyes of 44 patients treated with DEX implant due to noninfectious uveitis and followed up for at least a year. Best-corrected visual acuity (BCVA), central foveal thickness, intraocular pressure (IOP), vitreous haze score, indications, immunomodulatory therapy and steroid usage before/after injection, number of injections, and adverse events were analyzed retrospectively.

Results: Average follow-up was 20 months (range 12-64 months). The female/male ratio was 29/15. Mean age was 50 years (range 22-75 years). The most frequent uveitis etiologies were idiopathic (25 patients, 40.3%) and Behçet's uveitis. (17 patients, 27.4%) The most common indication for DEX injection was cystoid macular edema together with resistant vitreous haze (26 eyes, 41.9%). Twenty-two eyes (30%) received more than one DEX injection. Mean BCVA was improved from 0.55 logMAR at baseline to 0.38, 0.32, and 0.35 after 1, 3, and 6 months, respectively ($p<0.001$ for each). Mean CFT was decreased from 386 µm at baseline to 288, 311, and 302 µm after 1, 3, and 6 months, respectively ($p<0.001$ for each). Mean IOP did not change significantly during follow-up. Five eyes (8%) received topical anti-glaucoma medication (IOP ≥25 mmHg). Eighteen (46%) of 39 phakic eyes underwent cataract surgery during follow-up. Similar efficacy of the DEX implant was observed in eyes that received multiple injections. Systemic immunomodulatory therapy did not change significantly during follow-up.

Conclusion: Intravitreal DEX injection does not alter systemic immunomodulatory therapy, but may facilitate the management of noninfectious uveitis by suppressing local intraocular inflammation. Multiple injections yielded comparable visual and anatomical outcomes to single injections. Follow-up for ocular hypertension and cataract formation are important, especially in eyes receiving multiple injections.

Keywords: Dexamethasone implant, uveitis, Ozurdex, intravitreal injection

Introduction

Noninfectious uveitis accounts for 10-15% of all cases of blindness in developed countries.[1] The most common causes of vision loss are cystoid macular edema (CME), secondary cataract, high intraocular pressure (IOP), and vitreous haze (VH).[2] The treatment of noninfectious uveitis mainly aims to suppress inflammation and often employs antimetabolites and immunomodulatory agents such as calcineurin inhibitors and biological agents.[3]

Corticosteroids also play an important role in the treatment of uveitis because of their rapid, extensive, and effective

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anti-inflammatory properties.[4] However, the use of systemic corticosteroids is limited due to adverse effects such as high blood glucose, systemic hypertension, reduced bone density, depression, and weight gain.[5] This led to the use of local corticosteroids, which are believed to not cause systemic side effects. However, the periorbital and intravitreal triamcinolone acetonide injections used for this purpose also cause undesirable adverse effects such as cataract and elevated intraocular pressure, and require repeated injections. This in turn led to the introduction of slow-release implants, which are considered safer.[6,7]

Intravitreal dexamethasone implants (Ozurdex, Allergan, Irvine, CA, USA), which are suggested to be safer and have longer lasting effects, were developed for easy injection into the vitreous cavity. The dexamethasone implant (DEX) is a biodegradable polymer composed of a combination of 0.7 mg dexamethasone and poly(lactic-co-glycolic acid).[8] It slowly dissolves in the vitreous cavity and provides intravitreal dexamethasone release for 6 months. It is indicated for use in cases of CME due to retinal vein occlusions, diabetic macular edema, and noninfectious uveitis.[9,10,11] The HURON (cHronic Uveitis evaluation of the intRavitreal dexamethasONe implant) trial demonstrated that a single dose injection suppresses inflammation and is effective for up to 6 months in cases of noninfectious uveitis.[11]

The aim of this study was to evaluate the long-term outcomes of intravitreal 0.7 mg dexamethasone implant in eyes with noninfectious uveitis being followed at a single center.

Materials and Methods

Patient Selection

This retrospective study included noninfectious uveitis patients over 18 years of age who were treated with DEX injection(s) between July 2015 and December 2017 in the Department of Ophthalmology of Gazi University due to CME and/or refractory VH and intraocular inflammation such as posterior scleritis. All patients had newly started systemic therapy, required no change in existing systemic therapy, or had infrequent acute episodes. The study was approved by the local ethics committee and adhered to the principles of the Declaration of Helsinki. Patients who were not followed up for at least 1 year after injection were not included in the study.

Data Collection

Patient data analyzed in this study included age, sex, laterality, uveitis diagnosis, indication for DEX implant, anatomical classification of the uveitis, drugs used for systemic therapy before and after injection, number of DEX injections, period between injections if the patient received multiple injections, complications, and total follow-up time. We also evaluated the patients' best corrected visual acuity (BCVA), intraocular pressure (IOP), anterior segment examination findings (especially lens status), fundus examination findings, central foveal thickness (CFT) measured by optical coherence tomography (OCT), and VH score according to SUN (Standardization of Uveitis Nomenclature Working Group) criteria recorded before and at 1, 3, and 6 months after injection. BCVA values obtained using Snellen chart were converted from decimal system to Logarithm of Minimum Angle of Resolution (logMAR) prior to statistical analysis. CFT measurements made with OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) were made using the values automatically acquired by the device.

Statistical Analysis

SPSS software (version 22.0, SPSS, Inc. Chicago, IL, USA) was used for statistical analysis. Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. For normally distributed variables (first injection BCVA, CFT, and IOP), paired t-test was used to evaluate changes in BCVA, CFT, and IOP values between baseline and the other time points. For variables that did not show normal distribution (second and third injection BCVA, CFT, and IOP), these comparisons were made using Wilcoxon signed-rank test. Changes with p values <0.05 were considered significant.

Results

Sixty-two eyes of 44 patients were included in the study. The patients' demographic characteristics, uveitis diagnoses and anatomical locations, and systemic therapies received are shown in Table 1. The most common etiology of noninfectious uveitis

Table 1. Demographic characteristics and uveitis diagnoses, locations, and systemic treatments in the study patients

Demographic characteristics	
Number of patients	44
Number of eyes	62
Age (years)	49.93±14.55 (range: 22-75)
Sex (Female:Male)	29:15
Follow-up time (months)	20.16±11.65 (range: 12-64)
Diagnosis (n=44)	
Idiopathic	19 (43.2%)
Behçet's disease	13 (29.6%)
Sarcoidosis	2 (4.6%)
Posterior scleritis	2 (4.6%)
VKH	2 (4.6%)
Sympathetic ophthalmia	1 (2.2%)
Multiple sclerosis	1 (2.2%)
Ampiginous choroiditis	1 (2.2%)
Serpinginous choroiditis	1 (2.2%)
IRVAN	2 (4.6%)
Anatomical classification of uveitis (n=62)	
Intermediate uveitis	16 (25.8%)
Posterior uveitis	33 (53.2%)
Panuveitis	11 (17.7%)
Posterior scleritis	2 (3.2%)

VKH: Vogt–Koyanagi–Harada disease, IRVAN: Idiopathic retinitis, vasculitis, aneurysm, and neuroretinitis

was idiopathic (40.3%), followed by Behçet's disease (27.4%). Two patients (3.2%) who had received antituberculous therapy for ocular tuberculosis but subsequently developed a Jarish–Herxheimer-like inflammatory reaction were also included in the noninfectious uveitis group in this study. The most common anatomic involvement was posterior uveitis (53.2%). In terms of treatment, 40.9% of the patients were not receiving systemic therapy, while 17 patients were receiving systemic corticosteroids at a median dose of 16 mg (range: 2-72 mg). Indications for intravitreal DEX injection are shown in Table 2. The most common indication for DEX was CME (44 eyes, 70.9%). Twenty-six eyes (41.9%) had both CME and refractory VH. The clinical characteristics of the patients included in the study are shown in Table 3. The mean initial BCVA was 0.55±0.46. VH score was 2+ or higher in 24 eyes (39%). Twenty-three eyes (37.1%) had prior cataract surgery, while 25 (40%) eyes were phakic with clear lens. Twenty-two (35.4%) of the 62 eyes received multiple DEX injections.

Clinical outcomes after intravitreal DEX injection are shown in Tables 4, 5, and 6. BCVA was significantly increased at 1, 3, and 6 months after the first DEX injection compared

Table 2. Indications for intravitreal DEX implantation (n=62)

Indication, n (%)	
CME + refractory vitreous haze	26 (41.9%)
CME	18 (29%)
Refractory vitreous haze	5 (8.1%)
Choroiditis	3 (4.8%)
Vasculitis	2 (3.2%)
Preoperative inflammation control	2 (3.2%)
Posterior scleritis	2 (3.2%)
CME + panuveitis	2 (3.2%)
Refractory vitreous haze + vasculitis	2 (3.2%)

CME: Cystoid macular edema, DEX: Dexamethasone

Table 3. Initial clinical characteristics of eyes treated with intravitreal DEX (n=62)

BCVA (LogMAR)	**0.55±0.46 (0-2.00)**
Vitreous haze score	
0	29 (46.8%)
1	9 (14.5%)
2	16 (25.8%)
3	8 (12.9%)
CFT (µm)	386±145
IOP (mmHg)	14.2±2.5
Number of injections (n=62)	
1	40 (64.5%)
2	19 (30.6%)
3	3 (4.8%)

BCVA: Best corrected visual acuity, CFT: Central foveal thickness, IOP: Intraocular pressure, DEX: Dexamethasone

Table 4. BCVA levels after intravitreal DEX implantation

	Number of dexamethasone implants			
	1	**2**	**3**	**p value***
Baseline				
Number of patients	62	22	3	
Mean (minimum-maximum)	0.55 (0.00-2.00)	0.51 (0.00-1.70)	0.40 (0.00-0.70)	0.701
SD	0.46	0.42	0.36	
1 month				
Number of patients	62	22	3	
Mean (minimum-maximum)	0.38 (0.00-2.00)	0.40 (0.00-1.00)	0.40 (0.00-0.70)	0.152
SD	0.39	0.34	0.36	
p value**	<0.001	0.051	1.000	
3 months				
Number of patients	62	22	3	
Mean (minimum-maximum)	0.32 (0.00-2.00)	0.38 (0.00-1.30)	0.46 (0.00-0.70)	0.891
SD	0.40	0.34	0.40	
p value**	<0.001	0.077	0.317	
6 months				
Number of patients	52	22	3	
Mean (minimum-maximum)	0.35 (0.00-2.00)	0.36 (0.00-1.30)	0.46 (0.00-0.70)	0.533
SD	0.42	0.35	0.40	
p value**	<0.001	0.030	0.317	

BCVA: Best corrected visual acuity, SD: Standard deviation, DEX: Dexamethasone, *Difference in responses at the same time points after repeated DEX implantation, **Statistical results of comparisons between BCVA levels at baseline and 1-, 3-, and 6-month follow-up examinations after DEX implantation

Table 5. Central foveal thickness measurements (µm) after intravitreal DEX implantation				
	Number of dexamethasone implants			p value*
	1	2	3	
Baseline				
Number of patients	62	22	3	
Mean (minimum-maximum)	386 (161-779)	384 (161-696)	333 (267-399)	0.474
SD	145	148	93	
1 month				
Number of patients	62	22	3	
Mean (minimum-maximum)	288 (158-399)	281 (158-375)	322 (265-379)	0.974
SD	55	56	80	
p value**	0.001	0.001	0.180	
3 months				
Number of patients	62	22	3	
Mean (minimum-maximum)	311 (185-618)	288 (209-392)	313 (264-363)	0.145
SD	106	49	70	
p value**	0.002	0.007	0.180	
6 months				
Number of patients	52	22	3	
Mean (minimum-maximum)	302 (176-542)	314 (214-570)	317 (259-376)	0.890
SD	75	89	82	
p value**	0.004	0.008	0.180	

CFT: Central foveal thickness, SD: Standard deviation, DEX: Dexamethasone, *Difference in responses at the same time points after repeated DEX implantation, **Statistical results of comparisons between CFT values at baseline and 1-, 3-, and 6-month follow-up examinations after DEX implantation

Table 6. Intraocular pressure measurements (mmHg) after intravitreal DEX implantation				
	Number of dexamethasone implants			p value*
	1	2	3	
Baseline				
Number of patients	62	22	3	
Mean (minimum-maximum)	14.2 (6-21)	14.6 (9-20)	15.6 (14-18)	0.453
SD	2.5	2.5	2	
1 month				
Number of patients	62	22	3	
Mean (minimum-maximum)	15.8 (5-22)	15.27 (10-19)	15.3 (15-16)	0.255
SD	2.7	2.2	0.5	
p value	0.007	0.227	0.655	
3 months**				
Number of patients	62	22	3	
Mean (minimum-maximum)	15.8 (9-27)	15.18 (11-18)	14 (12-16)	0.663
SD	3.1	1.8	2	
p value**	0.202	0.172	0.180	
6 months				
Number of patients	52	22	3	
Mean (minimum-maximum)	15.4 (9-25)	14.25 (10-20)	16 (14-18)	0.985
SD	3.8	3.6	2	
p value**	0.848	0.820	0.655	

IOP: Intraocular pressure, SD: Standard deviation, DEX: Dexamethasone, *Difference in responses at the same time points after repeated DEX implantation, **Statistical results of comparisons between IOP levels at baseline and 1-, 3-, and 6-month follow-up examinations after DEX implantation

to baseline (p<0.001). Although IOP was significantly higher than baseline at 1 month after injection (p=0.007), it did not differ significantly at 3 or 6 months (p=0.202 and 0.848, respectively). According to CFT measurements, CME decreased significantly compared to baseline values at 1, 3, and 6 months after treatment (p=0.001, 0.002, 0.004, respectively). VH was detected in 33 (53%) eyes before injection and 6 (10%) eyes 6 months after injection (Figure 1). Reductions in VH from baseline examination results were significant at 1, 3, and 6 months (p<0.001).

In eyes treated with a second DEX injection (n=22, 35%), the median interval between the injections was 4.5 months (range: 3-25 months). Only 3 eyes (4%) received a third DEX injection. Eleven eyes (17%) required repeat DEX injection within 6 months. Compared to eyes that received a single dose of DEX and those who received repeat DEX after an interval of 6 months or longer, these eyes showed similar improvement in BCVA and reduction in CFT, but IOP increased during the first months (Figure 2). Changes in BCVA, CFT, and IOP according to number of DEX injections are shown in Tables 4, 5, and 6, respectively. Eyes that received a second DEX injection showed significant increases in BCVA and decreases in CFT at 1, 3, and 6 months compared to baseline values, similar to after the first injection. IOP did not change significantly from baseline at any of the time points. In eyes that received a third DEX injection, BCVA, CFT, and IOP values did not show significantly changes at 1, 3, or 6 months after injection when compared with baseline values. Eyes that received a single injection and those that received two injections had statistically equivalent BCVA, CFT, and IOP values at baseline and all post-injection time points.

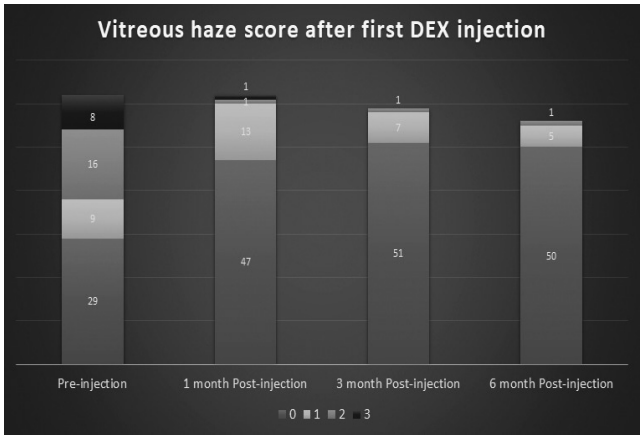

Figure 1. Distribution of the patients' vitreous haze scores before and at 1, 3, and 6 months after the first intravitreal dexamethasone implant injection. Vitreous haze decreased markedly in the first 3 months and this effect persisted to 6 months

DEX: Dexamethasone

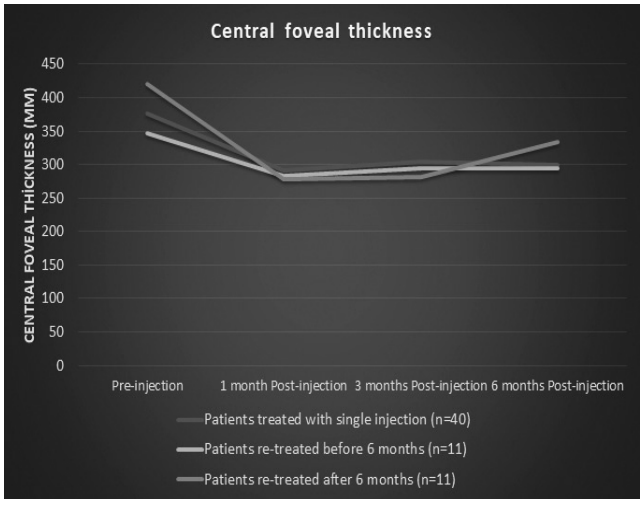

Figure 2. Central foveal thickness measurements before and 6 months after the first intravitreal dexamethasone implant injection in patients who received a single dose and those who received repeated doses after intervals of at least 6 months. The change in central foveal thickness was similar in all groups

At the beginning of follow-up, 25 of the 62 eyes were phakic with clear lens, 23 were pseudophakic, and 14 were phakic with cataract. At final examination, 9 of the 62 eyes were phakic with clear lens, 41 were pseudophakic, and 12 were phakic with cataract. Of the 18 eyes that were phakic at the beginning of follow-up and underwent cataract surgery during the follow-up period, 10 received a single DEX injection and 8 received two doses. Of the eyes that were initially phakic with clear lenses and developed cataract during follow-up but did not undergo surgery, 4 eyes received a single dose of DEX, 1 eye received two doses, and 1 eye received three doses. Five patients required topical antiglaucoma treatment during follow-up (IOP >20 mmHg). None of the patients required surgery due to high IOP. Prior to the first DEX injection, 28 (63.6%) of the 44 patients were receiving systemic therapy, with 16 (36.4%) using systemic steroids either alone or in combination with other drugs. At final examination, a total of 25 patients (56.9%) were receiving systemic therapy, with 8 (18.2%) patients receiving systemic steroid therapy either alone or in combination with other drugs (Table 7). There was no significant change when compared with their initial systemic therapies.

Discussion

In this study, we investigated the effectiveness of intravitreal DEX injections in noninfectious uveitis based on real-life outcomes. The results of this single-center, retrospective study showed that DEX injection was beneficial in suppressing ocular inflammation and that similar results could be obtained with repeated injections, but patients should be monitored closely for cataract and IOP. In addition, DEX injection was shown to facilitate systemic disease control and reduce the use of systemic steroids, but did not have a significant effect on systemic immunosuppressive therapy.

Suppressing intraocular inflammation and preserving vision are the main goals in the treatment of noninfectious uveitis. It was previously reported in the HURON trial that BCVA increases and is maintained for at least 6 months after DEX injection.[11] Although the HURON trial demonstrated the utility of DEX

Table 7. Number of patients using systemic drugs at initial and final examination (n=44)		
	Pre-injection	**End of follow-up**
No treatment	16 (36.4%)	19 (43.2%)
Systemic steroids only	5 (11.4%)	1 (2.3%)
At least 1 immunomodulatory agent	12 (27.2%)	17 (38.6%)
• Cyclosporine	3	2
• Azathioprine	1	3
• Interferon alpha 2a	3	4
• Leflunomide	1	-
• Infliximab	-	2
• Adalimumab	-	2
• Cyclosporine + Azathioprine	1	2
• Azathioprine + Colchicine	1	1
• Cyclosporine + Azathioprine + Colchicine	1	-
• Infliximab + Leflunomide	1	1
Steroid + at least 1 immunomodulatory agent	11 (25%)	7 (15.9%)
• Prednisolone + Cyclosporine + Azathioprine	1	4
• Prednisolone + Cyclosporine	3	1
• Prednisolone + Azathioprine	2	-
• Prednisolone + Azathioprine + Colchicine	1	-
• Prednisolone + Colchicine	2	-
• Prednisolone + Mycophenolate mofetil	1	1
• Prednisolone + Leflunomide	1	1

in the treatment of noninfectious uveitis, it was conducted in a limited patient group and provided short-term results, and thus provides limited information regarding patients encountered in real practice. In 2014, Zarranz-Ventura et al.[12] published a multicenter retrospective cohort study of DEX results in 82 eyes of 63 patients diagnosed with noninfectious uveitis. They reported statistically significant improvements in BCVA, CFT, and VH, though during the 1-year follow-up period, 40.7% of the patients required a second injection at a mean of 6.6 months. Tomkins-Netzer et al.[13] reported in another retrospective study that DEX remained effective for a median of 6 months. In their prospective study, Pohlmann et al.[2] showed that vision improved from 1 month and was preserved until 6 months. In the present study, visual acuity was significantly increased at 1, 3, and 6 months of follow-up compared to baseline BCVA and was well preserved. In this study, 31% (n=22) of the 62 eyes required a second dose injection at a median of 4.7 months, and 3 eyes (5%) received three doses of DEX.

The most common cause of vision loss in cases of noninfectious uveitis is CME.[14,15] Reduction in the frequency of CME results in improved visual acuity. Pohlmann et al.[2] determined that the effect of DEX on CME varies depending on the etiology. They reported that the decrease in CME lasts longer in patients with idiopathic uveitis than in cases of uveitis associated with sarcoidosis or other systemic diseases, and that CME decreases more rapidly in patients with birdshot retinochoroidopathy. It has also been reported that response to DEX is unaltered in chronic CME, and that visual improvement was achieved upon the complete resolution of CME even in cases resistant to other therapies.[16,17] The frequency of re-injection is higher in patients with chronic CME.[12,16] Our shorter re-injection period may be associated with the nonrandom patient selection, due to the probably long-term intraocular inflammation having limited response to the injection, the presence of chronic CME, or insufficiently suppressed systemic disease.

VH regresses as intraocular inflammation is suppressed. DEX suppresses local inflammation effectively as long as it remains in the vitreous.[2,12,18] Reduction in VH also increases visual acuity. In the present study, 33 of the 62 eyes had VH scores of 1+ or higher before the first injection, while only 6 eyes had VH scores of 1+ or higher 6 months after injection (1+ in 5 eyes, 2+ in 1 eye). DEX injection decreases VH in the long term by locally suppressing intraocular inflammation.

Management of noninfectious uveitis is challenging due to the severe and frequent side effects of systemic steroids, the short-lasting effect of off-label periocular or intravitreal triamcinolone injections, and IOP elevation frequently caused by these injections.[11] DEX has emerged as a safe and long-acting treatment for local inflammation control in combination with immunomodulatory and immunosuppressive systemic therapies.[11] With efficacy in noninfectious uveitis demonstrated by the HURON trial, DEX has provided intraocular inflammation control for approximately 6 months as well as significant increases in BCVA and significant decreases in VH and CFT. IOP increased by less than 10%. In a retrospective study of 1110 eyes treated with DEX, it was reported that only 65 eyes required topical antiglaucoma medication, 5 patients underwent selective laser trabeculoplasty, and none of the patients required surgery.[19] Similarly, in the present study we observed statistically significant increase in BCVA and decrease in CFT and VH. In

addition, IOP elevation requiring antiglaucoma medication (>25 mmHg) occurred in 5 of the 62 eyes in our study, consistent with the results of the HURON trial.

The main objective of DEX injection is local inflammation control. The main treatment approach for noninfectious uveitis is to control inflammation with systemic immunosuppressive agents and reduce the frequency of acute attacks. DEX injections facilitate rapid inflammation control in patients who do not have frequent exacerbations or have recently started receiving systemic therapy. In addition, it enables the rapid regression of pathologies that reduce vision, such as VH and CME. For patients already receiving systemic immunosuppressive therapy, DEX injection helps achieve local inflammation control before deciding to change their treatment regimen, which allows patients to continue with the same treatment they are used to and do not experience side effects with. Although the number of patients using systemic steroids decreased after DEX injection in our study, the number of patients receiving immunosuppressive therapy remained unchanged. In the earlier Multicenter Uveitis Steroid Treatment (MUST) trial of the fluocinolone acetonide implant, it was reported that it reduced the need for systemic immunosuppressive therapy and that disease control could be achieved with intravitreal injection.[20] Tomkins-Netzer et al.[13] found that 21 of the 33 eyes in their study did not require immunosuppressive therapy after a single DEX injection. In contrast, Tsang et al.[17] found that patients not receiving systemic therapy showed poorer response to DEX injection. Fabiani et al.[21] reported that the steroid dose given to patients was significantly reduced after DEX injection and described intravitreal DEX injection as a systemic steroid-sparing treatment. Although intravitreal DEX injection seems to reduce the need for systemic steroids, in general there is no evidence demonstrating its effect on systemic immunosuppressive therapy. Well-designed prospective studies on this subject are needed.

Study Limitations

One of the limitations of the HURON trial is that the patients were followed up for only 6 months and no long-term results are presented. Therefore, it does not provide sufficient information about the development of cataract in the longer term. In the MUST trial of fluocinolone acetonide implant, the prevalence of cataract was 80%.[20] Much lower cataract rates have been reported after DEX injection in other studies.[12,13,16] Nobre-Cardoso et al.[22] reported that all patients in their study who developed cataract had received multiple injections. In their prospective, single-center study, Pohlmann et al.[2] showed that the rate of pseudophakia was 50% in patients who were followed for an average of 22 months and increased to 94% before the fourth injection. In the present study, 23 of the 62 eyes were pseudophakic initially and 41 eyes were pseudophakic at the end of the mean 20-month follow-up period. Patients injected with DEX should be carefully monitored for cataract development in the long term, especially if repeated injections are needed.

The limitations of our study stem from its retrospective nature and small patient sample. Despite their small numbers, however, the inclusion of patient groups with various intraocular inflammation etiologies is a better representation of the patient profile encountered in real practice, which is a strength of our study.

Conclusion

In conclusion, intravitreal DEX injection is useful for suppressing intraocular inflammation, provides good visual and anatomical results in the long term, and preserves these effects with repeated injections. However, although it may seem safer than other intravitreal steroid treatments in terms of IOP and cataract formation, patients still require close follow-up. DEX appears to reduce the need for systemic steroids, but this phenomenon and its effect on systemic immunosuppressive therapies must be clarified by long-term prospective studies.

Ethics

Ethics Committee Approval: Ankara Numune Training and Research Hospital Clinical Research Ethics Committee E-18-2388.

Informed Consent: Written informed consent was obtained from each participant.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Murat Hasanreisoğlu, Zeynep Aktaş, Hatice Tuba Atalay, Şengül Özdek, Gökhan Gürelik, Concept: Murat Hasanreisoğlu, Hüseyin Baran Özdemir, Design: Murat Hasanreisoğlu, Hüseyin Baran Özdemir, Data Collection or Processing: Murat Hasanreisoğlu, Hüseyin Baran Özdemir, Kaan Özkan, Murat Yüksel, Analysis or Interpretation: Murat Hasanreisoğlu, Hüseyin Baran Özdemir, Literature Search: Murat Hasanreisoğlu, Hüseyin Baran Özdemir, Writing: Murat Hasanreisoğlu, Hüseyin Baran Özdemir.

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Original Article

Risk-based Algorithm-guided Treatment Protocol for the Management of Neovascular Age-related Macular Degeneration

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Abstract

Objectives: To assess outcomes of a risk-based algorithm-guided treatment protocol for neovascular age-related macular degeneration.

Materials and Methods: Two hundred and ten eyes of 184 patients managed with anti-vascular endothelial growth factor (anti-VEGF) agents according to a protocol consisting of one of three initial regimens depending on risk with at least 2 years of follow-up were retrospectively evaluated. The "short-term monthly injections" protocol was used for low-risk patients with low-risk lesions and good fellow-eye vision. Patients with low-risk lesions but without good fellow-eye vision, or those with good fellow-eye vision and high-risk lesions were managed according to the "short-term treat-and-extend (TREX)" protocol. The "extended TREX" protocol was for patients with high-risk lesions and low fellow-eye visual acuity.

Results: The initial treatment plan consisted of short-term monthly injections in 62 eyes (30%), the short-term TREX regimen in 120 eyes (57%), and the extended TREX regimen in 28 eyes (13%). Overall, 63% of cases met the criteria for cessation of treatment. Approximately 58% of these cases had recurrence, at a mean of 13 months. The mean change in VA from baseline was +9.0 letters at 12 months and +8.0 letters at 24 months. VA improved during a mean follow-up of 46.8±22 months, with a mean of 3.4±1.6 anti-VEGF injections per year.

Conclusion: The risk-based algorithm-guided treatment protocol yielded visual outcomes similar to those of the common alternative treatment and monitoring regimens, with a dramatically reduced number of injections, as required by the individual lesion and vision in the fellow eye.

Keywords: Anti-vascular endothelial growth factor, individualized medicine, neovascular age-related macular degeneration, treat and extend dosing

Introduction

Age-related macular degeneration (AMD) is the leading cause of vision loss and blindness among people aged 50 years and older in industrialized countries. Neovascular AMD (nAMD) affects only 10-15% of AMD cases, but accounts for more than 80-90% of cases of severe visual impairment.[1,2] The efficacy and safety of intravitreal anti-VEGF treatment (bevacizumab, ranibizumab, and aflibercept) has been demonstrated in multiple clinical trials and remains the initial treatment option for nAMD.[3,4,5,6,7,8,9,10]

Neovascular AMD includes a broad spectrum of genetic backgrounds and associated phenotypes. Unfortunately, individual responses to anti-VEGF treatment show substantial heterogeneity, and most eyes exhibit recurrent or resistant exudative features. Appropriate dosing of anti-VEGF therapy

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for patients with nAMD is essential for achieving the desired therapeutic outcomes. A fixed dosing regimen (monthly or bimonthly) has considerable visual acuity (VA) benefit.[3,4,7,13] However, frequent treatments are excessive for most patients and cause an economic burden and increase the risk of ocular and systemic side effects.[13] For this reason an individualized as-needed (PRN; pro re nata) dosing regimen involving close individualized monitoring and reactive treatment upon signs of disease activity has been widely adopted in clinical practice. Although the PRN therapy can reduce the number of injections, monthly assessment visits are still required to detect disease recurrence promptly. This places a heavy burden on clinicians and patients. At the same time, large-scale prospective trials and real-life studies have shown that these regimens often yield inferior visual outcomes, probably because of undertreatment, as shown by the low mean number of visits and injections.[5,6,15,16] The treat-and-extend (TREX) regimen, which attempts to take a proactive approach and tailor the treatment to the response of an individual patient, is becoming increasingly popular. This treatment regimen is associated with significantly fewer patient visits, injections, and annual direct medical costs than monthly injections, as shown in phase III trials.[10,11,12] Potential criticisms of the TREX approach include the possibility of overtreating a dry retina, an increased risk of atrophy, greater cost, and the need for treatment discontinuation criteria.

Neovascular AMD is a complex and chronic disorder. It is obvious that current treatment strategies may not be cost-effective, as the expected costs for a patient with newly diagnosed nAMD may reach $250,000 over 20 years.[17] A treatment strategy consisting of possibly indefinite anti-VEGF injections poses a financial, but also a social and psychological burden on elderly patients with other systemic comorbidities. It is known that a significant number of patients delay or discontinue treatment, and the early benefit gained from treatment could be lost over time. In observational studies, the number of patients who are lost to follow-up ranged between 17% and 34% at 1 year, between 16% and 47% at 2 years, to approximately 50% at 4-5 years.[18] Now the aim of therapy is shifting from merely saving distance VA to maintaining a good quality of life, reflecting the influence of treatment on daily living activities and emotional wellbeing.[18]

Treatment intervals and the number of injections need reassessment. Extensive research efforts have been directed to determining optimal management strategies for nAMD. A suitable treatment regimen remains an aim for individualized medicine.[19]

In this study, we describe a simple guide to risk classification according to lesion morphology and VA in the fellow eye, which is adjusted to real-life requirements. Also, we propose individualized therapeutic and treatment discontinuation criteria for patients treated with anti-VEGF agents for nAMD. We define this approach as a risk-based algorithm-guided treatment protocol. Rates of choroidal neovascularization (CNV) recurrence, the number of injections, and the VA outcomes using the proposed treatment approach have been evaluated.

Materials and Methods

This study was a retrospective chart review of patients with a diagnosis of nAMD who were managed with the newly defined "Risk-based Algorithm-guided Treatment Protocol" in a retina-only practice clinic (İstanbul Retina Institute, İstanbul, Turkey). The study protocol was approved by the ethics committee of Şişli Memorial Hospital, Istanbul. The study was performed in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained for each patient before anti-VEGF intravitreal therapy.

İstanbul Retina Institute's Protocol for Neovascular Age-related Macular Degeneration

The clinical risk assessment and stratification were based on the morphological features of CNV and the VA in the fellow eye (Table 1). According to our stratification of the lesions, larger classic and occult CNV lesions (>1 disc area), polypoidal choroidal vasculopathy (PCV), and retinal angiomatous proliferation (RAP) lesions require substantial attention and are considered high-risk. VA of less than 20/63 in a newly diagnosed nAMD patient suggests the need for careful monitoring and appropriate treatment. From our experience, this is an important risk factor for visual impairment. As a result, patients were classified into three risk groups.

Treatment strategies and regimens according to risk are presented in Table 2.

1) The short-term monthly injection protocol is used in low-risk patients with low-risk lesions and vision in the other eye that is adequate for everyday social activities. The treatment protocol consists of three intravitreal injections of anti-VEGF at monthly intervals (30±7 days) until the disease is inactive. From injection 3 and upon a dry macula on optical coherence tomography (OCT), patients undergo follow-up, initially monthly, and then, if the macula looks dry, with stepwise 2-week interval increase, to a maximum of a 3-month interval, until signs and symptoms of recurrent exudative activity are detected. Upon early recurrence (within 12 months after treatment cessation), the short-term TREX regimen is initiated. Upon late recurrence (12 months after treatment cessation), short-term monthly injections are re-initiated.

2) Patients with low-risk lesions but without good fellow-eye vision or those with good fellow-eye vision and high-risk lesions are classified as intermediate-risk patients and are managed according to the short-term TREX protocol. The short-term TREX protocol consists of a minimum of three monthly injections, until a dry macula is observed on OCT. Visit and treatment intervals are extended by 2 weeks. If there is increasing fluid on OCT, then the intervals are reduced by 2 weeks. The short-term TREX protocol is continued until treatments have been extended to a 3-month interval and patients have received at least eight intravitreal injections. After injection 8, if the macula is dry at the third 3-monthly visit, the treatment is stopped. Patients continue to be evaluated at 3-month intervals. Upon early recurrence, the extended TREX regimen is initiated. Upon late recurrence, the short-term TREX regimen is re-initiated.

3) The extended TREX protocol is for high-risk patients with high-risk lesions and low fellow-eye VA (i.e., those with a high risk of progression to bilateral blindness). The extended TREX protocol is initiated and implemented following the algorithm described above. In the 36 months after protocol implementation, if the macula is dry at each of three consecutive 3-monthly visits, then stopping treatment is considered. After treatment has been stopped, patients are followed up at 3-month intervals for any signs of recurrence. Upon recurrence at any follow-up time, the extended TREX regimen is re-initiated. If at any point during the treatment schedule patients fail to respond (no decrease in fluid or increase in VA) or if treatment response is inadequate (increasing fluid, decreasing vision, or both, related to the CNV process) as determined by VA and OCT findings, the anti-VEGF agent is switched to another agent or, in cases of PCV, a combination of photodynamic and anti-VEGF therapy.

Table 1. Risk-based algorithm approach: risk classification according to the morphological characteristics of the lesion and risk assessment according to visual acuity in the fellow eye (treatment-naïve eyes)

Baseline assessment			
1. Visual acuity testing 2. Optical coherence tomography 3. Fluorescein angiography 4. Indocyanine green angiography (RAP or PCV is suspected)			
Low-risk lesions		**High-risk lesions**	
· Active classic or occult choroidal neovasculopathy lesion with size ≤1.0 disc area		· Active classic or occult choroidal neovasculopathy lesion with size >1.0 disc area · Polypoidal choroidal vasculopathy · Retinal angiomatous proliferation	
Fellow eye visual acuity		**Fellow eye visual acuity**	
≥20/63	<20/63	≥20/63	<20/63
Low-risk patient	**Intermediate-risk patient**	**Intermediate-risk patient**	**High-risk patient**
1. Low-risk lesion + 2. Good vision in the fellow eye	1. Low-risk lesion + 2. Low vision in the fellow eye	1. High-risk lesion + 2. Good vision in the fellow eye	1. High-risk lesion + 2. Low vision in the fellow eye
RAP: Retinal angiomatous proliferation, PCV: Polypoidal choroidal vasculopathy			

Table 2. Flow chart for management of patients with neovascular age-related macular degeneration according to the risk-based algorithm approach

Risk-based Algorithm-guided Treatment Protocol		
Low-risk patient	**Intermediate-risk patient**	**High-risk patient**
Initial treatment plan		
Short-term monthly injections	**Short-term treat and extend**	**Extended treat and extend**
Dry macula at 3 months **Stop treatment*** Observe and extend (to maximum 3 months)	No recurrence at the third 3-monthly visit **Stop treatment†** Reevaluate at 3-month intervals	No recurrence at the third 3-monthly visit **Stop treatment‡** Reevaluate at 3-month intervals
Re-treatment plan		
Recurrence (>1 year): Previous protocol Recurrence (<1 year): Short-term treat-and-extend	Recurrence (>1 year): Previous protocol Recurrence (<1 year): Extended treat-and-extend	Recurrence: Previous protocol
The treatment regimen for patients who have been determined to be at low risk is a short-term monthly injection, which consists of 3 monthly intravitreal injections of anti-VEGF. Patients classified as intermediate-risk receive the short-term treat-and-extend protocol (8 injections in total) and those determined to be at high risk are managed using the extended treat-and-extend regimen (injections given up to 36 months). Subsequently, clinical features and optical coherence tomography findings define the pathway in the algorithm. *No conditions eligible to discontinue treatment; resume treatment with short-term TREX protocol. †No conditions eligible to discontinue treatment; resume treatment with extended TREX protocol, consider switching drug or combining with photodynamic therapy. ‡No conditions eligible to discontinue treatment; resume treatment with the same treatment protocol, consider switching drug or combining with photodynamic therapy (noncompliant patients, unable to have a timely follow-up visit).		

Data Collection

Medical records of 385 consecutive patients managed with anti-VEGF therapy for new nAMD between January 2010 and June 2018 were reviewed. Patients with irregular follow-up examinations and treatments, and those having less than 24 months of follow-up were excluded.

Exclusion criteria were: prior treatment of CNV in the study eye, advanced lesions composed of subfoveal and juxtafoveal fibrosis, geographic atrophy, retinal pigment epithelial tears, and extensive submacular hemorrhage.

All patients had been diagnosed with nAMD on the basis of clinical characteristics and multimodal imaging including spectral domain-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany), fluorescein angiography (FA), and indocyanine green angiography (ICGA) (particularly in cases of suspected PCV and RAP) and treated by two experienced retinal specialists (M.K. and S.A.) at a single institution. Indications for anti-VEGF therapy included hemorrhage and/or lipid exudation on ophthalmoscopy, presence of intraretinal and/or subretinal fluid accumulation with or without hyperreflectivity suggestive of CNV on OCT scan or any evidence of CNV disease activity on FA or ICGA. Treatments initially included intravitreal injections of bevacizumab (1.25 mg), ranibizumab (0.5 mg), or aflibercept (2.0 mg).

At every visit, patients were evaluated with OCT and best corrected VA was assessed by using ETDRS charts. FA and/or ICGA were performed at initial presentation and at other times at the discretion of the investigator. Patients were advised to return to the clinic sooner than scheduled if they noted any visual disturbance. If at any time there was a recurrence, as determined by clinical examination and OCT, treatment was re-initiated immediately.

Re-treatment criteria after discontinuation of therapy were: vision loss of ≥5 letters, intraretinal or subretinal fluid on OCT, or new hemorrhage. Extension criteria were based on absence of the following: macular fluid on OCT, vision loss of ≥5 letters, new macular hemorrhage, and increased lesion size or leakage on FA or ICGA.

Statistical Analysis

Pearson's chi-square tests were used to compare categorical variables. Student's t-test was used to explore differences in means among continuous variables. One-way analysis of variance (ANOVA) was used to compare means of three or more independent groups. Tamhane's test was used for post-hoc comparison of baseline VAs between initial treatment groups. A repeated-measures ANOVA was used to compares means across three or more repeated measures of VA. The Bonferroni post-hoc test was used to compare VA after cessation of anti-VEGF therapy and recovery of vision after the treatment re-institution due to recurrence of CNV. A p value less than 0.05 was considered statistically significant.

Results

Among 385 patients, 184 (210 eyes) met the inclusion criteria for the study cohort. The baseline demographic and clinical characteristics of participants in each initial treatment plan are detailed in Table 3. There were no significant differences in age and sex between the three initial treatment groups. About 14% (26/184) of the participants had bilateral study-eligible nAMD. No significant difference in lesion characteristics was observed between the short-term TREX and extended TREX groups. Mean baseline VA in the short-term TREX group was worse than in the short-term monthly injection group (p=0.003).

Overall, 133 eyes (63%) completed the initial planned treatment regimen and met the criteria for cessation of therapy. The remaining 77 eyes did not meet the criteria, and treatment was resumed in a stepwise manner, as determined by the

Table 3. Baseline demographic and clinical characteristics of patients managed with risk-based algorithm-guided treatment protocol for neovascular age-related macular degeneration

Characteristic	Initial treatment plan			
	Short-term Monthly	Short-term TREX	Extended TREX	All eyes
Number of eyes, n (%)	62 (30)	120 (57)	28 (13)	210 (100)
Sex, male/female %	34/66	37/63	57/43	39/61
Age (yrs), mean (range)	74 (54–92)	74 (50–90)	75 (55–90)	74 (50–92)
Visual acuity (Snellen equivalent), mean	20/45*	20/60*	20/53	20/54
Range	(20/20-20/100)	(20/20-20/400)	(20/20-20/100)	(20/20-20/400)
Visual acuity (EDTRS Letter Score)	67.5*	61.5*	64.0	63.5
Vision 20/40 or better, n (%)	30 (48)	51 (42)	16 (57)	97 (46)
Vision 20/200 or worse, n (%)	0 (0)	15 (13)	3 (11)	18 (9)
Lesion characteristics				
1. Occult, n (%)	53 (86)	57 (48)	18 (64)	128 (61)
2. Predominantly classic, n (%)	9 (14)	9 (7)	3 (11)	21 (10)
3. RAP, n (%)	0 (0)	37 (31)	6 (21)	43 (21)
4. PCV, n (%)	0 (0)	17(14)	1 (4)	18 (8)

n: Number, PCV: Polypoidal choroidal vasculopathy, RAP: Retinal angiomatous proliferation, TREX: Treat and extend, *Tamhane's post-hoc tests p=0.003

protocol. Of the eyes that completed the initial planned treatment regimen and for which treatment was stopped, 78 (59%) showed recurrence, and additional treatment was needed. A flowchart of the study showing the distribution and step-by-step directions regarding the algorithm is presented in Figure 1. The overall average time from completion of the initial treatment regimen to recurrence of CNV was 13.0±10.2 months (range, 2-43 months). The mean intervals from discontinuation of treatment to recurrence in the short-term monthly injection, short-term TREX, and extended TREX groups were 10.8±10 months (range, 2-24), 17.8±8 months (range, 2-43), and 6.2±2 months (range, 4-12), respectively. The recurrence interval for the short-term TREX group was significantly longer than for the short-term monthly injection (p=0.008) and extended TREX groups (p<0.001). Details are presented in Figure 2.

Mean VA after initial treatment with the short-term TREX regimen was significantly lower than the short-term monthly injection regimen at 12 months (20/38 vs 20/30) and 24 months (20/40 vs 20/30) (p=0.009 and p=0.001, respectively). The percentage of eyes with VA ≥20/40 at 12 months and 24 months was 57% and 52%, respectively. The proportions of patients at 12 months who had VA 20/40 or better after initial short-term monthly injections, short-term TREX, and extended TREX regimens were 82%, 64%, and 71%, respectively, slightly higher than for those who had VA 20/40 or better at 24 months (77%, 60%, and 57%, respectively). There was no patient with Snellen equivalent VA 20/200 or worse at 12 or 24 months.

Overall VA had improved significantly after 12 and 24 months of treatment (p<0.001). However, VA decreased in the subsequent years of treatment, but remained higher than baseline at 60 months after treatment. Overall, 66 eyes (31%) and 68 eyes (32%) gained ≥15 ETDRS letters and 4 (1.9%) and 10 (4.7%) eyes lost ≥15 letters from baseline to 12 months and 24 months, respectively. VA improved from 63.5 letters at baseline to 72.5 (+9.0) and 71.5 (+8.0) letters at 12 and 24 months, respectively. The overall mean VA at last follow-up was 20/47 (range, 20/20-20/400). There was no difference in mean VA at last visit between the three initial treatment groups. The overall mean follow-up period was 46.8±22 months (range, 24-92 months). There was no difference between the three initial treatment groups in mean follow-up duration.

The mean number of injections after initial short-term monthly injections (n=4.7) was significantly lower than number of injections after the initial short-term TREX (n=7.4) and extended TREX (n=7.8) regimens at 12 months (p<0.001). There were significant differences in the number of injections between the initial short-term monthly injection (n=8.5), short-term TREX (n=10.7), and extended TREX (n=13.2) regimens at 24 months (p<0.001). No significant differences in the number of injections between the initial short-term monthly injection (n=14.8) and short-term TREX (n=16.2) regimens was observed at the last visit, while the extended TREX (n=23.2) regimen group had a higher number of injections than these groups (p=0.001). Patients received a mean of 17.0±10 (range, 3–56) injections over a mean follow-up period of 46.8±22 months. The mean number of injections per year was 3.4±1.6 (range, 3-13).

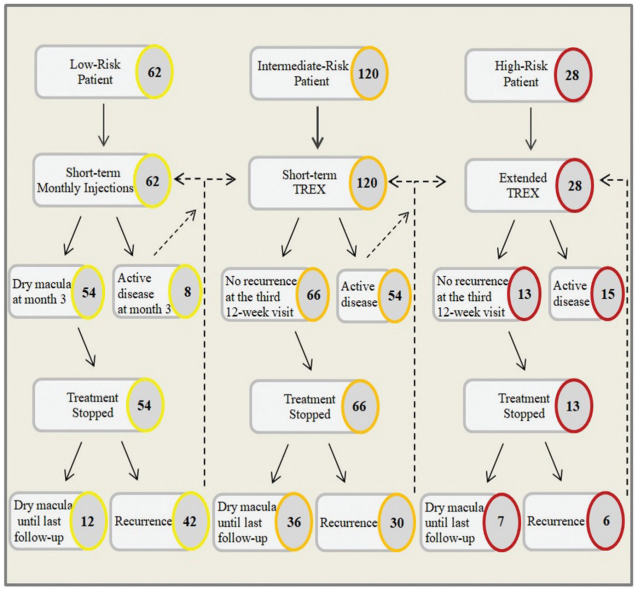

Figure 1. A flowchart of the study cohort showing the distribution of patients and step-by-step directions for the proposed risk-based algorithm-guided treatment protocol

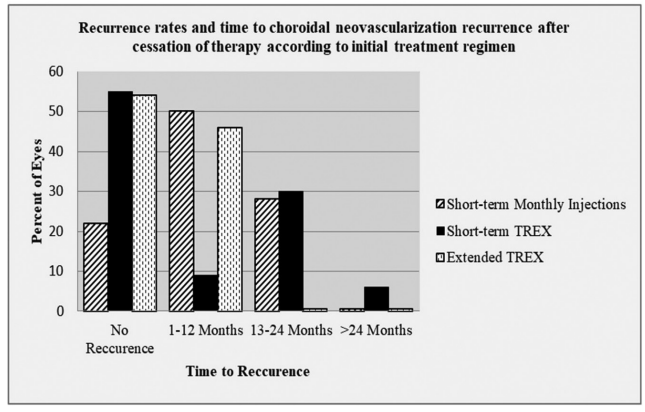

Figure 2. Recurrence rates and time to choroidal neovascularization recurrence after cessation of therapy.

Initial treatment approach short-term monthly injections: Overall, 87% (54/62) of the eyes met the necessary requirements for ceasing therapy. About 22% (12/54) of the eyes showed no recurrence during mean follow-up 47 months (range, 22–71 months), while 50% (27/54) of the eyes showed recurrence at 2–12 months, and 28% (15/54) showed recurrence at 13–24 months after cessation of therapy.
Initial treatment approach short-term TREX regimen: Overall, 55% (66/120) of the eyes met the necessary requirements for cessation of therapy. About 55% (36/66) of the eyes showed no recurrence during mean follow-up 25 months (range, 9–66 months), while 9% (6/66) of the eyes showed recurrence at 2–12 months, 30% (20/66) showed recurrence at 13–24 months, and 6% (4/66) showed recurrence at >24 months after cessation of therapy.
Initial treatment approach extended TREX regimen: Overall, 46% (13/28) of the eyes met the necessary requirements for cessation of therapy after mean 17 injections (range, 15–23). About 54% (7/13) of the eyes showed no recurrence during mean follow-up 15 months (range, 9–24 months), the remaining 46% (6/13) showed recurrence at 4–12 months (mean, 6.5 months) after cessation of therapy.

The overall mean yearly rate of change in VA and number of injections from baseline are shown in Table 4. Comparison of visual outcomes and number of injections between recent landmark clinical trials and our study population is presented in Table 5.

VA after CNV recurrence was compared with VA before the recurrence. The overall mean best corrected VA before initial recurrence was 20/38 and decreased significantly to 20/51 after recurrence (p<0.001). The mean VA of 20/44 in the period after re-institution of therapy was significantly lower than the mean VA before recurrence of CNV (p=0.001). There was no significant difference between the short-term monthly injection and extended TREX groups in mean VA before the recurrence and in the period after re-institution of therapy. Consequentially, the mean best corrected VA of 20/51 obtained in the period after re-institution of therapy was significantly lower than the mean VA of 20/44 before recurrence of CNV in patients managed with the short-term TREX regimen (p=0.01).

About 87% (n=54) of eyes in the short-term monthly injection group were fairly dry after three injections. Nineteen of these patients who completed the protocol and subsequently had recurrence were able to complete additional round(s) of short-term monthly injections (n=8), short-term TREX (n=10), and one patient completed a combination of short-term TREX and extended TREX regimens. Two patients from the short-term monthly injection group who did not meet the criteria

Table 4. Overall mean yearly rate of change from baseline in visual acuity and number of injections

Time (months)	Visual acuity		EDTRS letter gain/loss (mean)	Number of injections (mean)	Number of eyes
	Snellen equivalent (mean)	Letter score (mean)			
12	20/35	72.5	+9.0	6.7	210
24	20/37	71.5	+8.0	3.7	210
36	20/43	68.5	+5.0	3.6	139
48	20/44	68.0	+4.5	2.9	94
60	20/50	65.5	+2.0	3.0	60
72	20/60	61.0	-2.5	1.9	39
84	20/64	59.5	-4.0	1.8	26

Table 5. Findings of representative fixed dosing, as-needed, and treat-and-extend trials of anti-VEGF therapies compared with the risk-based algorithm-guided treatment protocol

Clinical trial	Baseline visual acuity (letters)	12-month results			24-month results		
		EDTRS letters gained (mean)	≥15 letters gained (%)	Number of injections (mean)	EDTRS letters gained (mean)	≥15 letters Gained (%)	Number of injections (mean)
Fixed-interval dosing							
ANCOR	47.1	11.3	40.3	12	10.7	41.0	24
MARINA	53.7	7.2	33.8	12	6.6	33.3	24
As-needed dosing (PRN)							
CATT							
Ranibizumab	61.5	6.8	24.9	6.9	6.7	30.7	12.6
Bevacizumab	60.4	5.9	28.0	7.7	5.0	28.3	14.1
HARBOR	54.5	8.2	30.2	7.7	7.9	33.1	13.3
Treat-and-extend							
LUCAS							
Ranibizumab	62.0	8.2	26.7	8.0	6.6	29.1	16.0
Bevacizumab	60.0	7.9	25.5	8.9	7.4	29.9	18.2
TREX AMD	59.9	10.5	25.0	10.1	8.7	30.0	18.6
ATLAS	58.9	7.2	27.5	8.0	2.4	22.5	14.5
Present study							
Risk-based Algorithm	63.5	+9.0	31.0	6.7	+8.0	32.0	10.4

PRN: Individualized as-needed, TREX: Treat and extend

for discontinuation of therapy were able to complete round(s) of short-term TREX and one completed an extended TREX regimen. About 55% (n=66) of eyes in the short-term TREX group were dry after eight injections. Fourteen patients who completed the short-term TREX protocol and subsequently had recurrence were able to complete additional round(s) of the short-term TREX protocol and three were able to complete the extended TREX protocol. Four patients who did not meet the criteria for discontinuation after initial short-term TREX were able to complete round(s) of the extended TREX regimen. Two patients who completed the extended TREX protocol and subsequently had recurrence were able to complete one additional round of the extended TREX protocol.

Most eyes received bevacizumab (65%, 136/210), aflibercept (11%, 23/210), or ranibizumab (2%, 4/210) treatment. The remaining eyes received a combination of bevacizumab and aflibercept (17%, 36/210), ranibizumab and aflibercept (2%, 4/210), or all three (3%, 7/210).

At baseline, 36% (75/210) of the eyes were pseudophakic. During follow-up, 13% (28/210) of the eyes underwent cataract surgery. About 21% (45/210) of the eyes had some degree of cataract at the last visit.

The proportion of eyes not lost to follow-up, before data collection, was 66% (139/210). The causes of loss to follow-up in the remaining 71 eyes included: death (n=19), relocation, missed or delayed examination due to systemic disease, or an unknown reason (n=52).

Discussion

This study investigated a cohort of treatment-naïve nAMD patients treated with anti-VEGF agents using a newly defined risk-based algorithm-guided treatment protocol based on individualized stratification according to the risk of visual impairment. This single-center retrospective series was managed by two physicians (M.K. and S.A.) over a period of 8.5 years. The VA outcomes obtained at 1 and 2 years were comparable to those in the large randomized trials of anti-VEGF therapy for nAMD and were maintained long term with continued treatment after a mean follow-up of 47 months. These benefits suggest that sustained long-term visual gains can be achieved in real-world settings with a significantly reduced number of anti-VEGF treatments (an average 3.4 injections per year), reducing loss to follow-up in the management of nAMD with a risk-based algorithm-guided treatment protocol.

Visual impairment following inappropriate management of nAMD has serious negative effects on patients' independence, productivity, and quality of life. Dilated fundus examination and use of advanced imaging modalities are essential for nAMD diagnosis and monitoring. Although there is no cure, timely and continuous treatment with intravitreal anti-VEGF injections is improving or maintaining VA and, on the basis of clinical trials, forms the mainstay of treatment.[3,4,5,6,7] On the other hand, it is well known that real-world challenges and unmet needs pose significant barriers to treatment goals, and unfortunately, visual outcomes in real-world evidence studies are usually worse.[18]

Frequent physician visits and imaging as well as therapy consisting of an uncertain number of anti-VEGF injections cause a significant burden on both patient and medical staff. Intravitreal injections may be associated with serious ophthalmic and systemic adverse events. Suboptimal outcomes can be associated with many complex factors: a significant number of patients delay or discontinue treatment owing to poor response, progression of untreatable aspects of the disease, or for financial and social reasons. Many questions relate to the optimal treatment regimen and duration, the frequency of follow-up and re-treatment, and which patients can discontinue treatment.[20]

Today, fixed dosing, PRN, and TREX regimens are offering the opportunity for a better balance of practicality and effectiveness when selecting the most appropriate treatment regimen. Because the effect of anti-VEGF agents is related to many complex factors, the benefit of therapy varies among patients. Consequently, optimal results cannot be obtained with any single regimen. This has encouraged us to develop a strategic plan for improving patient adherence to therapy and long-term visual benefit while optimizing follow-up and injection frequency. Our risk-based management strategy is based on recent scientific evidence and provides a risk classification according to CNV lesion morphology and VA in the fellow eye.

According to scientific evidence, some types of lesion are commonly associated with short- and long-term VA loss.[21,22,23,24] Post-hoc analyses of major phase III trials showed that eyes with the smallest lesions (≤1 disc area) had VA gains of approximately 10 ETDRS letters more than patients with the largest lesions.[21,22] Additionally, a larger baseline CNV area has been associated with a higher risk of fibrotic scar formation.[23] Larger baseline CNV lesions and the presence of baseline retinal pigment epithelium (RPE) elevation remain independently associated with worse short- and long-term VA.[24] Evidence from real-life studies has also shown significantly negative correlation between lesion area and visual change, and it has been suggested that individualizing anti-VEGF therapy on the basis of initial lesion characteristics could be a valuable approach.[25] It seems clear that baseline angiographic characteristics, such as larger CNV lesions, and OCT characteristics, such as greater subretinal tissue complex thickness, at baseline predict increased risk of VA loss. We strongly believe that larger CNV lesions deserve more attention, and according to our morphological classification criteria, are determined as lesions with high risk.

PCV is believed to be a subtype of nAMD.[26] The role of VEGF in the pathogenesis of PCV is not fully understood, and the optimal treatment strategy remains unclear. Based on clinical trial data, anti-VEGF monotherapy performed by PRN or fixed dosing can achieve anatomical and functional improvement and could be considered as first-line treatment for PCV.[27,28] There are limited data on the management of PCV with a TREX regimen using anti-VEGF agents. Recently, Pak et al.[29] reported outcomes of a TREX regimen using ranibizumab to treat 29 PCV patients for 12 months. The mean number of injections was 7, and after the loading phase, 41% (12/29) of the eyes had no recurrence.

It has been proposed that the number of injections could be expected to be higher when performed as monotherapy than when performed in combination with photodynamic therapy. Patients who were not receiving multiple injections (average, 7-8) over 12 months could not achieve the functional outcomes reported in clinical trials.[26,27] In view of the evidence, PCV lesions show a broad spectrum of clinical characteristics and according to our risk determination deserve considerable attention.

RAP is recognized as a variant of nAMD, characterized by abnormal communication between the choroidal and retinal circulation.[30] It has been proposed that as the anastomoses between the retinal and the choroidal circulation become more established, they become more resistant to anti-VEGF therapy.[31] Early in their evolution, RAP lesions are generally accompanied by intraretinal changes exquisitely sensitive to intravitreal anti-VEGF agents, so early aggressive therapy is essential for preventing irreversible neurosensory damage.[32,33] On the other hand, in RAP, choroidal thinning during continuous treatment may worsen RPE atrophy.[34] Certain clinical features related to RAP lesions should be taken into consideration, and according to our risk estimation, these lesions are determined high risk.

Clinical evidence has demonstrated that the severity of AMD in one eye tracks disease severity in the fellow eye.[35] This knowledge emphasizes the symmetrical nature of the disorder and has allowed us to be more certain when discussing prognosis, treatment, and monitoring strategies. It is well known that decreased VA is negatively associated with quality of life, and VAs between 20/50 and 20/100 cause decrements that require considerable help with daily functions.[36] VA in the better eye of less than 20/63 is defined as low vision and less than 20/400 is defined as blindness. Additionally, VA less than 20/63 in the worse-seeing eye is defined as unilateral low vision and less than 20/400 is defined as unilateral blindness.[37] Consequently, accelerated progression and inappropriate management of nAMD in a patient with low VA in their fellow eye could lead to restrictions in complex and social everyday activities. According to our criteria, fellow-eye VA of less than 20/63 in a patient with newly diagnosed nAMD is regarded as a significant risk factor for visual impairment and is considered a distinct entity establishing the protocol.

Multiple studies of monthly patient visits with PRN re-treatments have demonstrated that the number of injections varies between 3 and 24 over 2 years. The SUSTAIN study confirmed that approximately 20% of patients did not require re-treatment after the three initial monthly injections during the first 12 months, and 33% needed only one or two additional injections.[38] This supports individualized dosing and further suggests that good responders may be overtreated with monthly or TREX dosing strategies. Identifying this limited patient population of good responders means that overtreatment could be minimized. Some small lesions may require only the loading dosing, and may not need any treatment during the following years. Our risk-based approach aims to isolate this limited patient number among groups we have described as low risk. Patients who require infrequent treatment (>12-month recurrence-free) could continue short-term monthly injections, but if disease recurs within a few months, the TREX regimen seems to be a more suitable approach. Consistent with previous studies, a significant proportion (up to 22%) of low-risk cases in our study cohort had no recurrence during a mean follow-up of 47 months (range, 22-71) after the treatment was stopped following three monthly injections. More importantly, about 50% of the eyes showed early recurrence within 12 months after treatment cessation; however, a significant number of these eyes were able to complete subsequent round(s) of strict short-term TREX or extended TREX regimens.

Little is known about the outcomes of patients who discontinue anti-VEGF therapy. In the CATT 5 study, about 15% of the patients received no treatments between the end of the trial and the follow-up study visit.[39] Additionally, between the HORIZON exit and the SEVEN-UP evaluation, a mean of 3.4 years, 41% of study eyes received no treatment.[40] Recently, outcomes of a new treatment strategy, described as a treat-extend-stop protocol, have been reported. As soon as patients with nAMD managed with a TREX protocol achieved anatomical stability, the therapy was stopped. Approximately 40% of the eyes were able to stop treatment after mean of 22 injections (range, 7-48). Approximately 70% of these eyes remained stable, and the remaining 30% showed recurrence during a mean follow-up of 14 months.[41]

In our study, 63% of cases met the criteria and had treatment discontinued after a mean 6.8 injections (range, 3-23). Approximately 58% of these eyes showed recurrence a mean 13 months (range, 2-33) after cessation of treatment. Interestingly, 55% of the eyes managed with short-term TREX were able to stop treatment after eight injections. This percentage is higher than the percentage of those who stopped treatment in the treat-extend-stop protocol and was achieved with a lower number of injections. In the Aflibercept Treat and Extend Therapy for Neovascular Age-Related Macular Degeneration (ATLAS) study, 12-week or longer treatment intervals were achieved in 35% of the patients during the first year and in 41% during the second year.[12] The intervals for 68% of the patients in the TREX AMD Study were extended at the earliest possible visit or within one additional visit, and 30% had a macula that remained dry at every visit.[10] All of the data suggest that a significant number of patients managed with the TREX protocol could achieve substantial anatomic stability with early extension. It is important to emphasize that the mean initial baseline VA in our study cohort was considerably better than in other studies. It is well known that a higher initial VA, smaller CNV lesion, and early diagnosis and treatment with anti-VEGF agents is associated with better outcomes.[25,43,44,45] Consequently, the higher percentage in our study who achieved anatomical stability and could stop treatment after short-term TREX regimen could be explained by milder disease activity and prompt intervention. An important point that should be emphasized is that many patients treated with the treat-extend-stop protocol could stop therapy successfully and maintain improved vision even if the CNV recurred.[41] Interestingly, in a significant number

of patients who stopped treatment after short-term TREX, the vision loss after recurrence did not improve to the level of vision before recurrence. The recurrence of CNV after initial treatment cessation was associated with substantial mean VA loss of four letters. It is obvious that this last finding deserves special discussion and should be taken into consideration when discontinuation of scheduled treatment is planned.

In our study, the maximum mean gain in VA from baseline was recorded at 12 months and was largely maintained in more than 90% of the patients over a period of 36 months. It is noteworthy that the visual benefits obtained at 12 and 24 months were maintained to some extent long term in the subgroup of patients followed for 4 (n=94) and 5 years (n=60). However, mean VA at 6 years declined to 2.5 EDTRS letters worse than at baseline and 10.5 letters worse than at 2 years. There is limited evidence available on long-term follow-up in patients treated with anti-VEGF agents for nAMD. In the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) follow-up study (mean 5.5 years), mean VA declined to 3.3 letters worse than at baseline and 10.8 letters worse than at 2 years.[39] In the SEVEN-UP long-term follow-up study (mean 7.3 years), after baseline at entry into the ANCHOR or MARINA trials, there was a mean loss of 8.6 letters. From the therapeutic peak upon completion of 24 monthly injections in the ANCHOR or MARINA trials, mean vision had declined by 19.8 letters.[40] However, when interpreting such results it is important to consider that these long-term trials also had significant loss to follow-up and this may have influenced visual outcomes. In addition, treatment effectiveness under routine clinical practice conditions differs from that in well-conducted controlled prospective clinical trials. More recently, some single-center retrospective studies have evaluated the efficacy of the TREX dosing regimen of anti-VEGF treatment in real-life conditions.[25,45] Mrejen et al.[25] presented results of 210 eyes that were managed with the TREX protocol for a mean of 3.5 years (range, 1-6.6 years). Maximal visual benefits from baseline were obtained at 18 months, and despite a slight decrease long term, were maintained for 3 to 6 years. Jaki Mekjavic and Zaletel Benda[45] reported visual outcomes of 101 eyes that were continuously treated with anti-VEGF agents in the TREX protocol for 5 years. As a result, the improvement in VA was maintained for the first 3 years of treatment; however, after the fourth and fifth years of treatment, VA was not significantly different from baseline. Gillies et al.[46] designed an observational study (Fight Retinal Blindness [FRB] Study) and analyzed the long-term outcomes of 1212 eyes treated with anti-VEGF agents for a mean 53.5 months. VA improved after 6 months and remained above the baseline VA for approximately 6 years. After 7 years, mean VA was 2.6 letters lower than baseline.

At 5 years, 55% (33/60) of our patients had VA ≥20/40, compared to the CATT follow-up study[39] (50%), Gillies et al.[46] (43%), and Jaki Mekjavic and Zaletel Benda[45] (40%). Additionally, 20% (12/60) of our patients had VA ≤20/200, compared to the CATT follow-up study[39] (20%), Gillies et al.[46] (12%) and Jaki Mekjavic and Zaletel Benda[45] (8%). However, it should be noted that there are differences between the studies, including the mean baseline VA (present study: 63.5 letters; CATT follow-up study[39]: 62.2 letters; Jaki Mekjavic and Zaletel Benda[45]: 60.5 letters; Gilles et al.[46]: 55.1 letters; Mrejen et al.[25]: 52 letters) and the mean age at first injection (present study: 74.0 years; CATT follow-up study[39]: 77.5 years; Jaki Mekjavic and Zaletel Benda[45]: 81.8 years; Gilles et al.[46]: 79.1 years; Mrejen et al.[25]: 81.1 years). It seems that our study had a younger cohort with better baseline VA. Mrejen et al.[25] reported that older age at first injection correlated with worse VA in the short and long term. They also stressed that baseline VA and number of injections were predictors of visual change at all time points.[25] As has been already shown in long-term studies, a substantial proportion of our patients experienced gradual vision loss over periods of 3 to 7 years from the initial benefits obtained at 2 years, which could be related to the irreversible progression of untreatable aspects of this complex condition (expansion of the size of the neovascular complex, scarring, atrophy, and persistence of fluid).[39,40]

The mean number of injections received by patients in our study population was 3.4 per year. The mean number of treatments (6.7) was highest in the first 12 months. However, the mean number of treatments gradually decreased during the subsequent 6 years of follow-up (3.7, 3.6, 2.9, 3.0, 1.9, and 1.8, respectively). In the CATT follow-up study, the mean number of treatments in the 3 years after the 2-year clinical trial protocol was higher (15.4) than in our study from years 3 to 5 (7.8).[39] In the FRB study, the mean number of injections administered over the first year and over the second to seventh years were 6 and 5, respectively.[46] Jaki Mekjavic and Zaletel Benda[45] and Mrejen et al.[25] reported 6.1 and 8.3 mean injections per year, respectively, with a continuous TREX approach. Real-world studies in nAMD treatment have found that patients receive fewer treatments than in clinical trials, which results in worse visual outcomes.[18] This could be associated, in part, with the treatment burden of frequent visits leading to decreased patient adherence. Interestingly, recent papers reporting long-term real-world outcomes using the TREX regimen have concluded that initial VA is more important in predicting VA after treatment than the number of intravitreal injections received,[45] and patients with better initial VA preserve good VA after long-term treatment.[25] There is no doubt that prompt diagnosis and treatment at onset of nAMD is therefore essential. On the other hand, individualization of therapy is a current trend. In order to individualize therapy, we initially estimated the risk of visual impairment (initial lesion composition and fellow-eye VA) and initiated a treatment strategy that plays a key role in determining the injection number and injection intervals. Patients in our study had fewer visits and treatments, owing to the nature of the treatment protocol, thus reducing the treatment burden. The proportion of patients lost to follow-up (34%) for the entire cohort was better than previously reported.[25]

Despite the success of anti-VEGF therapy in restoring vision and preventing damage associated with CNV, there has been

increasing concern that anti-VEGF therapy may increase the risk of RPE atrophy in eyes with neovascular AMD. Some studies have identified an association between the number of anti-VEGF treatments over time and the growth rate of RPE atrophy.[34,47,48] It is unclear whether anti-VEGF therapy accelerates or increases the risk of macular atrophy. However, while the relationship is unclear, the number of anti-VEGF interventions should be limited to the minimum required to control the disease.[32] Because a higher treatment rate is associated with better VA results but could increased the risk of atrophy, an individualized therapeutic approach may keep the right balance between too many and too few treatments.[25] To obtain long-term results, we have proposed a strategic plan based on initial lesion composition and risk of visual impairment, in which re-treatment and follow-up periods are adjusted according to patients' responses to therapy. According to our data, it appears reasonable to consider discontinuing treatment when anatomical stability is achieved in order to minimize the burden of treatment and potential for atrophy. However, it should not be forgotten that patient adherence to follow-up plays a key role in reducing the risk of complications associated with recurrent CNV activity.

Study Limitations

There are inherent limitations to our study that need to be carefully considered, including its retrospective nature and single-center design. Additionally, the therapeutic agents available during our long follow-up period (up to 92 months) have changed, and the number of patients at each extended follow-up period of 6 and 7 years is small. A significant proportion of patients had some degree of cataract, which could affect the VA outcomes. The study population included bilateral cases, in which both eyes should be treated simultaneously. The results of the study may be difficult to interpret and not easily comparable because the risk-based protocol represents a unique approach in the management and monitoring of nAMD. Additionally, this treatment approach could be much more complex than presented here.

Conclusion

This study represents a treatment approach that takes into account real-life requirements and challenges in the management of nAMD on the basis of current evidence from clinical trials on anti-VEGF therapy. The risk-based algorithm-guided treatment protocol yielded visual outcomes similar to the common alternative treatment and monitoring regimens with a dramatically reduced number of injections as required by the individual patient pathology and vision in the fellow eye. The favorable functional and anatomical outcomes obtained in our study with a lower number of injections could be attributable to many factors: a younger study cohort, higher baseline VA (early presentation, mild CNV activity), prompt diagnosis, improved patient adherence, and strict regimentation of anti-VEGF injections and monitoring by the clinician. The risk-based algorithm-guided treatment protocol holds potential to provide clinicians and patients the opportunity for optimal vision gains and anatomic disease control with substantially decreased treatment burden and noncompliance, as well as a lower cumulative risk of injection-related adverse events. Additionally, preplanning of the injections enables optimization of use of the medical staff and technical resources. Despite some limitations, we believe our research findings are important in guiding routine clinical practice.

Ethics

Ethics Committee Approval: İstanbul Şişli Memorial Hospital Ethics Committe.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Murat Karaçorlu, Serra Arf, Concept: Murat Karaçorlu, Serra Arf, Design: Murat Karaçorlu, Serra Arf, Data Collection or Processing: Mümin Hocaoğlu, Işıl Sayman Muslubaş, M. Giray Ersöz, Analysis or Interpretation: Mümin Hocaoğlu, Murat Karaçorlu, Serra Arf, Literature Search: Mümin Hocaoğlu, Işıl Sayman Muslubaş, M. Giray Ersöz, Writing: Murat Karaçorlu, Mümin Hocaoğlu.

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Original Article

Clinical Results in Patients with Combined Penetrating Keratoplasty and Vitreoretinal Surgery Using Landers Wide-field Temporary Keratoprosthesis

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Abstract

Objectives: To evaluate the clinical results of combined pars plana vitrectomy (PPV) with Landers wide-field temporary keratoprosthesis and penetrating keratoplasty (PK).

Materials and Methods: From January 2016, traumatic eyes with coexisting corneal and vitreoretinal diseases that underwent combined keratoprosthesis/PPV/PK surgery were retrospectively evaluated. Demographic characteristics, visual acuity (VA), intraocular pressure (IOP) and clinical findings of the cornea, lens, and retina were recorded during the follow-up. Cases with clear corneal graft, attached retina, normotonic IOP, and improved or stable VA were considered successful.

Results: Eight eyes were enrolled in the study. The mean follow-up time was 21.1±8.20 months. Surgery was performed a mean of 23 (10-40) days after trauma. Preoperative VA ranged from no light perception to counting fingers from 50 cm. Postoperatively, corneal graft was clear in 5 patients (62.5%) and retina was attached in 6 eyes (75%). Chronic hypotonia developed in 3 patients (37.5%). VA was unchanged in 3 patients and improved in 5 patients. A total of 5 cases (50%) were considered successful. Shorter interval between trauma and surgery was associated with higher likelihood of success (p=0.043). No significant difference was observed between the groups in terms of type or location of trauma (p=1; p=0.143).

Conclusion: Although the functional results are not very satisfactory, the combined procedure provides a final opportunity for preserving remaining vision and anatomic reconstruction in eyes that will otherwise result in phthisis due to severe anterior and posterior segment pathologies.

Keywords: Temporary keratoprosthesis, pars plana vitrectomy, penetrating keratoplasty

Introduction

Visualization of the posterior segment during pars plana vitrectomy (PPV) may be impeded by diffuse corneal edema secondary to ocular traumas, distortions due to suturation of large and irregular corneal lacerations, or corneal scars. For cases like these which were previously considered inoperable, we now have alternatives such as open sky vitrectomy, endoscopic PPV, or PPV surgeries using temporary keratoprosthesis.

Temporary keratoprostheses are auxiliary instruments that are temporarily sutured to the trepanized corneal bed to provide a clear view during PPV in eyes with an opaque cornea. The first keratoprostheses described by Landers in 1981 were biconcave instruments made of polymethylmethacrylate (PMMA) with

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a cylindrical optical body 5 mm in length.[1] However, these keratoprostheses leaked, caused distortion, and had a narrow viewing field that made it difficult to see the anterior and peripheral retina, leading to the development of new interfaces. In 1993, the Landers wide-angle keratoprostheses with convex anterior surface and 1-mm cylindrical body were produced (Figure 1).[2] Another alternative, Eckardt keratoprostheses, are made of silicone but were not superior to the Landers keratoprosthesis because they lacked durability over multiple uses.[3]

In the present study, we report our anatomical and functional outcomes of combined penetrating keratoplasty (PK) and PPV using the latest generation Landers keratoprosthesis.

Materials and Methods

The study included traumatic patients who underwent the triple procedure of combined PK and PPV with Landers wide-angle keratoprosthesis (7.2 mm version, Ocular Instruments, Bellevue, USA) in the Manisa Celal Bayar University Department of Ophthalmology, a tertiary referral ophthalmology center, since January 2016.

This retrospective cross-sectional study was approved by the university ethics committee and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the patients before surgery.

The patients' demographic information (age, sex), follow-up time, findings in preoperative/postoperative full ophthalmological examinations, and postoperative complications (graft rejection, infection, glaucoma, phthisis, retinal detachment [RD]) were recorded.

Visual acuity (VA) could not be measured using Snellen chart, and were instead recorded as hand motion (HM), counting fingers (CF), light perception (LP), or no LP (NLP). Intraocular pressure (IOP) was measured using applanation tonometry. Patients with IOP between 8 and 21 mmHg were considered normotonic.

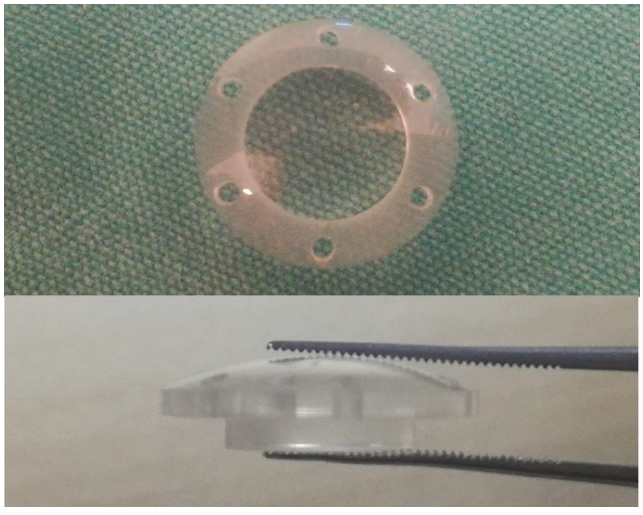

Figure 1. Landers wide-angle keratoprosthesis

Eyes included in the study had corneal pathologies secondary to open globe injuries, accompanied by vitreoretinal pathologies. The patients underwent primary corneoscleral suturation as an emergent intervention. The combined triple procedure was performed as a secondary surgical procedure in eyes found to be normotonic in follow-up following primary suturation.

Primary endpoints of the study were defined as corneal graft transparency, retinal attachment, IOP (normotonic/hypotonic), and VA (increased, maintained or decreased).

Patients with VA of HM or better at last follow-up visit were considered to have functional vision.

Eyes with transparent graft, attached retina, normotonic IOP, and maintained or increased VA were classified as successful.

Ocular Trauma Classification

Based on the Birmingham Eye Trauma Terminology[4], trauma cases were categorized as rupture, perforation, and penetration. Based on the Ocular Trauma Classification (OTC), wound sites were classified as Zone 1 if limited to the cornea, Zone 2 if extending into the sclera within 5 mm posterior of the limbus, and Zone 3 if posterior to Zone 2.[5]

Surgical Procedure

All surgeries were performed under general anesthesia by surgeons experienced in anterior segment surgery (H.M.) and vitreoretinal surgery (Ö.K.).

A 23-gauge (G) sclerotomy was made in the lower temporal quadrant for infusion cannula placement. After connecting the infusion line (Ocrosol Balanced Salt Solution, Polifarma, Turkey), ocular tone was achieved (Figure 2A, B).

The recipient cornea was trepanned (Hessburg Barron, Jedmed Ltd, St. Louis, USA) and full-thickness excision was performed using microcorneal scissors. A 7.2-mm Landers wide-angle prosthesis was sutured to the corneal bed using 6-0 vicryl (Johnson & Johnson, USA) (Figure 2C). Anterior segment procedures such as cataract extraction, secondary intraocular lens (IOL) implantation, scleral fixation IOL implantation, and synechiolysis were performed when necessary.

Vitrectomy trocars, endoillumination probe, and chandelier light probe were introduced through pars plana sclerotomies and standard 4-port 23-G PPV surgery was performed (Constellation, Alcon, Fort Worth, TX, USA). An Elbos wide-angle imaging system (Möller-Wedel, Wedel, Germany) was used during surgery (Figure 2D). Core vitrectomy, vitreous base cleaning, and fibrovascular membrane cleaning were performed in all cases. Perfluorocarbon fluid (Teknomek, Istanbul, Turkey), endolaser photocoagulation (Oculight SC, IRIDEX, California), and relaxing retinectomy procedures were also employed when indicated. Silicone oil (Mersilicon 1000, Meran, Istanbul) was used as intraocular tamponade when indicated.

In the third stage of the surgery, the keratoprosthesis was removed and a corneal graft that was 0.5 mm larger than the recipient corneal bed and stored in McCarey–Kaufman medium was sutured to the recipient corneal bed using 16 individual 10-0 nylon sutures (Visionary Medical Supplies Inc. Madison, USA) (Figure 2E).

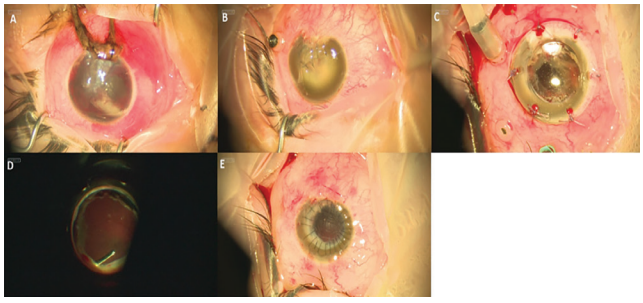

Figure 2. Stages of combined keratoprosthesis, pars plana vitrectomy, and penetrating keratoplasty surgery in a traumatic eye

Postoperative Care

Postoperative topical moxifloxacin (Vigamox, Alcon, Novartis Company, USA) and prednisolone acetate (Pred forte, Allergan, USA) were applied 8 times daily; cyclopentolate (Siklopleji n 1%, Abdi Ibrahim, Turkey) was applied 3 times daily. All patients continued to receive low-dose steroid (3 times daily) for at least a year.

Corneal graft transparency, VA, IOP, retinal attachment, and complications were evaluated in follow-up examinations.

Statistical Analysis

Statistical analysis was performed using SPSS 24.0 for Windows. Data were recorded as mean ± standard deviation. Distribution pattern was determined based on Shapiro-Wilk test. Categorical variables were compared using Fisher's exact test, numerical variables were compared using tests appropriate for their distribution patterns (Student's t test for normal, Mann-Whitney U test for nonnormal distributions). A p value <0.05 was considered significant.

Results

Table 1 summarizes the clinical and demographic characteristics of the patients. A total of 8 patients with open globe trauma were included in the study. Seven of the patients were male and 1 was female. The mean age of the cases was 47.50±15.91 years (16–64 years). The mean follow-up time was 21.13±8.2 months (3-28 months). Mean preoperative IOP was 12.88±4.05 mmHg (8-18 mmHg). In our study, the mean time from trauma to combined surgery was 23 days (10-40 days).

According to OTC, 6 of the cases were rupture and 2 were penetration. Wound sites were in Zone 2 in 3 cases and Zone 3 in 5 cases. The trauma patients who underwent combined surgery were those who underwent emergency primary corneoscleral suturation and were not hypotonic during follow-up.

In all cases, the intraocular structures could be visualized without distortion during surgery. The peripheral retina could be seen upon indentation. The keratoprosthesis did not leak during indentation. There were no intraoperative complications.

Preoperative Findings

Two eyes exhibited diffuse corneal edema secondary to trauma. One eye had leukoma and another had hematic cornea. In the other 4 eyes, corneal anatomy was severely disrupted due to irregular suturation secondary to trauma (Table 1).

Evaluation of preoperative and intraoperative posterior segment pathologies revealed vitreous hemorrhage in all cases. Four eyes also had RD. Nucleus drop was seen in 3 eyes (Table 1).

VA before combined surgery ranged from NLP to CF from 50 cm. Vision level was LP in 5 eyes and HM, CF 50cm, and NLP in the other 3 eyes.

Silicone oil was used as a tamponade during surgery.

Postoperative Findings

None of the corneal grafts showed postoperative wound leaks. At last follow-up visit, corneal graft failure was observed in 3 eyes (37.5%), while the other 5 eyes (62.5%) had transparent corneas. One eye underwent rekeratoplasty at 8 months due to infectious corneal ulcer, and the cornea was transparent at last follow-up (Patient 3). Early graft rejection (month 3) occurred in a young patient (Patient 6).

Retinal attachment was observed in 6 eyes (75%) during follow-up. Silicone was present in one of the eyes with attached retinas while it was removed in the other. Two eyes (25%) showed RD under the silicone.

The mean postoperative IOP of the eyes was 10±4.27 mmHg. In terms of complications, 3 eyes (37.5%) had chronic hypotony and 2 of those eyes resulted in phthisis. Proliferative vitreoretinopathy (PVR), macular atrophy, and graft rejection occurred in 1 eye each. One eye developed infectious corneal ulcer but had transparent graft in follow-up after the second PK.

VA at final visit was unchanged in 3 patients and improved in 5 patients. The greatest increase in VA was from LP to CF 20 cm in Patient 7. Functional vision (HM or better) was achieved in 6 cases (75%).

In total, 4 cases (50%) were considered complete success and 4 cases (50%) were considered failed. The demographic and clinical characteristics of the successful and failed cases are summarized in Table 2. In our study, successful trauma cases had significantly shorter mean time to surgery than failed cases (p=0.043). Success was not associated with type or location of trauma (p=1, p=0.143).

None of the cases had indications for enucleation or sympathetic ophthalmia.

Discussion

In this series of patients with corneal opacification secondary to trauma and coexisting vitreoretinal pathologies, combined PPV and PK surgery performed with Landers wide-angle keratoprosthesis resulted in retinal attachment in 6 cases (75%), normotony in 5 cases (62.5%), and graft transparency in 5 cases (62.5%). VA did not decrease in any of the cases, increased in 5 cases (62.5%), and was unchanged in 3 cases. In total, 4 cases (50%) were considered completely successful.

Various alternatives have been used in attempts to perform posterior segment surgeries in eyes with corneal opacities. The main alternatives are performing PK followed by PPV in a separate session, performing simultaneous open sky vitrectomy with corneal excision, or performing PPV with endoscopic methods or temporary keratoprostheses.[6]

Table 1. Detailed demographic and ocular features of the patients

Patient No	Age (years)	Gender	Trauma classification	Visual acuity		IOP (mmHg)		Preoperative/intraoperative findings			Postoperative findings			Complications	Follow-up time (months)	Time to surgery (days)
				Preop	Postop	Preop	Postop	Cornea	Lens	Retinal	Cornea	Lens	Retinal			
1	51	Male	Penetration, Zone 2	HM	HM	15	12	Leukoma	Dislocated nucleus	VH	Clear	Scleral fixation lens	Attached		27	10
2	48	Female	Rupture, Zone 3	LP	LP	9	Hypotony	Diffuse edema	Traumatic cataract	VH, RD	Opaque	Aphakic	Detachment, silicone+	PVR, hypotony	24	35
3	64	Male	Rupture, Zone 3	LP	HM	13	Hypotony	Cornea with central sutures, Leukoma	Lens rupture	VH, RD	Clear	Scleral fixation lens	Attached, silicone+	Postop month 8: infective corneal ulcer, hypotony	28	28
4	60	Male	Penetration, Zone 3	NLP	NLP	18	Hypotony	Total hyphema	Nucleus drop	VH, RD	Opaque	Scleral fixation lens	Detachment, silicone+	Prephthisis, hypotony	19	40
5	62	Male	Rupture, Zone 3	LP	HM	8	14	Cornea with irregular sutures	IOL drop	VH, RD	Clear	Aphakic	Attached		23	15
6	16	Male	Rupture, Zone 3	LP	HM	15	12	Cornea with irregular sutures	Lens rupture	VH	Opaque	Aphakic	Attached	Graft rejection	3	20
7	39	Male	Rupture, Zone 2	LP	CF 20cm	8	15	Cornea with irregular sutures	Traumatic cataract	VH	Clear	Scleral fixation lens	Attached		27	12
8	40	Male	Rupture, Zone 2	CF 50cm	0.05	17	12	Diffuse edema	IOL drop	VH	Clear	Scleral fixation lens	Attached	Macular atrophy	18	26

IOP: Intraocular pressure, HM: Hand motions, VH: Vitreous hemorrhage, LP: Light perception, NLP: No light perception, RD: Retinal detachment, IOL: Intraocular lens, CF: Counting fingers (from distance of)

Table 2. Demographic and ocular features of successful and unsuccessful cases

	Successful (n=4)	Failed (n=4)	p value
Male/female	4/0	3/1	1.00*
Age (years)	48±10.80	47.78±21.75	0.831¥
Follow-up time (months)	23.75±4.27	18.50±10.97	0.669¥
Time to surgery (days)	15.75±7.13	30.75±8.69	**0.043¥**
Preoperative IOP (mmHg)	12±4.69	13.75±3.77	0.915¥
Rupture/Penetration ratio	3/1	3/1	1.00*
Zone 2/Zone 3 ratio	3/1	0/4	0.143*

* Fisher's exact test, ¥ Mann–Whitney U test, IOP: Intraocular pressure

When PK and PPV surgeries are performed in separate sessions, PPV may be delayed due to risks such as persistent corneal edema or graft rejection. Moreover, it has been reported that fluid movements in the anterior chamber and ocular manipulations during PPV also risk damaging the corneal graft.[7]

In the open sky method, ensuring rotational eye movement and eye positioning is difficult, and there is risk of extracortical hemorrhage.[8]

Temporary keratoprostheses are auxiliary surgical instruments that enable posterior segment visualization in eyes with corneal opacities. These devices have been shown in the literature to allow all maneuvers without leaking any fluids during surgery.[8,9,10] This technique is also recommended for the subacute management of massive ocular traumas.[11] It has been found superior to other methods because it allows closed-system surgery, wide-angle stereoptic vision, and bimanual surgery.

Consistent with the literature, there were no complications in terms of peripheral vision, scleral indentation, or leaks during the surgeries utilizing the wide-angle Landers keratoprosthesis in this study.

In PK surgery, it has been reported that preparing a corneal graft 0.5 mm larger than the recipient bed prevents postoperative angle-closure glaucoma.[12] In our case series, we used grafts of similar dimensions and encountered no problems.

Different results have been reported in the literature regarding anatomical reconstruction and visual gains after combined triple surgery with keratoprosthesis. The reported corneal graft survival rates are 25-79% and retinal attachment rates are 48-100%, while the proportion of postoperative normotonic eyes is 20-75%. In terms of VA, the proportion of eyes in the literature that achieve a functional level of vision is 25-75%.[7,8,13,14,15,16,17,18]

The most commonly reported complications in triple combined surgeries are graft failure and hypotony. Glaucoma and graft rejection occur less frequently.[3,7,8,14,19,20] In our case series, hypotony occurred in 3 eyes, graft failure in 2 eyes, and graft rejection in 1 eye. One eye developed PVR and another exhibited macular atrophy.

One of the most important causes of such discrepancies in the literature has been associated with the inclusion of eyes with varying severity of primary pathology and separate groups such as traumatic and nontraumatic cases. Some authors have suggested that postoperative complications observed in trauma cases are more related to the severe damage resulting from the primary trauma rather than the stress caused by combined surgery.[21] They cited their cases in which positive outcomes were attained despite undergoing more invasive procedures as support for this hypothesis.[21] In another study supporting this hypothesis, OTC rupture or Zone 3 traumas, scleral lacerations larger than 10 mm, and ciliary body damage were determined to be poor prognostic factors.[22]

Conflicting results have also been reported regarding the prognosis of traumatic and nontraumatic cases. Gelender et al.[21] found that trauma cases had a poorer prognosis in their small case series, whereas Garcia-Valenzuela et al.[8] reported that prognosis was poorer in nontraumatic cases due to the more chronic disease course.

In the present case series, two of the traumas were penetrating and six were ruptures. For both types, the success rate was 50%. Trauma location was Zone 3 in five cases and Zone 2 in three cases. Anatomic reconstruction was achieved in only one (20%) of the Zone 3 cases (20%) and all of the Zone 2 cases. The relatively poor prognosis of Zone 3 cases in our series was consistent with the literature, but we observed no significant correlation between success rate and whether the trauma cases were rupture or penetration.

Another factor reported to impact surgical success is postoperative contact of the silicone oil tamponade with the corneal endothelium.[23,24] Type of tamponade used in case series and differences between cases in terms of tamponade permanence and lens status may be other causes of the discrepant results found in the literature. In this study, silicone tamponade was used during surgery in all cases and was not removed from three eyes that were prephthisic. However, we did not encounter graft failure due to silicone oil/endothelium contact in our case series. In some of our patients, IOL prevented silicone/endothelium contact, while in other cases the silicone oil was removed before any damage occurred. In this respect, we believe that the small number of aphakic cases (37.5%) had a positive impact on prognosis.

Due to the risk of graft failure associated with long-term silicone exposure and aqueous humor deficiency, Chen et al.[25] suggested suturing the removed corneal tissue back in place rather than placing an allograft in the same session, then performing PK in selected eyes with IOP higher than 8 mmHg. However, in their study, 62% of the eyes developed persistent hypotony and 13.5% had indications for enucleation. They reported that anatomic correction was achieved in only 15 eyes (20%).

Persistent corneal edema is one of the most important poor prognostic factors in combined surgeries. In their large series of 34 trauma cases, Roters et al.[23] reported phthisis in 8 eyes, hypotony in 10 eyes, and graft failure due to silicone/endothelium

contact in 21 eyes. In eyes that definitely did not have graft rejection, decreased aqueous humor secretion, inadequate feeding of the corneal endothelium due to low hydrostatic pressure, and postoperative inflammation have been implicated in the etiopathogenesis.[26,27,28] In this regard, hypotony is a risk factor on its own. Three eyes in the present study had corneal edema, two of which also exhibited hypotony. A 16-year-old patient with corneoscleral rupture in Zone 3 did not have hypotony but early graft rejection was observed at postoperative 3 months.

In such cases, timing of the surgery is another controversial issue. Roters et al.[23] recommended postponing the surgery to promote graft survival. They speculated that the risk of graft rejection is higher in surgeries performed within the first 8 months after trauma, and recommended that PK surgery be postponed until ocular inflammation subsides. However, inability to visualize the retina in postoperative follow-ups is an important drawback of this approach. Lee et al.[29] reported that performing surgery within the first month improved prognosis in terms of retinal reconstruction. In our study, the mean interval between trauma and surgery was significantly shorter in successful cases.

Endoscopic PPV is performed as another alternative to temporary keratoprostheses. Studies comparing the two methods have shown that outcomes are similar in terms of anatomical and functional success. Endoscopic surgery was found to be superior in terms of the shorter time to diagnosis and surgery.[17,19] Disadvantages of endoscopic surgery are that it does not allow for bimanual surgery, does not provide stereopsis, and is costly.[6]

Study Limitations

Limitations of our study are its retrospective design and small number of cases. However, our results suggest that the combined triple procedure of PPV and PK with temporary keratoprosthesis enables intervention in a single surgical session as a last chance for anatomic and functional rehabilitation of eyes which would otherwise be considered inoperable. In such cases, patient selection is extremely important and patients must be well informed about the prognosis.

Conclusion

In these cases, saving the eye seems to be a more realistic goal than improving vision. Although it depends on the severity of the preoperative findings, prognosis appears to be better than the natural disease course.

Ethics

Ethics Committee Approval: Manisa Celal Bayar University, 20.478.486.

Informed Consent: Informed consent was obtained from the patients before surgery.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Özcan Kayıkcıoğlu, Hüseyin Mayalı, Concept: Özcan Kayıkcıoğlu, Emin Kurt, Design: Muhammed Altınışık, Data Collection or Processing: Faruk Bıçak, Analysis or Interpretation: Özcan Kayıkcıoğlu, Muhammed Altınışık, Emin Kurt, Literature Search: Muhammed Altınışık, Hüseyin Mayalı, Writing: Muhammed Altınışık.

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Original Article

Dislocated Intraocular Lens Extraction and Iris-Claw Lens Implantation in Vitrectomized and Non-vitrectomized Eyes

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Abstract

Objectives: To compare the outcomes and complications of dislocated intraocular lens (IOL) extraction and secondary iris-claw IOL (ICIOL) implantation in vitrectomized and non-vitrectomized eyes.

Materials and Methods: This retrospective study included 19 vitrectomized eyes and 11 non-vitrectomized eyes that underwent dislocated IOL extraction and secondary anterior chamber ICIOL implantation between June 2014 and September 2017 and had at least one year of follow-up.

Results: There were no significant differences between the groups in terms of demographic data, operative time, baseline anatomic and functional measurements, or postoperative changes in these measurements (all $p>0.05$). Postoperative best corrected visual acuity was significantly higher than preoperative values in both groups (both $p<0.05$). Complication rates did not differ between the groups (all $p>0.05$). In both groups, endothelial cell density was significantly lower at postoperative 1 year compared to preoperative measurements. There was no significant difference between groups regarding endothelial cell loss ($p=0.49$). One vitrectomized eye had corneal decompensation. Other complications included hyphema, transient increase of intraocular pressure, secondary glaucoma, pupillary irregularity, and dislocation of ICIOL. Mean operative time was 26.4±5.9 minutes.

Conclusion: Dislocated IOL extraction and secondary anterior chamber ICIOL implantation is a safe treatment option in both vitrectomized and non-vitrectomized eyes.

Keywords: Aphakia, intraocular lens dislocation, iris-claw lens, secondary lens implantation, vitrectomy

Introduction

In cataract surgery, implantation of the intraocular lens (IOL) in the capsule is the ideal position and provides excellent visual outcomes. With the introduction of multifocal and toric IOLs, cataract surgery has now become a form of refractive surgery and is performed at earlier ages. In patients who sustain capsular damage during cataract surgery but have adequate capsular support, monofocal IOLs can be placed in the sulcus in the posterior chamber. For cases with inadequate capsular support or dislocated intraocular or crystalline lens due to zonular damage, options include the use of an angle-supported anterior chamber IOL (ACIOL), a posterior chamber IOL fixated to the sclera or sutured to the iris, or iris-claw IOL (ICIOL).[1]

Although ACIOL implantation is an easy and rapid procedure, the risk of corneal decompensation and secondary glaucoma is higher than with other methods.[2] Scleral fixation of a posterior chamber IOL is more similar to normal anatomic position of the lens. However, it is a longer and more difficult procedure. It also

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carries risks such as retinal detachment, choroidal hemorrhage, pigment dispersion, IOL decentration, and cystoid macular edema, as well as conjunctival erosion and endophthalmitis if transscleral suturing is used.[3,4] Suturing posterior chamber IOLs to the iris is also not commonly performed due to factors such as its technical difficulty, long operative time, and high complication rates.[5] ICIOL implantation, on the other hand, is easier, quicker, and associated with low intraoperative and postoperative complication rates.[6] Although designed primarily for placement on the anterior surface of the iris, retropupillary placement is also possible.[7]

In addition to ocular trauma, pseudoexfoliation syndrome, high myopia, uveitis, and retinitis pigmentosa, a history of pars plana vitrectomy is also a risk factor for zonular dialysis.[8] Because vitrectomized eyes lose the support provided by the vitreous, intraocular pressure (IOP) is difficult to maintain during surgery and the risk of suprachoroidal hemorrhage increases, especially in prolonged surgeries.[9] In this study, we aimed to compare the outcomes and complications of dislocated IOL extraction with simultaneous ICIOL implantation in vitrectomized and non-vitrectomized eyes.

Materials and Methods

This retrospective study included 19 vitrectomized eyes (group 1) and 11 non-vitrectomized eyes (group 2) that underwent IOL removal due to IOL dislocation and secondary ICIOL implantation to the anterior chamber and were followed up for at least 1 year at the Istanbul Retina Institute between June 2014 and September 2017. The study protocol was prepared in accordance with the Declaration of Helsinki and approved by the İstanbul Şişli Memorial Hospital Ethics Committee. Patient records were reviewed for the following data: medical history, systemic diseases, age, sex, previous ocular surgeries, surgical procedure, operative time, best corrected visual acuity (BCVA), spherical equivalent refractive error (SERE), IOP, corneal endothelial cell density (ECD) assessed using CEM-530 (Nidek Co., Ltd., Gamagori, Japan) specular microscope, preoperative anterior chamber depth and axial length measured by IOLMaster (Carl Zeiss Meditec AG, Jena, Germany), and intraoperative and postoperative complications.

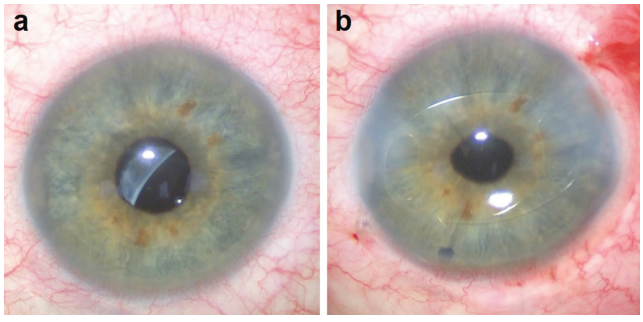

Figure 1. Images of a 58-year-old vitrectomized patient with intraocular lens (IOL) dislocation. a) preoperative image shows that the IOL is dislocated together with the capsular bag; b) postoperative image shows an iris-claw IOL placed in the anterior chamber and peripheral iridectomy

Patients younger than 18 years of age, those who had previously undergone refractive surgery, and those who had been followed for less than 1 year were excluded from the study.

A biconvex polymethylmethacrylate ICIOL (Artisan, Opthec BV, Groningen, Netherlands) 8.5 mm in diameter with a 5.0 mm optical zone was fixed to the anterior iris surface in all patients. IOL power was calculated using IOLMaster (Carl Zeiss Meditec AG, Jena, Germany) with an A-constant of 115.0 and residual myopia of -1.0 D.

Surgical Technique

Pupillary dilatation was induced in all patients preoperatively by instilling 1 drop of 0.5% tropicamide. All surgical procedures were performed under general anesthesia by the same surgeon (M.K.). Patients who had previously undergone pars plana vitrectomy for any reason and had IOL subluxation or luxation were included in group 1. Group 2 included patients with IOL subluxation only. Patients who had luxated IOL and underwent pars plana vitrectomy during secondary implantation were excluded from the study. In all patients, after opening the conjunctiva, a 23-gauge (G) sclerotomy was made 3.5 mm from the lower temporal limbus and an infusion cannula was placed. Infusion flow was started only when needed. A scleral tunnel 6 mm in diameter was prepared on the 12 o'clock line 2 mm from the limbus, but was not advanced to the anterior chamber. A second 23-G sclerotomy was created 3.5 mm from the limbus in the upper temporal region and the luxated/subluxated IOL was moved into the anterior chamber using forceps. In non-vitrectomized eyes, anterior vitrectomy was performed through this sclerotomy before the IOL was moved into the anterior chamber. In vitrectomized eyes with luxated IOL, illumination was provided transsclerally and a separate sclerotomy was not created. The anterior chamber was accessed via the prepared scleral tunnel and the dislocated IOL was removed. Carbachol 0.01% (Miostat, Alcon, TX, USA) and cohesive viscoelastic substance were administered to the anterior chamber consecutively. Corneal incisions perpendicular to the iris plane were made with a 1-mm blade at the 3 and 9 o'clock positions. The ICIOL was placed in the anterior chamber convex side up. The IOL was stabilized through the scleral tunnel using special forceps (Ophtec Artisan Implantation Standard D02-74 Forceps) and fixated to the iris at 3 and 9 o'clock by aspiration. A peripheral iridectomy was made at 12 o'clock. The scleral tunnel and sclerotomies were sutured with 8/0 vicryl. Four interrupted sutures were used to close the scleral tunnel and one suture was placed at each sclerotomy. After removing the viscoelastic substance, the corneal incisions were made edematous. The conjunctiva was closed with 8/0 vicryl.

Postoperatively, all patients were prescribed topical antibiotic and corticosteroid drops 4 times a day for 1 month. The antibiotic drops were discontinued after 1 month, while the corticosteroid drops were tapered and discontinued within 2 weeks.

Statistical Analysis

All statistical analyses were performed using the SPSS software package (Version 21, IBM Corp., Armonk, NY, USA).

A p value less than 0.05 was considered statistically significant. Mann–Whitney U test was used to compare continuous variables and chi-square test was used to compare categorical data between groups. A Wilcoxon signed-rank test was used for comparisons of preoperative and postoperative 1-year data.

Results

Indications for previous pars plana vitrectomy in group 1 included rhegmatogenous retinal detachment in 15 eyes (79%), vitreous hemorrhage secondary to proliferative diabetic retinopathy in 1 eye (5.25%), epiretinal membrane in 1 eye (5.25%), macular hole in 1 eye (5.25%), and nucleus dropped into the vitreous cavity during cataract surgery in 1 eye (5.25%).

There was no significant difference between the groups in terms of demographic data, operative time, initial anatomical and functional measurements, or postoperative changes in these measurements (p>0.05 for all) (Table 1).

Preoperative and postoperative data are compared in Table 2 (group 1) and Table 3 (group 2).

There was a significant increase in BCVA in both groups postoperatively (group 1 p=0.01, group 2 p=0.04). Although preoperative BCVA and postoperative letter gain were higher in Group 2 (mean 0.6±0.8 LogMAR, 14.4±26.2 letters) compared to group 1 (mean 0.8±0.6 LogMAR, 9.5±16.3 letters), these differences were not statistically significant (p=0.14, p=0.49). Postoperative SERE was -1.49 diopters in group 1 and -1.32 diopters in group 2. There was no difference between preoperative and postoperative IOP or astigmatism values in either group (p>0.05).

There was no significant difference between the groups in terms of complication rates (p>0.05). None of the patients in either group exhibited rhegmatogenous retinal detachment, epiretinal membrane, cystoid macular edema, choroidal detachment, suprachoroidal hemorrhage, or vitreous hemorrhage perioperatively or postoperatively. ECD was decreased in both groups at postoperative 1 year compared to preoperative measurements (group 1 p<0.001, group 2 p=0.003). There was no difference between the two groups in terms of postoperative decrease in ECD (p=0.7). However, endothelial decompensation

Table 1. Between-group comparisons

	Vitrectomized (n=19)	**Non-vitrectomized (n=11)**	**p**
	Mean ± standard deviation		
Age (years)	**61.8±8.7**	**66.7±17.6**	**0.16***
Sex (% female)	26.3	36.4	0.56†
Operative time (min)	26.9±5.8	25.9±6.3	0.70*
Axial length (mm)	24.8±1.7	24.2±2.1	0.29*
Anterior chamber depth (mm)	4.2±1.0	3.8±0.6	0.33*
Preoperative BCVA (LogMAR)	0.8±0.6	0.6±0.8	0.14*
Postoperative letter gain	9.5±16.3	14.4±10	0.71*
Preoperative IOP (mmHg)	14.1±3.7	17.7±6.4	0.19*
Postoperative IOP change (mmHg)	-0.9±2.9	-2.9±5.1	0.29*
Preoperative SERE (diopters)	8.4±4.4	6.4±6.7	0.36*
Postoperative SERE change (diopters)	-9.9±4.3	-7.7±7.1	0.34*
Preoperative astigmatism (diopters)	1.2±0.6	1.5±1	0.16*
Postoperative astigmatism change (diopters)	0.3±0.6	-0.1±0.6	0.06*
Preoperative ECD (cells/mm^2)	2199±423	2137±666	0.81*
Postoperative ECD decrease (%)	13.8±17.5	11.3±11.3	0.49*

ECD: Endothelial cell density, BCVA: Best corrected visual acuity, IOP: Intraocular pressure, SERE: Spheric equivalent refractive error, *Mann-Whitney U test, †Chi-square test

Table 2. Comparison of preoperative and postoperative data in vitrectomized eyes

	Preoperative (n=19)	**Postoperative (n=19)**	**p**
	Mean ± standard deviation		
BCVA (LogMAR)	0.8±0.6	0.5±0.4	0.01*
IOP (mmHg)	14.1±3.7	13.7±4.9	0.29*
SERE (diopters)	8.4±4.4	-1.5±1	<0.001*
Astigmatism (diopters)	1.2±0.6	1.4±0.6	0.09*
ECD (cells/mm^2)	2199±423	1899±544	<0.001*

ECD: Endothelial cell density, BCVA: Best corrected visual acuity, IOP: Intraocular pressure, SERE: Spheric equivalent refractive error, *Wilcoxon signed-rank test

Table 3. Comparison of preoperative and postoperative data in non-vitrectomized eyes			
	Preoperative (n=19)	Postoperative (n=19)	p
	Mean ± standard deviation		
BCVA (logMAR)	0.6±0.8	0.2±0.3	0.04*
IOP (mmHg)	17.7±6.4	14.8±3.4	0.07*
SERE (diopters)	6.4±6.7	-1.3±1.1	0.02*
Astigmatism (diopters)	1.5±1	1.4±1.1	0.55*
ECD (cells/mm^2)	2137±666	1931±753	0.003*
ECD: Endothelial cell density, BCVA: Best corrected visual acuity, IOP: Intraocular pressure, SERE: Spheric equivalent refractive error, *Wilcoxon signed-rank test			

occurred in one eye in group 1. This patient had previously undergone a total of six intraocular surgeries, including silicone endotamponade removal procedures due to rhegmatogenous retinal detachment and recurrences. The patient's anterior chamber depth was 4.02 mm and ECD was 1580 cells/mm^2 before ICIOL implantation. Hyphema was observed in two eyes in group 1 (10.5%) and in one eye in group 2 (9.1%) on postoperative day 1 (p=0.9) and resolved in all eyes within 1 week without treatment. Corectopia persisting at 1 year was observed in only one eye (5.3%) in group 1 (p=0.4). IOP elevation was detected in the early postoperative period in one eye (5.3%) in group 1 and two eyes (18.2%) in group 2. In one eye in each group, IOP returned to normal levels without medication after discontinuation of the corticosteroid drop used postoperatively, while one eye in group 2 (9.1%) developed secondary glaucoma associated with topical antiglaucomatous drops (p=0.2). IOL dislocation was observed in one eye in both group 1 (5.3%) and group 2 (9.1%) (p=0.7).

Discussion

Although ICIOL implantation in aphakic eyes is easier and safer than other methods, complication rates vary widely between publications.[6,7,10,11,12,13,14,15,16,17,18,19,20,21,22,23] These differences may result from variation in surgical histories, placement of the ICIOL in the anterior chamber or retropupillary space, and surgeon experience. Reported complications of ICIOL implantation include endothelial cell loss, corneal decompensation, pigment dispersion, hyphema, transient IOP elevation, secondary glaucoma, IOL dislocation, pupillary block, anterior uveitis, cystoid macular edema, hypotonia, choroidal detachment, retinal detachment, and vitreous hemorrhage.[6,7,10,11,12,13,14,15,16,17,18,19,20,21,22,23] None of the patients in this study showed pigment dispersion, uveitis, cystoid macular edema, hypotonia, choroidal detachment, retinal detachment, or vitreous hemorrhage within the first postoperative year, while other complications occurred at rates considered acceptable in terms of safety, as stated in the literature.

Corneal decompensation following decreased ECD is one of the most important complications of ICIOLs. The rate of ECD reduction in long-term follow-up after ICIOL implantation has been reported as 6-24%.[10,11,12,14,18,19] Recently, ICIOLs have mostly been placed in the retropupillary space on the grounds that it leads to less endothelial cell loss. However, studies have revealed no significant difference in ECD decrease between anterior chamber and retropupillary implantation of ICIOLs.[13,16] Güell et al.[20] compared eyes that underwent anterior chamber ICIOL implantation with fellow eyes that underwent uncomplicated cataract surgery and observed no difference in ECD at 2 years, although endothelial decompensation occurred in some eyes in the ICIOL group. In eyes undergoing phakic ICIOL implantation, ECD decrease was found to be greater in eyes with anterior chamber depth of <3.0 mm compared with those with anterior chamber depth of >3.40 mm,[24] but there is no study demonstrating the same phenomenon in aphakic eyes. In the present study, corneal decompensation was observed in one eye (3.3%) with an anterior chamber depth of 4 mm and preoperative ECD of 1580 cells/mm^2. We speculated that the corneal decompensation may have been due to the total of six vitreoretinal surgeries this eye had undergone before ICIOL implantation.

Because it is more difficult to maintain a stable IOP during surgery in vitrectomized eyes, secondary implantation surgeries are more susceptible to complications. The present study showed that complication rates did not differ between the vitrectomized and non-vitrectomized eyes of patients who underwent concurrent dislocated IOL extraction and ICIOL implantation. Labeille et al.[13] observed a 20.5% mean ECD reduction in the first 3 months in eyes that underwent concurrent ICIOL implantation and pars plana vitrectomy due to a dislocated nucleus or IOL. They reported that using an endofragmatome did not cause greater endothelial loss. However, their operative time was calculated as 72 minutes if the surgery was performed within 2 days of dislocation and 60 minutes if performed after 2 days, which is much longer than the mean operative time of 26.4 minutes in the present study. They also reported complications that were not observed in our study, such as cystoid macular edema (25%), retinal detachment (12.5%), vitreous hemorrhage (12.5%), and choroidal detachment (3%), at higher rates than other studies that employed a similar surgical procedure.[6,23] This difference may be related to operative time. In two studies conducted in vitrectomized aphakic eyes instead of eyes with dislocated IOLs as in our study, Acar et al.[18] reported a 24% decrease in ECD over a mean follow-up period of 15 months, while Riazi et al.[19] reported an ECD decrease of 8.1% at 6 months. When all of the eyes in our study were taken into account, the decrease in

ECD at 1 year after simultaneous dislocated IOL removal and ICIOL implantation was 12.9%, consistent with the literature. Furthermore, the vitrectomized and non-vitrectomized eyes in our study showed no significant difference in ECD decrease.

In a study including 148 vitrectomized eyes, epiretinal membrane, proliferative vitreoretinopathy, pupillary capture of the IOL, endophthalmitis, and choroidal hemorrhage were reported after secondary scleral fixation IOL implantation in addition to the ICIOL-related complications described in the literature.[25] A comparison of ICIOL implantation and scleral fixation IOL implantation performed concurrently with pars plana vitrectomy showed that ICIOLs yielded better corrected and uncorrected visual acuity.[3]

In our study, BCVA increased postoperatively in both groups. Studies comparing anterior chamber and retropupillary ICIOLs revealed no differences in BCVA.[15,16] Postoperative astigmatism was found to be lower in patients who underwent scleral tunnel incision compared to those who had corneal incisions. Accordingly, uncorrected visual acuity was higher in the scleral tunnel incision group.[16] In the present study, we achieved both low postoperative astigmatism by using scleral tunnel incision and good IOP stability by not opening the connection between the tunnel and anterior chamber until moving the dislocated IOL into the anterior chamber. We also showed that, as with other parameters, there was no difference between vitrectomized and non-vitrectomized eyes in terms of change in astigmatism.

The complete absence of complications such as cystoid macular edema, hypotonia, choroidal detachment, retinal detachment, and vitreous hemorrhage in our study may be attributed to minimizing operative time by making as few manipulations as possible and ensuring good stabilization of the anterior chamber.

Increased IOP after ICIOL implantation may occur due to the use of corticosteroid drops, inadequate iridectomy, pigment dispersion, or surgical trauma, and has been reported at rates of 2.6-11.4% in the literature.[6,16,17,22] The prevalence of secondary glaucoma is 0-6.2%.[6,16,17,22,23] In the present study, IOP elevation was observed in three patients (10%) in the early postoperative period. IOP returned to normal levels in two of these patients without medication after discontinuing corticosteroid drops, but one patient (3.3%) developed secondary glaucoma. There was no difference between vitrectomized and non-vitrectomized eyes in terms of IOP elevation and glaucoma development.

Study Limitations

The limited number of patients, retrospective design, and lack of a retropupillary ICIOL group are limitations of this study. More comprehensive prospective studies may provide insight into issues that remain uncertain.

Conclusion

As in non-vitrectomized eyes, simultaneous dislocated IOL extraction and secondary ICIOL implantation in the anterior chamber is a fast and safe surgical procedure in vitrectomized eyes as well. In these patients, aspiration can be used for iris enclavation. Excellent postoperative astigmatism results can be obtained with scleral incision.

Ethics

Ethics Committee Approval: İstanbul Şişli Memorial Hospital Ethic Committe-30.11.2018.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Murat Karaçorlu, Concept: M. Giray Ersöz, Murat Karaçorlu, Serra Arf, Design: M. Giray Ersöz, Murat Karaçorlu, Serra Arf, Data Collection or Processing: M. Giray Ersöz, Mümin Hocaoğlu, Işıl Sayman Muslubaş, Analysis or Interpretation: M. Giray Ersöz, Murat Karacorlu, Serra Arf, Literature Search: M. Giray Ersöz, Mümin Hocaoğlu, Işıl Sayman Muslubaş, Writing: M. Giray Ersöz.

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Review

The Management of Uveitic Glaucoma in Children

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Abstract

Children comprise a unique population of patients in regard to the diagnostic and therapeutic approach of uveitic glaucoma. The management of glaucoma secondary to uveitis in children is extremely challenging and presents various difficulties, which are associated both with the underlying uveitis and the young age of the patients. The treatment of uveitic glaucoma calls for a thorough and individualized approach, involving both pharmacotherapeutic and surgical modalities. It appears that the efficient control of inflammatory activity plays a significant role in the final visual outcome of these patients. This study aims to review the current literature about the management of uveitic glaucoma in pediatric patients.

Keywords: Glaucoma, uveitis, children

Introduction

The evaluation and management of uveitis in children is extremely challenging for the ophthalmologists that have to confront this clinical entity, whereas glaucoma in children is a potentially blinding condition. Uveitis can lead to several complications, such as secondary glaucoma, cataracts, synechiae, band keratopathy, and macular edema.[1] There is some evidence that the rates of complications differ between adults and children, and some of the complications may be unique to children.[1] Uveitic glaucoma represents a special category of secondary glaucoma in both adult and pediatric populations. The clinical outcomes of uveitic glaucoma in children depend on several factors (e.g., type, severity, and duration of the disease) and are often guarded, especially in complicated cases. The successful management of uveitic glaucoma in children calls for an early and accurate diagnosis and control of inflammation and intraocular pressure (IOP) to reduce the risk of progressive damage to the optic nerve and the risk of amblyopia.[2] Treatment with ocular and systemic steroids, as well as with corticosteroid-sparing therapy has significantly contributed to the control of inflammation and improved the visual prognosis.[3] In many cases, the successes of medical treatments are limited because of poor compliance or intolerable local or systemic side effects.[2] Moreover, many uveitic patients with glaucoma may need surgical intervention to control IOP and preserve vision. There is high risk of significant visual loss from complications of uveitis and/or glaucoma over the lifespan of these patients, and this has significant impacts in terms of financial burdens, quality of life, and loss of productivity for the patients.[2] This study focuses on the clinical features and management of uveitic glaucoma in childhood.

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Epidemiology

The overall annual incidence of uveitis among children in North America and Europe is lower compared to the rates for adults, which are approximately 4.3 to 6 in 100,000 population.[4,5] The same epidemiological studies found that the prevalence of uveitis in childhood is roughly 30 cases in 100,000 population.[5] The prevalence of pediatric glaucoma in uveitic patients varies between 5 and 13.5%.[6] It has been reported that one third of these patients end up with poor vision due to the complications of uveitis. It appears that in children with glaucoma, uveitis may be the underlying cause at a percentage of 6 to 9%. According to the British Infantile and Childhood Glaucoma Eye Study, uveitis led to 19% of the glaucoma cases among 52 children with secondary glaucoma.[7] Kaur et al.[2] reported that among 385 children with glaucoma, 150 patients were diagnosed with acquired glaucoma but uveitis was the underlying cause in only 8 of them (5.3%). A previous study by Paroli et al.[8] found that 25% of children with uveitis developed secondary glaucoma.

To our knowledge, there are many reviews and cases series about uveitis in childhood, but only a few prospective studies that highlight the specific issues of uveitis and uveitic glaucoma in children.

Risk Factors

The eyes of children with uveitis seem to have an inherent predisposition to developing secondary glaucoma in comparison with adults.[2] The underlying cause and the duration of the disease have been correlated with the prevalence of uveitic glaucoma. As mentioned above, the risk of developing uveitic glaucoma depends on the cause of uveitis, with higher incidences in Posner-Schlossman syndrome, uveitis associated with juvenile idiopathic arthritis (JIA), and herpetic infections.[9] Interestingly, approximately 42 to 48% of the affected eyes, especially those with early onset glaucoma, are expected to have a poor visual outcome.[10] It has been estimated that approximately half of cases with JIA-related glaucoma require surgical treatment for glaucoma.[11]

Pathogenetic Mechanisms

Uveitic glaucoma can arise through either open or closed angle mechanisms. Secondary angle closure mechanism is commonly due to progressive peripheral anterior synechiae formation. Open angle mechanism is commonly due to obstruction of the trabecular meshwork by debris and inflammatory cells, and chronic remodeling of the trabecular meshwork and the Schlemm's canal, causing increased resistance to aqueous outflow.[12] Elevation of IOP has been attributed to a wide spectrum of inflammatory factors leading to increased resistance in the outflow pathways, which is often exacerbated by the required topical treatment with steroids.[5] Topical and in some cases systemic steroids are commonly needed long-term for the control of inflammation. However, steroid-induced glaucoma may hinder IOP control through accumulation of extracellular matrices in the trabecular meshwork.[5,12]

It is important to underline that in patients with uveitic glaucoma there is also a higher propensity for postoperative hypotony due to the impairment of ciliary body functions caused by the chronic and relapsing nature of the intraocular inflammatory activity. As can be expected, inflammation is likely to be more pronounced in eyes of uveitic patients after intraocular surgery and this can lead to a rapid and undesirable subconjunctival scarring response. The application of antimetabolite to reduce this scarring process can further increase the risk of hypotony.[5,12]

However, the analysis of the pathogenesis of uveitic glaucoma is not within the scope of this review and the reader is referred to our recently published study that focuses on the pathophysiology of uveitic glaucoma.[12]

Therapeutic Approach and Management

1. Pharmacotherapeutic Options for the Management of Uveitis

Corticosteroids have been the gold standard for the treatment of noninfectious types of uveitis. Over the last decade, there has been a trend of early and aggressive administration of immunomodulatory agents both for adults and children. The aim of this approach is to avoid the side effects of topical and systemic steroid treatments and prevent severe complications related to noninfectious uveitis.[2] According to the more traditional approach, the ophthalmologist should wait until visual acuity begins to deteriorate or complications develop before starting the patient on immunomodulatory treatment. However, this strategy is not considered appropriate by the majority of uveitis specialists recently. An individualized approach for each patient is highly recommended in order to investigate the risk factors for developing complications and consider the option of selective immunomodulatory therapy.[2] Children being treated with systemic steroids and/or immunosuppressive medication must be monitored very carefully, as these agents may affect their general health, growth, nutrition, school and other activities, or even their fertility.[13]

As can be expected, parents are concerned about how long uveitis will last and how long the course of treatment will be. It is important to explain to them that the course of the uveitis depends on the type and form of the disease. Some clinical entities (e.g., HLA-B27-associated uveitis, toxoplasmic retinochoroiditis) can completely resolve if the appropriate treatment is administered. On the other hand, some cases of idiopathic uveitis or uveitis associated with systemic disorders (e.g., Kawasaki disease, post-streptococcal syndrome) may be less aggressive and transient.[2] However, when there are prominent and persistent signs of inflammation, ophthalmologists should be prepared to plan their therapeutic strategy accordingly and take into account the possible complications. Interestingly, JIA-related chronic anterior uveitis may become less severe over time but is likely to continue even in adult life, and it is not uncommon for a joint inflammation to subside in cases of persistent iridocyclitis.

a. Antimetabolites

Methotrexate remains the most commonly used immunosuppressive medication in the pediatric population. It is considered to be safe, does not affect future fertility, and is well-tolerated and easily administered. It has been shown that treatment with methotrexate is significantly safer for long-term use in comparison with oral steroids. Methotrexate is known for its efficacy in the treatment of JIA-related joint inflammation in children and is believed to also be effective in cases of JIA-related uveitis and chronic idiopathic anterior uveitis in children.[14] Although several studies have reported the use of methotrexate in children with uveitis, there is a lack of randomized controlled trials and only sparse specific articles with regard to the response rates.[14] In the clinical setting it appears that methotrexate is effective in more than 60% of patients with chronic uveitis,[2] a rate which is comparable to the response rates for arthritis.[14] It is suggested that methotrexate doses need to be higher on a mass-adjusted dosage scheme in children as it is metabolized more quickly in pediatric than in adult patients. The usual oral dose is 10-30 mg/m^2 once weekly.[15] Absorption may vary among individuals and the option of subcutaneous injection of methotrexate can be considered before deducing that the agent is ineffective. Additionally, subcutaneous injections may be better tolerated than per oral use in children, which may cause sickness and irritable or upset stomach.

Currently there is lack of evidence and experience in the use of other antimetabolites (i.e., azathioprine, leflunomide, and mycophenolate mofetil) in children with uveitis. However, mycophenolate mofetil has been reported as an alternative to methotrexate in cases of intolerance in children.[2]

b. Cyclosporine and Cytotoxic Agents

Cyclosporine has been successfully used in several forms of uveitis in pediatric patients.[16] Cyclosporine is generally administered to children with uveitis in the same dosage range (3-5 mg/kg daily) used in adults and is considered to be safe as it does not affect growth or gonadal function.[2]

Chlorambucil cyclophosphamide has been utilized in the treatment of various diseases such amyloidosis, Behçet's disease, severe systemic lupus erythematosus, and other vasculitis. Due to the little experience in their use for the treatment of ocular inflammation and the potential of long-term side effects, their use is not suggested for non-life-threatening diseases.[2]

c. Biologic Agents

Cytokine inhibitors have been reported to achieve significant success rates in several types of arthritis and other inflammatory diseases (e.g., Crohn's disease) in children and therefore their use has been seriously considered for the treatment of uveitis as well.[2] Until recently, etanercept (Enbrel, Immunex Corporation, Seattle, Washington, USA) and infliximab (Remicade, Centocor, Inc., Malvern, Pennsylvania, USA), which inhibit tumor necrosis factor (TNF), were the two main biological agents evaluated for patients with uveitis. More specifically, etanercept is a fusion protein that contains a portion of TNF receptor and binds with TNF, prohibiting the activation of cells. On the other hand, infliximab is a monoclonal antibody against TNF.[2]

However, these two agents have different mechanisms and it has not been yet determined which is more effective in children with uveitis. Apart from that, these drugs may affect various types of uveitis in different ways. It should be noted that infliximab is known to have a higher rate of complications, including development of antibodies to the agent and increased risk of tuberculosis.[2] Moreover, it is not always easy to predict the long-term effects of drugs that target only one factor in the whole complex dynamics of the human immune system and the perplexity of immune responses. On the other hand, a human monoclonal antibody, the anti-TNF agent adalimumab (already administered for noninfectious intermediate and posterior uveitis and panuveitis), has also been recently approved for the treatment of pediatric chronic noninfectious anterior uveitis.[17]

More recent studies showed that of the TNF-α inhibitors, adalimumab and infliximab are the most effective in the control of ocular inflammation.[18] More specifically, 87% and 72% of children with autoimmune chronic uveitis responded to adalimumab and infliximab, respectively, whereas they were refractory to other disease-modifying medications.[18] One of the main advantages of adalimumab is that it can be administered subcutaneously at home (fortnightly), presenting more stable serum concentrations and a favorable safety profile with reduced risk of anaphylactic reaction. It has been recently demonstrated that the combined treatment of adalimumab with methotrexate is effective in cases of JIA-related uveitis. Interestingly, this study showed that a substantially larger proportion of children treated with adalimumab had reduced topical steroid dose or even discontinued topical steroids in comparison with the placebo group.[19] Nevertheless, these patients had an increased incidence of adverse effects, including minor infections and gastrointestinal or respiratory disorders.

In cases that do not respond to TNF-α inhibitors, other biologic agents such as rituximab, interferon, or intravenous immunoglobulin can be alternatively administered. At present though, there are insufficient with regard to their use. Subsequently, clinicians should weigh the potential risks (e.g., malignancies, demyelinating disease, opportunistic infections) and benefits before proceeding to these therapeutic approaches.[20]

d. Nonsteroidal Anti-inflammatory Drugs (NSAIDS)

Oral NSAIDS play a critical role in the management of joint inflammation in individuals with JIA. They have been deployed as an adjunctive therapy to other anti-inflammatory drugs in the therapeutic schemes in children with uveitis.[16] However, their true benefit is yet to be confirmed as there is still inadequate evidence of their effect for this particular indication.[13] Despite the demonstration of a link between NSAIDS and improved visual outcomes in patients with JIA-related uveitis, a causal relationship could not be proved. According to our experience and regarding the route of administration, the topical use (eye drops) of NSAIDs may contribute to the improvement of intraocular inflammation. Systemic NSAIDs can also be used while tapering the corticosteroids in order to avoid recurrence

of inflammation, but some believe that their efficacy is also. It is also important to consider that the oral use of NSAIDs has been associated with gastrointestinal irritation, skin rashes, renal toxicity, and central nervous system rections.[21]

2. Pharmacotherapeutic Options for the Management of Glaucoma

Medical management of uveitic glaucoma in children is challenging and depends on the etiology, the patient's age at presentation and general health, and the known efficacy and safety profiles of each drug. The main targets of medical treatment for pediatric glaucoma should be to achieve target IOP while maximizing compliance and minimizing side effects. A relatively wide spectrum of antiglaucoma medications is commercially available for the control of IOP but of these, only latanoprost has been officially licensed by the regulatory agencies for use in children.[22] The range of drugs includes b-blockers, prostaglandin (PG) analogs, a-adrenergic agonists, topical and systemic carbonic anhydrase inhibitors, parasympathomimetics, and combined preparations. Timolol and PG are usually prescribed as monotherapy, and generally provide good diurnal control of IOP. With respect to combined preparations, the combination of timolol and dorzolamide is the most preferred therapy. Interestingly, most drugs have been found to have comparable ocular hypotensive effects, with the lowest occurrence of systemic side effects reported with PG analogs. Brimonidine is not that favored by the vast majority of pediatric ophthalmologists due to the potentially life-threatening side effects reported in infants. It is known to cause syncope in children as it crosses the blood-brain barrier easily in children. It is always important to take into account that systemic absorption of topical drops may have a greater impact in infants than in adults, leading to higher plasma levels for a longer period and eventually to a higher risk of serious systemic adverse effects. Moreover, the use of beta-blockers in children can cause unpleasant side effects such as asthma attacks, nightmares, and night-wetting.[23] Some ocular adverse events related to latanoprost have been reported in adults, including ocular surface disorders and irritation, periocular skin pigmentation, cystoid macular edema, anterior uveitis, and reactivation of herpes simplex keratitis due to potential excitation of inflammation.[24] Cytomegalovirus anterior uveitis has been also described in two immunocompetent individuals following travoprost and latanoprost eye drops.[25] However, patients of this cohort were also on immunomodulatory therapy and therefore it is difficult to draw firm conclusions. Moreover, clinicians should keep in mind that parasympathomimetics (miotics) should be avoided in children with uveitic glaucoma.[26] Other events of the ocular surface, such as irritation, itching, dry eye, sensation, blurred vision, allergy, blepharitis, and discharge can occur at a similar incidence with the use of all PG analogs.[22] Despite controversies, some authors suggest that PG analogs and prostamides may be first-line therapy in patients with uveitic glaucoma,[27] but only in cases of quiescent uveitis without previous complicated intraocular surgery or pre-existing CME and in eyes without a history of herpetic keratitis or keratouveitis. However, several clinicians are cautious with regard to the administration of those medications even in cases of quiescent uveitis. In every case, it is always necessary to check regional regulations with respect to off-label use and licensure of topical antiglaucoma drugs for children, as this can vary from one region to another. For detailed information about the available pharmacotherapeutic options for pediatric glaucoma, including their safety considerations and efficacy data, the reader is referred to the studies of Samant et al.[22] and Chang et al.[26]

At the moment, evidence obtained from randomized controlled trials in children remains inadequate and we lack of knowledge especially in regard to the use of newer antiglaucoma preparations. Therefore, existing medical therapies for glaucoma need further and thorough evaluation in well-designed randomized control trials with pediatric populations in terms of their safety, effectiveness, and effect on central corneal thickness, ocular surface stability, and effectiveness of PF preparations.

Surgical Treament of Glaucoma

Special Considerations

Surgical treatment is one of the greatest challenges in the field of uveitic glaucoma and its successful management. Some of the difficulties that present derive from the inflammatory status, the legacy of previous surgeries,[27] and intraocular sequelae secondary to complications from chronic uveitis. Most glaucoma procedures involve creating an alternative passage for aqueous humor drainage (e.g., trabeculectomy or glaucoma drainage device [GDD]).[27] The aggressive healing response is considered to play a critical role in the lower surgical success rates in children compared to those of adults in these procedures. Therefore, trabeculectomy is often combined with the use of anti-scarring agents, though these may be associated with significant complications.[27] The limited ability for children to cooperate and cope with the intensive postoperative topical drop therapy adds to the complexity of the situation. Caregivers have to overcome these difficulties and achieve cooperation with the children. Resistance from school and activity restrictions are not uncommon, whereas sometimes other caregivers may need to provide assistance while instilling the postoperative eye drops. A commitment to frequent visits to the eye hospital for postoperative follow-up is necessary, but this may affect the child's school attendance and the carer's work commitments.[27]

Postoperative manipulations (e.g., suture removal) and in some cases the clinical examination (especially in younger children) present two more obstacles that ophthalmologists need to overcome. For this purpose, examination under anesthesia may be required more than once.[27] Generally speaking, uveitic glaucoma in children occurs in the older age group, usually after 5-7 year of age, therefore most will be cooperative in clinical examination. Examination under anesthesia is rarely performed for children with uveitic glaucoma unless there are associated learning disabilities. Moreover, concurrent ametropia correction and amblyopia therapy, when required, is necessary to achieve a favorable long-term visual outcome. It is noteworthy that

amblyopia is not commonly seen due to uveitic glaucoma as most visual difficulties come after the sensitive period. Many visual disabilities are secondary to cataracts, glaucoma, band keratopathy, and then phthisis.

Making the "Right" Choice

In regard to surgical approach, the success of controlling IOP and maintaining vision depends on the primary surgical approach (i.e., the first operation chosen) and developing a long-term surgical strategy.[27] In uveitic glaucoma, the optimal surgical procedure calls for more than setting an algorithm, as the clinician has to consider the age of the patient, their general health, the underlying cause, past ophthalmic history (including previous ocular surgeries), the possibilities of further ophthalmic interventions (e.g., cataract extraction), the degree of glaucomatous optic nerve damage, and visual prognosis. Additionally, important factors such as family and social conditions (e.g., likelihood of follow-up, availability of carers, etc.), as well as the local facilities, cannot be ignored.[27]

Every ophthalmic surgeon needs to devote sufficient time discussing the potential risks and benefits of any surgical treatment with the parents, especially in refractory cases when the fellow eye is stronger and healthier or if the child has only eye.[27]

Generally, the main surgical options can be divided into the following categories:

1. Glaucoma drainage device (GDD),
2. Trabeculectomy,
3. Angle surgery,
4. Minimally-invasive glaucoma surgeries (MIGS),
5. Cyclodestructive procedures (to reduce aqueous humor production).

1. Glaucoma Drainage Device

The first use of GDDs in pediatric patients was described by Molteno in 1973. Various GDDs were later introduced, but the Ahmed implant (96 mm^2/184 mm^2) (New World Medical Inc., Rancho Cucamonga, CA, USA) and the Baerveldt implant (250 mm^2 and 350 mm^2) (AMO Inc., Abbott Park, IL, USA) are the most commonly used.[28] It is difficult to compare the success rates of GDDs among published studies, but all of them report reduced success over time and the need for adjunctive medication as two of the main common features. Although the success rate has been reported as approximately 80% at 1 to 2 years of follow-up,[7] it drops around 50% in the longer term.[29] It is hard to determine which GDD is the best choice for children and it appears that none of them is clearly superior. However, it has been reported that the Baerveldt implant may achieve better long-term IOP control, whereas the Ahmed implant may provide fewer short-term complications.[30] Choice of implant depends on several factors, including the diagnosis, positioning, the surgeon's experience, the child's condition, and of course implant availability and affordability. Interestingly, GDD has been proposed as the primary surgery for children with uveitis (either aphakic or pseudophakic), children who develop glaucoma after cataract extraction, or those that will require cataract extraction in the near future.[27]

One of the most common and sight-threatening complications of GDD surgeries in children is postoperative hypotony. The risk may be mitigated by reducing aqueous flow with external ligation of both flow-restricted and unrestricted implants.[31] Absorbable-suture external ligation is commonly used for non-valved implants to restrict the amount of aqueous outflow in the early postoperative period. The suture should open spontaneously at 6-7 weeks, therefore delaying aqueous drainage onto the footplate and reducing the risk of encapsulation of the tube footplate.[27] Furthermore, unrestricted implants can be restricted by an intraluminal stent suture, which may be used in addition to reduce aqueous outflow and avoid hypotony when the external ligature dissolves in 6-7 weeks' time. Despite these measures, hypotony remains a possibility unless a watertight tunnel into the anterior chamber is achieved. Otherwise, it has been suggested that hypotony may be minimized by implantation of GDD in a two-stage procedure (securing the plate to the sclera in the first stage and inserting the plate when encapsulation has been achieved as the second stage).[32] However, surgeons rarely use a two-stage procedure nowadays.

Other than hypotony, a wide range of complications may occur, including lens touch with cataract formation, corneal touch with corneal decompensation, and iris touch with persistent iritis or dyscoria. Moreover, tube migration either into the anterior chamber or posteriorly out of the anterior chamber has been documented. Tube obstruction from iris, vitreous, hemorrhage, and fibrinous or inflammatory membrane can also occur, whereas tube erosion and exposure can lead to infections and endophthalmitis. In some cases, GDDs may cause cosmetic or eye motility issues. The Baerveldt 250-mm^2 implant is mostly preferred for uveitic eyes, which are prone to aqueous hyposecretion, or microphthalmic eyes with smaller anterior chamber.[27]

For children with good immunomodulatory control of inflammation and appropriate follow-up, Ahmed valve implantation can be an effective and safe procedure for treating pediatric uveitic glaucoma, providing immediate IOP reduction. However, there is evidence that early drainage can lead to early bleb encapsulation over the footplate and patients may experience a hypertensive phase that requires early re-introduction of glaucoma medications.[27]

Tube exposure is an important complication in the long term. Differential diagnosis between uveitis relapse and endophthalmitis is important in patients who received GDD implantation. The incidence of endophthalmitis in GDD was reported at about 6% in the pediatric group in a single-center study by Mandalos and Sung.[33] Early recognition of endophthalmitis is extremely important, and most will require emergency removal of tube and plate in order to prevent further proliferation of the infection, which can lead to total loss of sight.

GDD can reduce endothelial cell density over time, leading to corneal decompensation.[33] Although there is no statistical difference, adults are expected to develop corneal decompensation

more frequently than pediatric patients. However, there is no direct comparison of corneal decompensation rates between adults and children in the current literature. Chronic uveitis can also reduce endothelial cell count over time; therefore, adding a GDD to the microenvironment of the anterior chamber may increase the risk of corneal decompensation in uveitic glaucoma patients.[34] Therefore, tube placement is paramount in patients with chronic uveitis. Routine shortening of the tube after stabilizing eye pressure may reduce the risks of future corneal complications, which is a strategy employed by one of the co-authors of this paper.

Over the years, GDD implantation techniques have changed greatly to improve the safety profile of this procedure. The use of intraluminal suture (e.g., 3/0 Supramid suture) in non-valved GDD and external ligature (6/0 vicryl suture) to delay drainage have improved the safety profile of GDD implants. The risk of complications has been reduced with other changes such as making small entries with 25-gauge needle to prevent entry site leakage, and fenestration of the extraocular portion of the tube (Sherwood slit) proximal to the external ligature with dissolvable suture to avoid excessive intraocular pressure elevation. The use of mitomycin C with GDD is more controversial and there is only anecdotal evidence that its use can enhance the long-term success of GDD,[35] but high-dose mitomycin C (MMC) can increase the risks of profound hypotony and related serious complications. There have also been improvements in the management of postoperative hypotony, which uveitis patients are at much higher risk of. Chiam et al.[36] reported the use of fixed-volume (0.1 mL) viscoelastic (Healon GV) may be an effective and safe method to resolve acute hypotony after the dissolution of the external ligature, but repeat injections were necessary in most cases.

Regarding the risk of tube exposure, apart from utilizing a patch graft material (i.e., sclera), it is advised that the tunnel should be created at least 1-2 mm from the limbus, although various techniques have been described.[25,27,28] Posterior insertion through the pars plana or ciliary sulcus may be considered when there is a high risk of corneal decompensation or if the anterior chamber is very shallow, especially for pseudophakic or aphakic eyes. However, the higher incidence of complications (e.g., choroidal effusions, retinal detachment, etc.) with this approach cannot be ignored.

Mandalos and Sung[33] investigated the outcomes and complications of GDD surgery in both children and adults and underlined how important it is for the surgeon to remain vigilant for postoperative complications. Ophthalmologists need to be alert for signs of bleb encapsulation or endophthalmitis in pediatric patients.[33] Fibrosis and encapsulation around the plate remain the main reasons of GDD failure. In contrast with trabeculectomy, the advantage of reducing fibrosis with anti-scarring agents has not been established in GDD surgeries in pediatric eyes. However, some authors support that after failed GDD surgery, repeat GDD surgery with MMC may be successful. After GDD failure, the introduction of topical glaucoma medication is considered to be the simplest and lowest risk option. Alternatively, needling or surgical revision of the bleb over the plate (capsule excision) can be considered.[33]

Overall, surgical techniques have improved over time, leading to increased success rates and fewer complications. At present, the insertion of a glaucoma drainage tube seems to be the most promising surgical option, providing sufficient and long-term IOP control in children with secondary glaucoma.[22]

2. Trabeculectomy

Although the success rates in children have been shown to be much lower than in adults, this procedure is still probably one of the commonest first-line surgical treatments for children with uncontrolled uveitic glaucoma. The first published studies on trabeculectomy in children presented results of eyes with very advanced glaucoma and several previous surgeries. As expected, the results were poor and the complication rates were high.[37] MMC, which is a potent inhibitor of fibroblast function, has been used to improve success rates. However, MMC can be used at various potencies requiring only intraoperative exposure, which is a great advantage over 5-fluorouracil (5FU) in pediatric patients. MMC is suggested for eye surgeons experienced in its use,[27] as it has been correlated with higher complication rates, including early complications associated with hypotony (i.e., shallow or flat anterior chamber, choroidal effusion, hypotony maculopathy, suprachoroidal hemorrhage) and late complications related to thin, avascular, cystic blebs, which are generally more prone to leakage and potentially blinding infection. Due to these potential complications, trabeculectomy is a challenging procedure in pediatric glaucoma. Nevertheless, other authors[39] reported that according to their experience and by suitable modifications to the surgical technique in combination with appropriate anti-scarring potency and its application technique (Moorfields Safer Surgery System),[27] trabeculectomy can lead to satisfactory outcome in most cases. An anterior chamber maintainer can be used in these cases, not only for minimizing intraoperative hypotony, but for enabling the precise judgment of flow through the scleral flap.[27] With the modified technique, many glaucoma specialists consider trabeculectomy to be the first-line procedure for the majority of secondary glaucomas in children with the exception of those known to have a poor prognosis, such as aphakic or pseudophakic eyes associated with uveitis. Similarly, in other secondary glaucomas, the presence of cataract or corneal disorder that may soon require lens extraction or corneal transplantation, respectively, should be considered contraindications for trabeculectomy.[27]

A more recent study by Wang et al.[38] evaluating trabeculectomy outcomes in 33 pediatric patients with uveitic glaucoma showed that IOP control improved and the number of anti-glaucoma medications decreased without any major complications. Additionally, visual acuity and intraocular inflammation remained stable ($p>0.05$), suggesting that trabeculectomy is safe and effective for these patients. The suitability of trabeculectomy specifically in JIA-related uveitic glaucoma was highlighted in a retrospective study of 21 children showing good IOP control and an overall success rate (with

topical anti-glaucoma medication) of 71.4% after 5 years.[39] Leinonen et al.[40] examined the results of the potential effect of treatment with systemic tumor necrosis factor (TNF) inhibitor on the success of an MMC-augmented trabeculectomy for individuals with JIA-related uveitic glaucoma. They reported that trabeculectomy success rates at 1, 5, and 10 years after surgery were higher among patients treated with TNF inhibitors (at the time of their trabeculectomy to control uveitis, arthritis, or both) when compared with those who were not treated with TNF inhibitors.

In cases where trabeculectomy fails to control IOP, bleb needling with an anti-scarring agent may be required, but only if the bleb architecture allows this intervention and the sclerostomy is patent. It is noteworthy that needling may be necessary with early failure. Repeat trabeculectomy with a stronger dose of MMC may be required. Otherwise, a GDD can be considered if further surgery is needed.[41]

3. Angle Surgery

The main concept of angle surgery is to control the innate or "natural" outflow mechanism by facilitating aqueous access to Schlemm's canal and the collector channels. Originally, this approach was deployed as primary surgery for primary congenital glaucoma (PCG), but some have supported its use in some types of secondary glaucoma, such as juvenile open-angle glaucoma (JOAG) or aphakic glaucoma. However, it is regarded as less successful except for uveitic glaucoma and in cases with 'PCG-like' angles, such as in congenital rubella or infantile presentations of Sturge-Weber syndrome.[27]

Goniotomy provides an internal approach through a paracentesis and trabeculotomy from an external approach using a scleral cut down to access Schlemm's canal.[42] Since its introduction, goniotomy has undergone only minor modifications, such as using needles instead of a tapered knife for the angle incision, several goniolenses, viscoelastic or anterior chamber infusion for maintaining anterior chamber depth, and hyperosmotic solutions to clear the epithelial edema. However, the procedure can provide satisfactory IOP control in many cases of uveitic glaucoma and has several advantages over GDD surgery in these patients, including shorter operative time and preservation of conjunctiva for future procedures. Moreover, re-operation is not necessary in many cases, as it may be with GDDs (e.g., tube exposure, suture removal, etc.).[41] During goniotomy, an endoscopic approach enables visualization of the angle in conditions of poor corneal clarity, but this technique has not been adequately studied. Goniotomy represents a fairly successful and low-risk surgical treatment for uveitic glaucoma in children. However, it must be underlined that not all eyes (e.g., aphakic eyes with peripheral anterior synechiae) are ideal for angle surgery. Overall, goniosurgery is considered to be generally successful in children with glaucoma secondary to uveitis.

On the other hand, the trabeculotomy technique of angle incision has been modified, from the trabeculotome (which is a metal probe) to a blunted suture filament or an illuminated microcatheter (which allows visualization of its passage via Schlemm's canal) that potentially facilitates the treatment of the whole angle in one surgery.[43] The main debate with respect to the choice between goniotomy and trabeculotomy was based on the potential impact of the chosen procedure on future glaucoma surgical procedures and corneal clarity. However, the number of relevant randomized controlled trial studies among these two approaches is small. In general, the success rates of these two procedures are similar.[44] Those who advocate goniotomy do so on the basis of the long-term effects in pediatric patients who are likely to undergo further glaucoma surgery at some point in their life. The long-term success of trabeculotomy is uncertain when there have been previous surgeries involving the conjunctiva, as the scleral cut-down distorts the conjunctiva and sclera, making a future trabeculectomy challenging and prone to failure. A temporal approach could preserve the superior site for future trabeculectomy.[41]

Goniotomy and trabeculotomy have been widely used since their introduction and their difference has to do with the approach to the angle. The main advantage of trabeculotomy over goniotomy is the ability to access potentially 360º of the angle and the fact that it can be carried out even in eyes with opaque cornea. Even in cases with corneal haziness attributed to epithelial microcystic edema, special maneuvers can be performed in order to achieve adequate corneal clarity and achieve a favorable goniotomy. Both goniotomy and trabeculotomy (less than 360°) with probes can be repeated in cases of insufficient response.[41,44]

Goniosynechialysis (GSL) is another alternative for angle surgery. Initially described by Campbell and Vela in 1984, GSL is a surgical technique that aims to strip the peripheral anterior synechiae (PAS) from the trabecular surface in the angle and make a renewed pathway for aqueous to the trabecular meshwork. The procedure can be performed using an iris spatula, a cyclodialysis spatula, an Ahmed micro-grasper, or a bent 25-gauge needle to manually release the PAS. GSL appears to be effective for the treatment of chronic angle closure glaucoma and has been described as a combined technique with phacoemulsification.[45,46] GSL could potentially be considered in some patients with glaucoma secondary to uveitis in order to resolve the PAS and improve trabecular outflow. However, there are limited data to support the use of this surgical modality in pediatric uveitic glaucoma.

If IOP is still not acceptable after angle surgery, filtration surgery can be considered as the next step. Unfortunately, especially for uveitic glaucoma, there are still not adequate randomized control trials to define the optimal primary surgical treatment. Most surgeons usually perform trabeculectomy surgery after angle surgery fails.

4. Minimally Invasive Glaucoma Surgeries

Over the last few years, there has been an increasing interest in the development of new devices and surgical techniques for MIGS. At the moment there is still not a widely accepted definition of MIGS.[46] The term MIGS comprises a group of surgical procedures which are defined by five basic characteristics:

(1) an ab interno approach via a clear corneal incision, (2) a minimally traumatic technique to the target tissue, (3) a justified approach based on IOP lowering efficacy, (4) a high safety profile with low rate of complications compared to other surgical modalities, and (5) a quick recovery taking into account the patient's quality of life. In February 2014, during a workshop of the American Glaucoma Society and US Food and Drug Administration (FDA), MIGS was described as the insertion of a surgical device in order to lower IOP through an outflow mechanism with either an ab interno or ab externo approach, associated with minimal or no scleral dissection.[47]

As a matter of fact, many of these devices do not require a scleral incision and can be implanted ab interno via a clear corneal incision. Therefore, these procedures are frequently combined with phacoemulsification and intraocular lens (IOL) implantation. The main target of MIGS is to achieve a lower IOP with shorter operative times, and ideally accompanied by a medication-sparing effect. This is accomplished by increasing the outflow of aqueous humor from the anterior chamber by (i) directly accessing Schlemm's canal, (ii) shunting aqueous humor to the suprachoroidal, or (iii) shunting aqueous humor to the subconjunctival space.[46,47]

In conventional glaucoma surgery (e.g., trabeculectomy), potential complications include bleb infection/inflammation, hyphema, hypotony, bleb revision, and endophthalmitis, and may occur in up to 35% of patients. These complications may be avoided with MIGS, offering an important therapeutic alternative in individuals with glaucoma. However, it is important to underline that efficacy and the incidence of complications and adverse effects may vary among the different types of MIGS procedures.[46,47]

The first three devices, iStent, iStent inject (Glaukos Inc., Laguna Hills, CA, USA), and Hydrus (Ivantis Inc., Irvine, CA, USA) aim to increase trabecular outflow by targeting the juxtacanalicular area of the trabecular meshwork, which likely represents the greatest resistance to aqueous humor outflow in eyes with OAG.[46,47] These devices provide more direct access of aqueous humor from the anterior chamber into Schlemm's canal. However, this approach does not allow postoperative IOP to decrease below the episcleral venous pressure (EVP), which may be increased in some glaucomatous patients.[46,47] On the other hand, the CyPass micro-stent (Alcon Inc., Fort Worth, TX, USA) and iStent® Supra aim to create an outflow pathway from the anterior chamber to the supraciliary space.[46] Finally, the surgical concept of the XEN gel stent is to create a non-physiological route for the outflow of aqueous humor via subconjunctival filtration. This pathway is actually the basis for conventional trabeculectomy and for glaucoma epibulbar shunt surgeries.[46]

Apart from the implantation of the micro-stents mentioned above, MIGS includes the following more surgical techniques: trabectome, gonioscopy-assisted transluminal trabeculotomy, excimer laser trabeculotomy (increase of trabecular outflow), and endocyclophotocoagulation (reduction of aqueous production).

MIGS devices can lower IOP but the efficacy of these new surgical modalities, especially in childhood, needs to be confirmed by more studies. Existing studies have several limitations, including their retrospective nature, lack of standardization, lack of knowledge about the IOP lowering effect, concomitant use of more than one surgical procedure (e.g., phacoemulsification/IOL implantation and micro-stents) and inadequate information about ideal patient selection for these therapeutic tools.[46]

The concomitant application of various treatments and glaucoma devices in clinical studies, together with the variable populations and diverse study designs make it more difficult to evaluate and compare the final outcomes.

5. Cyclodestructive Procedures

The aim of cyclodestruction is to reduce aqueous humor production by using cyclocryotherapy, which has been associated with major complications and poor long-term outcomes in children. It is generally only reserved for selected challenging refractory cases. Over the course of time it was replaced with laser cyclophotocoagulation, which is a less destructive technique. More specifically, transscleral diode laser (810 nm) gained popularity over Nd:YAG laser.[48] Transscleral diode laser is better tolerated and causes fewer complications. The ciliary processes can be precisely treated with endoscopic diode laser,[51] but this requires an intraocular approach and caution when it comes to phakic eyes. Possible complications of diode laser include conjunctival burns, uveitis, hypotony, scleral perforation, cataract, retinal detachment, loss of vision, and phthisis.[48] It is suggested that transscleral diode laser can be used together with transillumination of the eye in order to enhance laser accuracy and ensure better placement, avoiding scleral thinning, hemorrhage, or areas of pigmentation. Transscleral diode laser can be used in painful and blind eyes or in eyes with poor visual potential. Other indications include surgery with poor prognosis (that may be difficult or impossible), severe scarring of conjunctiva, or other ophthalmic abnormalities that may be present after filtrating surgeries.[27] It has been reported that short-to-midterm success rates of transscleral diode laser are over 50%, but the high retreatment rate and the continuation of medication must be taken into account. The success rates of endoscopic diode laser have been found to be similar.[49]

The use of cyclodiode laser is not advised in children with uveitis, as it aims to reduce ciliary body function, which may already be compromised due to the inflammatory process and has generally been correlated to poor outcomes in this patient group. Additionally, a future, more invasive surgery can potentially lead to severe issues related to chronic hypotony.[27]

Discussion

In the past, patients with uveitic glaucoma had poor visual outcome due to delayed diagnosis and the limited anti-inflammatory and antiglaucoma therapeutic options.[1,2] Over the last two decades, advances in diagnostic tools and new systemic anti-inflammatory medications have provided clinicians with more sophisticated approaches that can prevent late consequences of uveitis.[1] However, uveitis remains a potentially devastating condition that can have severe impacts on vision through various

complications such as glaucoma, cataract formation, macular edema, and formation of synechiae.[3] More specifically, cataracts are very often associated with uveitis, either directly due to the inflammation or indirectly due to the use of topical and oral steroids. In eyes with chronic inflammation activity, cataract extraction can cause an exuberant postoperative inflammatory reaction, which can lead to complications including glaucoma, hypotony, macular edema, and optic disc swelling.[50]

In young children, regardless of whether reduced visual acuity derives from glaucoma, uncontrolled inflammation, or other complications, it can lead to amblyopia and consequently to life-long visual disability. This is also expected to affect the child's education and performance at school. Early, prompt, and efficient management of uveitic glaucoma is significant, especially in patients of amblyogenic age (i.e., younger than 7-8 years old).[21] Amblyopia should be treated with occlusion therapy, and when the issue is resolved and the eye is not inflamed, the child can have a refraction test for optimizing visual function. Furthermore, in children that have gone through postoperative aphakic rehabilitation, the presence of a specialist pediatric contact lens optometrist would be more than helpful.[21]

The treatment of glaucoma secondary to uveitis has several challenges, especially when it comes to surgical intervention. One of the major issues is the fact that in many cases there is an intense inflammatory reaction, which complicates both the control of uveitis and eye pressure.[41] The administration of topical and periocular steroids has been correlated with high risk of several ocular complications in children. IOP elevation and steroid-induced glaucoma in particular can develop rapidly in children, become refractory to treatment, and persist even after stopping topical corticosteroids. Likewise in the adult population, systemic corticosteroids should be used mainly for limited periods due to the wide spectrum of adverse systemic effects. Moreover, systemic steroids can cause adverse ocular effects including glaucoma, cataract, and retinal and choroidal emboli.[1,2] Additionally, when it comes to deciding the most suitable surgical intervention in those patients, it is important to take into account the status of the angle (i.e., whether the angle is open and the extent of synechiae formation). Ophthalmic surgeons should have a strategy that will offer the maximal chances of preserving vision and IOP over the long term with minimal ocular damage.[41]

Holistic management is one of the cornerstones of a successful approach to pediatric glaucoma. The management of this vulnerable group of patients calls for the expertise and collaboration of a multidisciplinary team. It is vital for the ophthalmologist to be in direct and continuous communication with the pediatricians and rheumatologists in order to ensure a thorough investigation for underlying systemic diseases and prompt initiation of disease-modifying agents if required. Before the administration of systemic medications, clinicians and pharmacists need to check that any kind of immunomodulatory was prescribed only if laboratory investigations were within normal limits.[21] A pediatric glaucoma or uveitis nurse specialist could play a critical role in the training of patients and family in the administration of medications, especially when it comes to subcutaneous drugs.

Adequate monitoring of the uveitic glaucoma and response to treatment is crucial in children. Special attention should be paid to visual acuity and any changes in vision in children at risk for amblyopia. Regular and periodic follow-up examinations should be carried out to assess levels of inflammation (i.e., anterior chamber cells and flare, vitreous humor cells and vitreous haze), signs of uncontrolled inflammation (i.e., keratic precipitates and iris nodules), possible complications, and evidence of drug toxicity.[2] Children should be followed up more closely than adults for evidence of uveitic glaucoma, as glaucomatous optic disc changes can progress very quickly in pediatric patients. Therefore, frequent visual field testing and dilated pupil examination of the optic discs along with optical coherence tomography when needed are strongly recommended. Chronic anterior uveitis patients with no previous systemic disorders (at presentation) should be questioned about the development of joint symptoms due to the fact that arthritis may present after the onset of ocular inflammation in some patients.[21]

Assessment of compliance with the treatment regimen is also critical, because children may need to receive their medications while at school or even apply the topical medications on their own. Compliance issues are common among teenagers that may need to receive a long-term drug therapy. Thus, parents and/or guardians must support and assist with the administration of medications, making sure that doses are not skipped. Considering that pediatric glaucoma can be a chronic, sight-threatening, and stressful condition, support from a team of child psychologists would be beneficial to help the patients and their parents cope with the disease and to improve compliance to treatment and regular follow-up.[21]

Conclusion

Childhood uveitic glaucoma is one of the most challenging entities in the field of glaucoma, not only because of the unpredictable nature of uveitis but also the difficulty of surgical management due to the risk of failure and complications. Over the last 70 years, a number of operations have been incorporated in the management of childhood glaucoma. Interestingly, most of them have stood the test of time, whereas others have still to prove their efficacy. The fact that there is a wide spectrum of approaches in regard with the management of uveitic glaucoma in children reflects the diversity of its causes and the complexity of its pathogenesis. The challenge of controlling both the inflammatory process and the glaucoma progression together with the absence of controlled trials to facilitate decision-making adds to the perplexity of the situation. The prognosis for childhood uveitic glaucoma has improved substantially over the last decades. However, increasing surgical success rates and reducing complications remains a Gordian knot in modern ophthalmology for specialists who want to ensure a favorable and long-lasting visual outcome for their young patients.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Case Report

Endogenous *Candida* Endophthalmitis as a Rare Complication of Trans-Urethral Lithotripsy in a Healthy Woman: A Case Report

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Abstract

Endogenous endophthalmitis is a serious sight-threatening ocular emergency that usually occurs in patients with serious underlying risk factors. In this report, we describe a case of endogenous *Candida* endophthalmitis following trans-urethral lithotripsy in an immunocompetent woman. In our case, the retinal lesion regressed completely and vision was restored. We discuss diagnostic procedures and management strategies in this article.

Keywords: Endogenous endophthalmitis, *Candida* endophthalmitis, lithotripsy, ureteral stone

Introduction

Endogenous endophthalmitis is an ocular emergency that can lead to catastrophic ophthalmic complications. Endogenous fungal endophthalmitis (EFE) results from dissemination of fungal organisms from infected organs to the ocular vascular network following fungus seeding in the choroid and retina.[1,2,3] The organisms responsible for EFE are *Candida, Aspergillus,* and *Coccidious.*[2,3] Trans-urethral lithotripsy (TUL) is a minimally invasive endoscopic procedure performed using a rigid or flexible uretroscope.[4] Here, we report a rare case of endogenous *Candida* endophthalmitis (ECE) after TUL in a healthy woman.

Case Report

A 31-year-old woman presented to the ophthalmology emergency room complaining of painless, gradual reduction in visual acuity in her left eye starting 1 week earlier. The patient had undergone TUL with double-J stent placement for a 19-mm proximal left ureteral stone 2 weeks before presentation to the ophthalmology clinic. Past medical and drug history was negative. Pre- and postoperative urine and blood cultures were negative and urine analysis was unremarkable. Upon examination, her best-corrected visual acuity (BCVA) in the left eye was 1/10. Intraocular pressure was 11 mmHg. Slit-lamp examination revealed +1 ciliary injection with no signs of keratic precipitate (KP), and hypopyon and +1 cells in the anterior chamber. The iris and lens were normal. Mild vitritis was seen in the vitreous cavity. On fundus examination, media was clear and a creamy, mildly elevated lesion 1/4 disc diameter in size with indistinct borders was observed in the inferior parafoveal region (Figure 1a). Spectral-domain optical coherence tomography showed subretinal fluid aggregation and macular edema (Figure 1b,c). Examination of the right eye was unremarkable.

Following hospital admission, a diagnostic vitreous tap was performed and a sample was sent for smear, culture, and real-time polymerase chains reaction (RT-PCR) analysis. The

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smear was unremarkable, but RT-PCR was positive for *Candida albicans*. Therefore, intravitreal injection of amphotericin-B (0.5 µg/0.1 mL) was performed. Treatment with topical levofloxacin, hematropin, and prednisone acetate 1% every 6 hours and oral fluconazole 200 mg every 12 hours was initiated. Blood and urine culture at the time of presentation were negative and urine analyses were unremarkable. Viral markers including hepatitis B virus surface antigen and core antibody, hepatitis C virus antibody, and human immunodeficiency virus antibody (HIV Ab) were negative. Serology was negative for *Toxoplasma* (IgM and IgG), *Borrelia*, and *Bartonella*. In systemic workup, antinuclear antibody, antineutrophil cytoplasmic antibody, antimitochondrial antibody, venereal disease research laboratory, fluorescent treponemal antibody absorption, Mantoux, and interferon-γ tests were all negative. Erythrocyte sedimentation rate, C-reactive protein, complete blood count, platelet count, fasting blood glucose, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, angiotensin converting enzyme, and immunoglobulin G, M, and A levels were within normal limits. Peripheral blood smear and paranasal sinus and chest x-rays were normal.

Forty-eight hours after initiating treatment, the patient's BCVA increased to 3/10. Conjunctival injection and vitritis disappeared, and the borders of the infiltrative lesion became sharp. She was discharged with oral fluconazole 200 mg every 12 hours for 6 weeks. Vitreous tap culture was negative after 72 hours.

After 6 weeks, her BCVA was 9/10 and the fungal infiltrative lesion had completely disappeared. Macular edema was resolved with no scarring or epiretinal membrane formation (Figure 2a, b, c). The final BCVA outcome was 10/10 and there was no recurrence in 3-year follow-up.

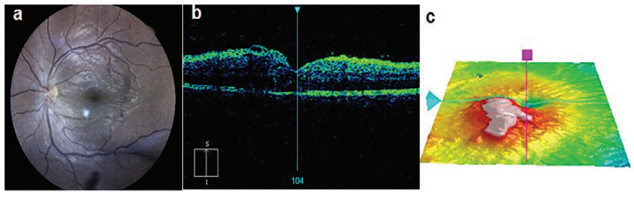

Figure 1. Initial appearance at time of presentation. (a) Color fundus photo showed a creamy lesion in the parafoveal area; (b) Spectral-domain optical coherence tomography revealed macular edema and micro-abscess formation in the sensory retina; (c) Topographic macular map displayed an elevated lesion on the macula

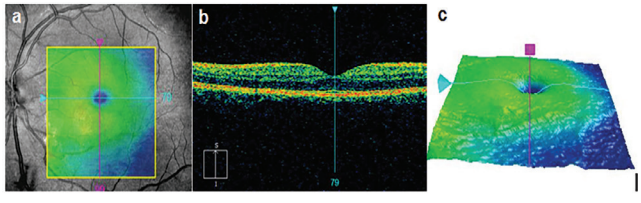

Figure 2. Regression of the fungal lesion 6 weeks after antifungal treatment. (a) Infrared fundus image showed complete disappearance of the fungal lesion; spectral-domain optical coherence tomography (b) and topographic macular map (b) revealed resolution of the macular edema without scarring or traction formation

Discussion

ECE is a devastating ocular infection. Predisposing conditions include long-term systemic antibiotic usage, hospitalization, indwelling catheters, candiduria, major gastrointestinal intervention, prolonged intravenous line, hemodialysis, liver cirrhosis, intravenous drug abuser, immunomodulatory therapy, chemotherapy, diabetes mellitus, hematopoietic, organ transplantation, abortion, and HIV.[1,2,3,5]

Fungi may enter bloodstream during urinary tract interventions due to mechanical abrasion and epithelial trauma, leading to candidemia and intraocular candidiasis. Some reported infectious complications after urinary tract procedures include urinary tract infection, urosepsis and candidemia, perinephric and renal abscesses, urinoma, *Klebsiella* endophthalmitis, and retroperitoneal abscess.[6] We found 5 case reports of ECE following urinary tract lithotripsy in our literature review.[7,8,9,10,11] In 3 cases, ECE occurred after ESWL and uretroscopy for double-J stent placement.[7,8,9] In one case, ECE occurred following TUL and ureteral stent placement[10] and in the last case report it occurred after decompressive nephrostomy.[11] In 4 cases, preoperative urine culture was positive for *C. albicans* and the patients suffered from debilitating diseases (liver cirrhosis, rheumatic arthritis, alcoholic liver disease, or diabetes mellitus).[8,9,10,11] In our case, ECE occurred in an immunocompetent woman after TUL double-J stent placement while pre- and postoperative urine and blood cultures were negative and there were no underlying risk factors.

The diagnosis of ECE is difficult due to its various ocular manifestations and low positive culture rate, especially in cases with minimal vitreous involvement. The condition does not only occur in patients with underlying risk factors, but also in healthy individuals. Thus, there is the risk of misdiagnosis, leading to delay in initiating appropriate treatment. For more accurate diagnosis, vitreous tap sampling or diagnostic vitrectomy is recommended in suspicious cases, since diagnostic vitrectomy shows a higher positive culture rate and intravitreal injection can be performed simultaneously.[1,2,3,5,8] Moreover, RT-PCR is more sensitive than culture, but more expensive and might be unavailable.[1,2,3] In this case report, RT-PCR analysis of the vitreous sample was positive for *C. albicans,* but vitreous smear and culture were negative.

Timely diagnosis and rapid antifungal therapy are associated with better visual outcomes.[2,3] ECE treatment depends on the severity of inflammation and the patient's visual acuity. Appropriate treatment in patients with isolated choroidoretinitis is systemic medication with good intravitreal penetration, such as voriconazole and fluconazole. When a patient presents with choroidoretinitis and mild to moderate vitritis, systemic therapy accompanied by intravitreal injection of amphotericin-B or voriconazole is appropriate. In sight-threatening conditions and severe vitritis, pars plana vitrectomy with intravitreal medication during vitrectomy and systemic medication are recommended.[1,2,3] Although intravitreal injection of amphotericin-B is very effective, intravenous injection of

amphotericin-B is not recommended due to poor intravitreal penetration and systemic complications such as nephrotoxicity.[1] In our case, swift diagnosis and appropriate antifungal treatment (systemic fluconazole + intravitreal amphotericin-B) led to good visual outcome.

ECE after urinary tract interventions is a rare but vision-threatening infection that may occur in immunocompetent individuals. Early detection and timely treatment can lead to better visual prognosis.

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Ethics

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Surgical and Medical Practices: Mohammad Shirvani, Concept: Mohammad Shirvani, Mehrnoosh Maalhagh, Design: Mohammad Shirvani, Mehrnoosh Maalhagh, Data Collection or Processing: Mohammad Shirvani, Mehrnoosh Maalhagh, Analysis or Interpretation: Mohammad Shirvani, Shahla Hosseini, Mehrnoosh Maalhagh, Sahar Mohaghegh, Literature Search: Mohammad Shirvani, Shahla Hosseini, Writing: Mohammad Shirvani, Sahar Mohaghegh.

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Case Report

Intermediate Uveitis as the Initial and Only Presentation of Syphilis

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Abstract

We report a patient with unilateral syphilitic intermediate uveitis without dermatological, neurological, or any systemic involvement. He presented to our clinic with complaints of eye floaters and worsening visual acuity in the left eye. He had intermediate uveitis and cystoid macular edema in that eye and both venereal disease research laboratory and microhemagglutination assay for *Treponema pallidum* serological tests were confirmatory for syphilis. Ocular manifestations of syphilis have variable presentations, and it should be considered when diagnosing unexplained ocular inflammatory diseases, even if the patient's recent history and systemic evaluation are not compatible.

Keywords: Syphilis, intermediate uveitis, cystoid macular edema

Introduction

Syphilis is a sexually transmitted infectious disease caused by *Treponema pallidum*.[1] Syphilis progresses through three stages: primary, secondary, and tertiary (late-stage).[2] Ocular involvement is rare in the primary stage and mainly presents as chancres of the eyelids and conjunctiva. In secondary syphilis (after 6-8 weeks), patients develop the symptoms of influenza, arthralgia, myalgia, headache, sore throat, lymphadenopathy, fever, and maculopapular skin rashes, especially on the palms and soles. After the latent period of the disease, which follows the secondary stage and ranges from 1 year to decades, tertiary syphilis starts. In the tertiary stage, patients develop cardiovascular syphilis and neurosyphilis as well as granulomatous lesions called gumma, which can be seen in the iris and choroid.[3] Syphilitic patients can present with granulomatous or nongranulomatous uveitis. Focal or multifocal chorioretinitis, usually associated with a variable degree of vitritis, is the most common finding, and placoid chorioretinitis in the macula is the pathognomonic finding in syphilitic uveitis. Neuro-ophthalmic symptoms include oculomotor nerve paralysis, optic neuropathy, and retrobulbar neuritis, which are seen in tertiary syphilis and neurosyphilis. Although syphilis is considered to be responsible for only 1-2% of all uveitis cases, it should be noted that it is a great masquerader and should be considered in case of any kind of intraocular inflammation.[4] Recently, patients diagnosed with ocular syphilis were associated with coinfections such as human immunodeficiency virus (HIV). Here, we report a syphilis case that presented with unilateral intermediate uveitis (IMU) with no other systemic findings in an HIV-negative patient.

Case Report

A 22-year-old man presented with a long history of floaters in his left eye. Visual acuity of the right eye was 10/10 and that of

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the left eye was 7/10. Intraocular pressure was measured as 11/12 mmHg. Slit-lamp and fundus examinations of the right eye were normal, while slit-lamp examination of the left eye showed +2 cells in the vitreous. Fundus examination showed minimal hyperemia in the optic disc. Fundus fluorescein angiography revealed a normal right eye and focal leakage in the macula of the left eye as well as fluorescein leakage in the optic disc. Optical coherence tomography (OCT) demonstrated cystoid macular edema in the left eye (Figure 1). The patient reported a history of sexual promiscuity. His laboratory tests showed normal results for complete blood count, liver function tests, and blood urea nitrogen. Toxoplasma and HIV immunoglobulin G (IgG) and IgM tests were negative. He had elevated C-reactive protein, erythrocyte sedimentation rate of 54 mm/h, and negative purified protein derivative test. His chest radiography and brain magnetic resonance imaging were normal. As the results of the venereal disease research laboratory (VDRL) and *T. pallidum* hemagglutination tests were positive, the patient was diagnosed with ocular syphilis. In consultation with the Department of Infectious Diseases, the patient was evaluated for systemic infectious diseases and there was no evidence of past or current dermatological, neurological, or systemic involvement of the disease. The patient underwent a lumbar puncture and VDRL test of the cerebrospinal fluid was negative. The patient was treated with intravenous ceftriaxone 2 g/day for 14 days because he had allergy to penicillin. In addition, 1 mg/kg/day oral methylprednisolone was added after 48 hours of treatment and was discontinued 2 days before the antibiotherapy. Improvement

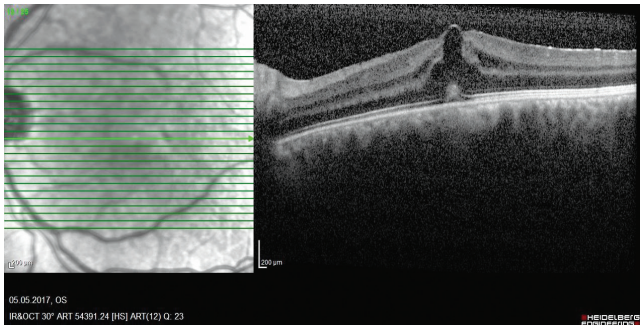

Figure 1. Optical coherence tomography showing cystoid macular edema in the left eye

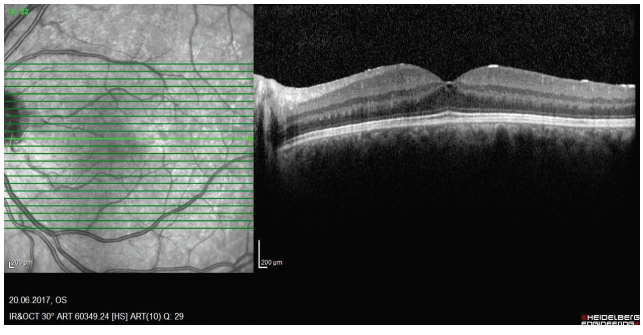

Figure 2. Optical coherence tomography showing regression of cystoid macular edema at week 3

in the patient's clinical symptoms was observed after 3 weeks of therapy and the patient's condition was stable at 6-month control examination. Visual acuity of the left eye was 10/10, vitreous cells were negative, and optic disc and macula were normal. OCT showed regression of the cystoid macular edema (Figure 2). At 12 months, we did not observe any systemic involvement of infectious disease and repeated laboratory tests including *Toxoplasma* and HIV IgG and IgM were negative.

Discussion

In this article, we aimed to present a case of syphilis that had only ocular symptoms without any dermatological, neurological, or systemic findings. Syphilis can involve any segment or layer of the eye. The ophthalmologic manifestations of syphilis include uveitis, retinitis, scleritis, vitritis, retinal vasculitis, optic nerve involvement, and papillary abnormalities. Ocular involvement in syphilis mainly occurs in the secondary and tertiary stages.[5] In a review analyzing the data of 143 patients with syphilitic uveitis, 55.2% of the patients had posterior uveitis, 25.2% had panuveitis and 19.6% had anterior or intermediate uveitis.[6] Anshu et al.[7] found in their study that nongranulomatous anterior uveitis was a more frequent presentation in syphilitic uveitis.

Guidelines from Europe (International Union against Sexually Transmitted Infections) and the United States (Centers for Disease Control and Prevention [CDC]) recommend the standard use of intravenous benzyl penicillin at a dose of 12-24 million units (MU) per day, with 3-4 MU given every 4 hours for 10-21 days.[8,9] The recent World Health Organization Sexually Transmitted Infection guidelines recommend benzathine penicillin G administered intramuscularly at a dose of 2.4 MU once weekly for 3 consecutive weeks to treat late syphilis (including ocular syphilis).[10] In case of neurosyphilis, however, 12-24 MU/day crystalline penicillin G should be administered as intravenous 2-4 MU every 4 hours for 10-14 days.[11] Cases with ocular involvement should be treated as those with neurosyphilis. As immunological reactions are also believed to be involved in the pathogenesis of late syphilis, it seems reasonable to administer corticosteroids in combination with standard antibacterial regimens to treat syphilitic uveitis.[12] Patients with penicillin allergy should be treated with ceftriaxone 2 g daily intramuscular or intravenously for 10-14 days.[13]

In recent years, there has been an increase in the incidence of syphilis, which causes various types of ocular involvement.[14] Jones[15] reviewed 3000 new uveitic cases and found that the incidence of syphilitic uveitis was <1%. Sahin and Ziaei[16] found that 1.07% of uveitic patients in Turkey were diagnosed with ocular syphilis. In another recent study from Turkey, Yalçındağ et al.[17] analyzed a nationwide web-based registry of patients (4863) with uveitis and reported that syphilitic uveitis was diagnosed in 5 cases (0.1%).

The CDC reported that there is an increased risk of all primary and secondary syphilis cases occurred in men who have sex with men and rise in incidence of ocular syphilis patient who is co-infected with HIV.[18,19]

Although our patient did not show systemic symptoms specific to syphilis at the time of admission, we were able to diagnose ocular syphilis thorough a detailed anamnesis and ensured that he received appropriate treatment. Medical history-taking has a significant role in diagnosis. As the ocular symptoms of the disease can be seen at any stage and may be the initial symptoms in some cases, clinical manifestations of syphilis in the eye are similar to many other infectious uveitic diseases. Therefore, syphilis should be considered for all ocular inflammatory conditions in patients with a history of risky sex, even in the absence of any other clinical symptoms of primary or secondary syphilis, and they should be followed long-term for syphilis reinfection and HIV coinfection.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sevcan Yıldız Balcı, Concept: Sevcan Yıldız Balcı, Design: Sevcan Yıldız Balcı, Data Collection or Processing: Sevcan Yıldız Balcı, Ece Turan Vural, Şehnaz Özçalışkan, Analysis or Interpretation: Sevcan Yıldız Balcı, Literature Search: Sevcan Yıldız Balcı, Ece Turan Vural, Şehnaz Özçalışkan, Writing: Sevcan Yıldız Balcı

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Case Report

Microvascular Changes Associated with Optic Disc Drusen: Case Report

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Abstract

Optic disc drusen (ODD) is an important clinical entity that is sometimes misdiagnosed as papilledema because of elevated and blurred disc margins. A 17-year-old male who presented with headaches underwent detailed ophthalmological examination as well as colored fundus photography, B-scan ultrasonography (USG), fundus autofluorescence (FAF), optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), and visual field testing. His visual acuity was 10/10 in both eyes. Fundus examination revealed bilateral blurred and elevated optic disc margins. Diagnosis of bilateral ODD was confirmed with B-scan USG. FAF imaging revealed hyperautofluorescent areas on both optic discs. Optic nerve head OCT scans showed elevated irregular disc borders and thinning of the retinal nerve fiber layer in both eyes. On visual field testing, loss of the nasal visual field was detected in the left eye. OCTA imaging showed focal capillary dropout, especially in the nasal peripapillary area, in both eyes and reduced peripapillary and macular vessel density. In this case report, we evaluated the clinical findings and the structural features of bilateral ODD with multimodal imaging modalities including OCTA.

Keywords: Optic disc drusen, optical coherence tomography angiography, imaging modalities, pseudopapilledema, microvascular changes

Introduction

Pseudopapilledema is an abnormal and elevated appearance of the optic nerve head that is not associated with increased intracranial pressure or edema in the nerve fiber layer. Optic disc drusen (ODD) is the leading cause of this condition.[1] The prevalence of ODD in the population is between 3.4 and 24 per 1000 according to clinical studies, while the rate is 1-2.4% in histological examinations.[2] It is more common in females and usually bilateral.[3,4] In most patients, it is not associated with any ocular or systemic disease and is detected incidentally during routine examination.[4]

Superficial ODD are easily recognizable by the presence of yellow hyaline-like deposits on ophthalmoscopic examination. However, because deep or buried ODD (which are more common in children especially) are not visible during examination, additional imaging methods are needed to differentiate from more serious conditions such as increased intracranial pressure and tumors.[5] A wide variety of imaging methods are used for diagnosis, including ultrasonography (USG), fundus autofluorescence (FAF), optical coherence tomography (OCT), fluorescein angiography (FA), and computed tomography (CT).[6,7] With the recent introduction of optical coherence tomography angiography (OCTA), peripapillary and macular retinal vessels

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can now be visualized noninvasively without the use of contrast agents. This provides more detailed information about optic nerve head perfusion.[8]

In this case report, we aimed to present the clinical features of a patient with ODD and the diagnostic methods used.

Case Report

A 17-year-old male presented with a 2-month history of headaches. The patient had no known systemic disease or history of trauma, drug use, or smoking. His family history was unremarkable, with no consanguinity. On ophthalmologic examination, his uncorrected visual acuity was 10/10 (0.0 LogMAR) in both eyes. His pupils were isochoric and light reflexes were normal in both eyes; no afferent pupillary defect was observed. Color vision test using Ishihara cards was normal in both eyes. Slit-lamp anterior segment examination was also normal. Intraocular pressure was 14 mmHg in the right eye and 16 mmHg in the left eye. Fundus examination revealed bilateral optic disc swelling and blurred disc margins (Figures 1a, b).

Visual field was evaluated using the Swedish Interactive Thresholding Algorithm (SITA) standard 24-2 threshold test on a Humphrey Field Analyzer III 750 (Zeiss Humphrey Systems) automated perimetry device. Scotoma was not detected in the right eye, while a significant visual field defect was evident in the inferonasal quadrant in the left eye (Figures 2a, b). B-mode USG (AVISO, Quantel Medical, Clermont-Ferrand, France) revealed a hyperechogenic appearance consistent with bilateral ODD on the papilla (Figures 3a, b). FAF (Heidelberg Retinal Angiography 2, Heidelberg, Germany) imaging revealed oval hyperautofluorescent areas on the optic disc that were more prominent in the left eye (Figures 4a, b). On spectral domain OCT (Cirrus, Carl Zeiss Meditec Inc., Dublin, CA, USA), the mean retinal nerve fiber layer (RNFL) thickness was 69 µm in the right eye and 57 µm in the left eye despite the bilateral optic disc head swelling (Figure 5a, b). OCTA (RTVue XR 'Avanti', Optovue, Fremont, California, USA) of the optic disc revealed areas of capillary dropout in the retinal peripapillary layer that were more prominent in the nasal quadrant and reduced vascular density in both eyes (Figure 6a-f). Macular OCTA revealed a decrease in vascular density suggesting ischemia in the superficial and deep capillary plexus layers bilaterally (Figure 7a-f, Figure 8a-f).

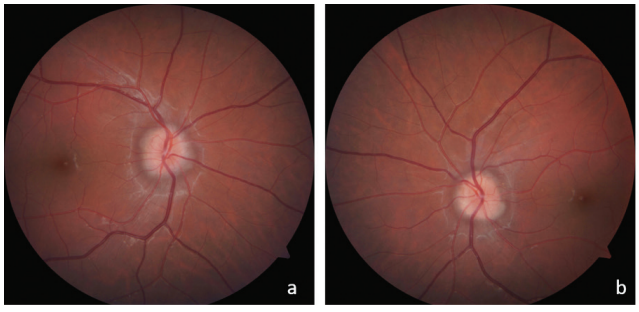

Figure 1. Optic disc swelling and blurred disc margins in the right (a) and left (b) eyes

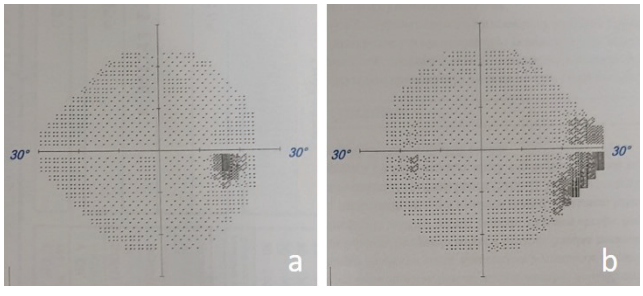

Figure 2. Visual fields of the right (a) and left (b) eyes demontrate unilateral scotoma involving the nasal area

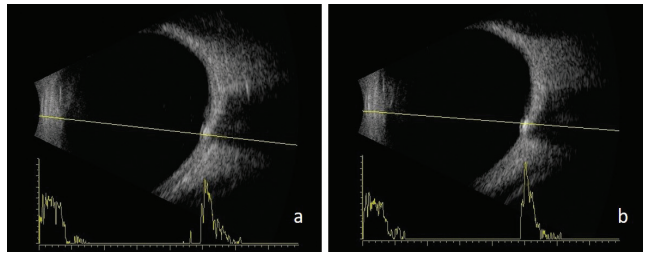

Figure 3. Hyperechogenic appearance on the papilla on ultrasonography in the right (a) and left (b) eyes

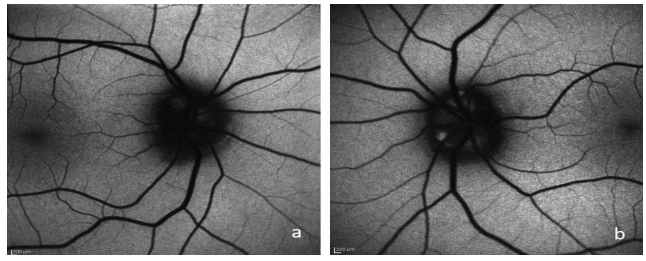

Figure 4. Oval-shaped drusen showing disc hyperautofluorescence on fundus autofluorescence imaging in the right (a) and left (b) eyes

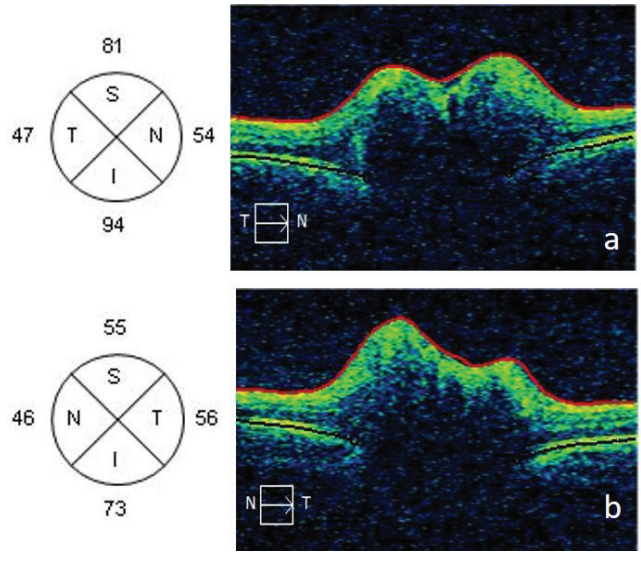

Figure 5. Optic disc nerve head swelling and retinal nerve fiber layer analysis on optical coherence tomography of the right (a) and left (b) eyes

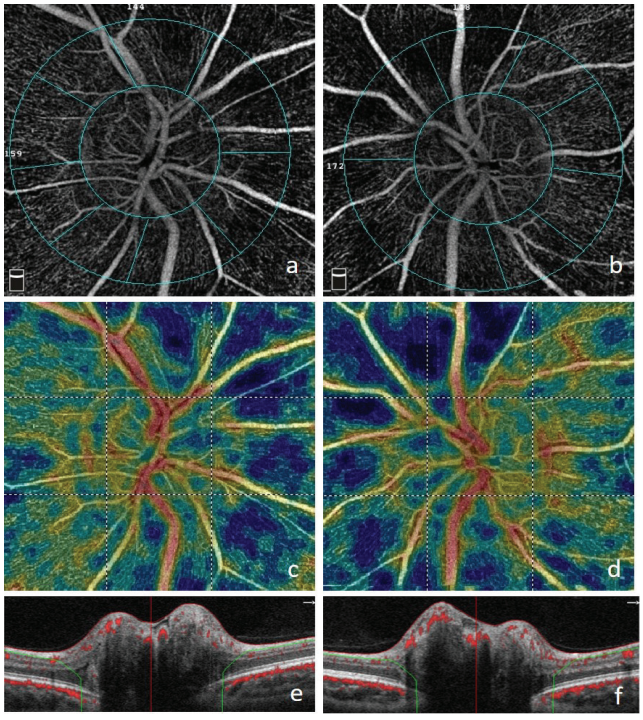

Figure 6. Nonperfusion areas in the radial peripapillary capillaries on optical coherence tomography angiography in the right (a) and left (b) eyes; reduced vascular density consistent with the blue areas on color vascular density map in the right (c) and left (d) eyes; B-scan optical coherence tomography images of the right (e) and left (f) eyes

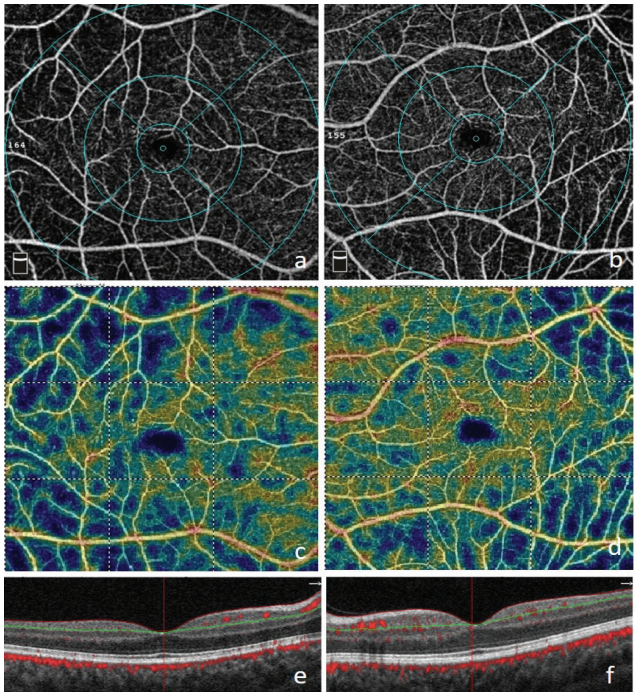

Figure 7. Nonperfusion areas in the macular superficial capillary plexus layer on optical coherence tomography angiography in the right (a) and left (b) eyes; reduced vascular density consistent with the blue areas on the color vascular density map in the right (c) and left (d) eyes; B-scan optical coherence tomography images of the right (e) and left (f) eyes

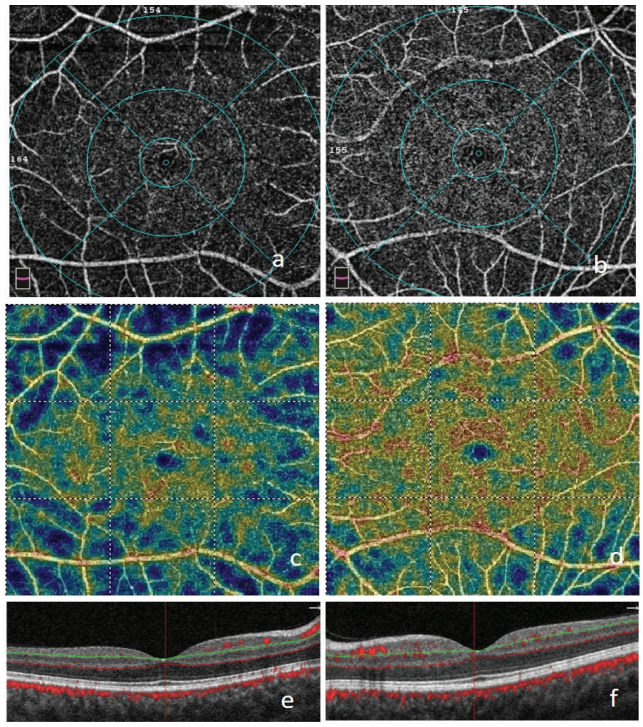

Figure 8. Nonperfusion areas in the macular deep capillary plexus layer on optical coherence tomography angiography in the right (a) and left (b) eyes; reduced vascular density consistent with the blue areas on the color vascular density map in the right (c) and left (d) eyes; B-scan optical coherence tomography images of the right (e) and left (f) eyes

Discussion

The prevalence of ODD is reported to be 0.2-2% in adults and 0.37-1% in children. The lower than expected prevalence in children has been attributed to difficulty in the use of imaging techniques in the diagnosis of deeply buried non-calcified drusen.[9] ODD are typically deeply situated in very young children and may eventually become superficial in late childhood, around 12 years of age.[10]

Although the pathogenesis is not known, drusen are believed to directly damage the retinal nerve fibers by axonal compression and indirectly cause ischemia in the nerve fiber layer as a result of vascular compression.[11] It has been reported in the literature that vascular complications such as nonarteritic anterior ischemic optic neuropathy, choroidal neovascularization, and central retinal artery and vein occlusions may occur due to ODD, albeit rarely.[12]

Kovarik et al.[13] reported that 76% of children presenting with suspected papilledema had pseudopapilledema. Misdiagnosis leads to unnecessary radiological imaging and invasive and expensive tests such as lumbar puncture or magnetic resonance imaging. Therefore, it is extremely important to be able to differentiate pseudopapilledema from papilledema, which has very different treatment, follow-up, and diagnosis. Fundus examination findings in favor of ODD are an absence of dilated capillary vessels over the disc, no blurring of the vessels around

the disc, a nonhyperemic disc, and the absence of peripapillary RNFL thickening.[4] Additional imaging methods are often needed to confirm the diagnosis.

B-mode USG remains the most reliable method for diagnosing ODD. While FAF imaging is useful for the diagnosis of superficial drusen, it can detect only 12-27% of buried drusen. OCT provides objective data through quantitative evaluation of the RNFL. Peripapillary RNFL thickness was reported to be greater in patients with papilledema compared to ODD. While RNFL values are often normal in patients with buried ODD, peripapillary thinning is observed in all quadrants in cases of superficial ODD.[2,7,9] In accordance with literature, OCT revealed peripapillary RNFL thinning in our patient.

Visual field defects have been detected in 73% of superficial drusen cases, compared to only 36% for buried drusen.[14] Visual field defects are less common in children (11-51%) than adults (50-90%). In patients with ODD, visual field defects have been related to older age, vision loss, and superficial, calcified drusen.[9] In children, the most common visual field problems associated with ODD are nasal defects (54%), concentric narrowing (21%), and blind spot enlargement (18%). In addition, defects were reported to be more common in the inferonasal retinal nerve fiber bundles than superotemporal.[15] Gaier et al.[16] detected inferotemporal microvascular attenuation in OCTA consistent with a visual field defect in the superonasal quadrant in a patient with ODD. The authors also reported macular microvascular attenuation only in the superficial capillary plexus. Although our patient had a visual field defect only in his left eye, reduced vascular density in both eyes was detected, especially in the nasal peripapillary area. Macular vascular density was found to be reduced in the deep capillary plexus layer as well as the superficial capillary plexus. It was interesting that the areas of nonperfusion were different in the superficial and deep capillary layers. This may be related to the superficial location of the ODD in the left eye, which caused less compression of the deep capillary layer.

In recent studies, OCTA imaging of the optic nerve head has revealed capillary narrowing in the superficial capillary plexus layer, areas of capillary dropout, and decreased vascular density in ODD patients.[8,16] Cennamo et al.[17] reported that ODD patients had lower flow index and reduced vascular density on optic nerve head OCTA compared to the control group. In addition, OCTA findings were positively correlated with ganglion cell layer thickness on OCT, and the authors emphasized that flow rate measurements made with OCTA may be an early predictor of axonal damage in ODD patients.[17] Unlike in other studies, our patient showed decreased vascular density on macular OCTA as well as optic nerve head OCTA. Therefore, areas of reduced vascular density detected by OCTA may be a predictor of future central scotoma. These findings support the hypothesis that enlarged ODD may cause acute or chronic ischemia by compressing nerve fibers or surrounding vessels. The prominent hyperautofluorescence on FAF, visual field defect, and RNFL thinning in our patient were compatible with superficial drusen. Additionally, the superficial capillary plexus was more affected than the deep capillary plexus on macular OCTA due to the superficial location. Macular OCTA findings also supported the FAF, visual field, and OCT outcomes.

In conclusion, OCTA has become more widely used for the evaluation of optic nerve pathologies as well as retinal diseases because it is a noninvasive, easy, fast, and practical method. OCTA can be used as an auxiliary diagnostic method to USG and FAF in the diagnosis of ODD. Although ODD is generally asymptomatic, OCTA evaluation of the optic nerve head and macula may play an important role in the early detection of ischemic complications. This should be further investigated in prospective studies with long-term OCTA follow-up of ODD patients.

Ethics

Informed Consent: Received.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Özlem Biçer, Huban Atilla, Concept: Özlem Biçer, Huban Atilla, Design: Özlem Biçer, Huban Atilla, Data Collection or Processing: Özlem Biçer, Huban Atilla, Analysis or Interpretation: Özlem Biçer, Huban Atilla, Literature Search: Özlem Biçer, Huban Atilla, Writing: Özlem Biçer, Huban Atilla.

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

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Case Report

Choroidal Melanoma Metastatic to the Contralateral Medial Rectus After Orbital Exenteration

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Abstract

A 78-year-old Caucasian woman presented with pain in her right and only eye that was worse on abduction. Her history was significant for a choroidal melanoma affecting her left eye for which she underwent an orbital exenteration 12 years previously. Computed tomography and magnetic resonance imaging of the right orbit identified a mass lesion affecting the medial rectus, suspicious for metastatic melanoma. A histopathological diagnosis of metastatic melanoma was subsequently made following biopsy of the right medial rectus.
Keywords: Melanoma, orbital metastasis, exenteration, cancer

Introduction

Metastases to the orbit are rare, comprising 1-13% of all orbital tumors and occurring in 2-3% of cancer patients.[1] Most are carcinomas and over 90% are unilateral.[1]

Melanoma represents 5.3-15% of all metastases to the orbit.[1,2,3,4] Primary sites include the skin and uveal tract, but may be unidentifiable in some cases.[3] In one review, the primary tumor was a cutaneous melanoma in 5 cases, a uveal melanoma in the contralateral eye in 1 case, and was unidentified in another case.[2]

Melanoma may tend to metastasize to the extraocular muscles.[3,5,6] There are two reports of bilateral extraocular muscle metastases from uveal melanoma[7,8] and three reports of bilateral extraocular muscle metastases from non-uveal melanoma.[9,10,11] Tumor was found in one or several extraocular muscles in 4 of 7 cases (57%)[2] and in 8 of 29 cases (28%)[5] in two reviews of melanoma metastases to the orbit.

We describe an unusual case of choroidal melanoma metastatic to the contralateral medial rectus 12 years after orbital exenteration for extrascleral choroidal melanoma as an illustration of the important clinical features of metastatic malignant melanoma to the extraocular muscles.

Case Report

A 78-year-old Caucasian woman presented with a 3-week history of pain behind her right and only eye that worsened when looking to her right. She had not noticed a change in her appearance.

Twelve years previously she had undergone orbital exenteration with postoperative radiotherapy for extrascleral

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spread of left choroidal melanoma. Five years after this, surveillance imaging identified an FDG-avid mass in her right kidney. Radical nephrectomy confirmed metastatic choroidal melanoma. Postoperative imaging did not show residual or distant metastatic disease. She visited her oncologist regularly for follow-up and had a positron emission tomography (PET) scan every 4 months.

Her past ocular history was also significant for a right hemiretinal vein occlusion with cystoid macular edema, for which she received treatment with ranibizumab.

Her past medical history was significant for hypertension, hypercholesterolemia, and gastroesophageal reflux disease. Her medications were candesartan, atorvastatin, and rabeprozole.

On examination her Snellen visual acuity was 6/5. Her anterior segment was normal. Fundoscopy showed signs of prior hemiretinal vein occlusion without cystoid macular edema. Intraocular pressure was 15 mmHg. Optic nerve function was intact. Adduction was limited (Figure 1) and abduction was painful.

Orbital computed tomography (CT) showed homogenous, fusiform enlargement of the right medial rectus muscle which involved its tendon. Magnetic resonance imaging (MRI) showed hyperintensity of the medial rectus on T1-weighted imaging and hypointensity on T2-weighted imaging (Figure 2) compatible with melanoma metastases. PET did not show any further metastases elsewhere.

Under general anesthetic, she underwent right medial rectus biopsy. An incision was made behind the caruncle and dissection to the medial rectus was performed. After the biopsy sample was retrieved and hemostasis achieved, the incision at the caruncle was closed with two 6/0 vicryl interrupted sutures. A dark brown vascular lesion within the muscle was noted. Histopathological examination revealed this to be metastatic malignant melanoma (Figure 3). Next-generation sequencing identified a somatic mutation in the *GNA11* gene. A sensitizing BRAF mutation was not found in this tumor.

The patient commenced dual immunotherapy with ipilimumab and nivolumab. Following three cycles of such treatment, she developed immune-related enteritis and pneumonitis necessitating intensive care unit admission, ventilation, and treatment with high-dose intravenous corticosteroids. Though she recovered well medically, MRI demonstrated disease progression in the right orbit, to which she subsequently received 36 Gy stereotactic radiotherapy. Repeat MRI and PET showed no regression of the lesion. She is currently being re-challenged with nivolumab. It is now 16 months following the diagnosis of right orbital disease.

Discussion

The commonest malignancies to metastasize to the eye and orbit are breast, lung, unknown primary, and prostate cancers, which together account for 75% of all such metastases.[1,3,4,12,13] Cutaneous malignant melanoma is the ninth most common cancer[14], the fifth most common source of ophthalmic metastases, and may account for up to 15% of metastases to the orbit.[2]

Proptosis (58%) and diplopia (54%) are the most common presenting symptoms of orbital metastases.[5] Pain, as in the case described here, is also recognized as a presenting symptom and may be related to scleral indentation by the tumor. Some patients present with eyelid abnormalities such as ptosis or distorted lid margin. Chemosis and conjunctival injection are presenting features in others and may indicate vascular congestion or an inflammatory response. Fewer patients present with visual disturbances such as reduced vision and/or metamorphopsia, which may be related to choroidal folds and/or papilledema.[5]

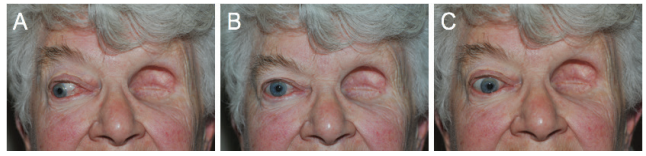

Figure 1. Clinical photographs showing right eye in abduction (A), primary gaze (B), and adduction (C)

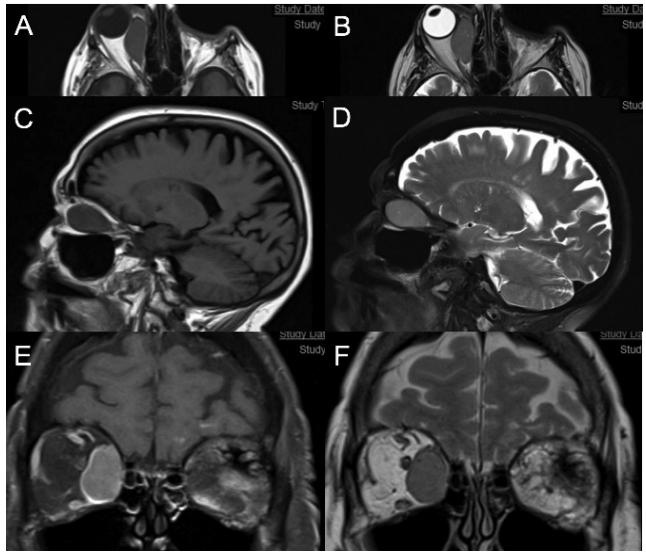

Figure 2. Magnetic resonance imaging of our patient demonstrating a large mass in the right medial rectus: Axial T1 (A) and T2 (B); sagittal T1 (C) and T2 (D); coronal T1, fat suppressed (E), and T2 (F). In general, the mass is hyperintense in T1-weighted images and hypointense in T2-weighted images

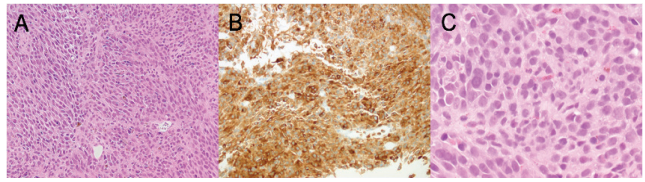

Figure 3. Histopathological examination of muscle biopsy. (A) Hematoxylin and eosin stain, 200X; diffusely infiltrative nested malignant cells, some with intracytoplasmic brown pigment; (B) Melan A immunohistochemistry stain, 200X; diffusely positive staining consistent with melanoma; (C) hematoxylin and eosin stain, 600X; abnormal plump spindle and epithelioid cells showing nuclear pleomorphism with some nuclei bearing inclusions and others intracytoplasmic pigment consistent with melanoma cells (C).

In one study, 24 patients with primary cutaneous melanoma developed orbital metastases at a mean of 3.3 years after initial diagnosis.[5] In another review, the mean interval from the diagnosis of the primary tumor to the diagnosis of orbital metastases was 7.8 years for choroidal melanoma and 5.5 years for cutaneous melanoma.[2] The interval from the diagnosis of our patient's choroidal melanoma to the onset of her ocular symptoms was 12 years, which is somewhat longer than the mean reported in each of these studies. Many studies have reported shorter intervals between diagnosis of the primary tumor and the development of intraocular metastases relative to the development of orbital metastases.[6,15]

On MRI, the extraocular muscle in our patient showed T1 signal hyperintensity and T2 signal hypointensity, which is consistent with the paramagnetic properties of melanin found in malignant melanoma.[7] Due to the incidence of concurrent metastases, patients suspected of having metastatic melanoma should be evaluated by total body PET, as with our patient.[16]

A higher predilection for muscle of metastatic melanoma compared with carcinoma has been reported in several reviews.[3,5,6] This muscle tropism of orbital metastatic melanoma explains why diplopia is one of the main presenting symptoms and limited ocular motility the main presenting sign of extraocular muscle involvement with metastases. In one reported series, the metastasis was situated in the extraocular muscle in 4 of 7 cases of metastatic melanoma to the orbit.[2] Tumor adhesion molecules may play a role in such site-specific metastases to the orbit.[17]

The differential diagnosis of extraocular muscle enlargement includes thyroid-associated orbitopathy, lymphoproliferative disease (especially lymphoma), inflammatory orbital disease (orbital myositis, IgG4-related disease, idiopathic orbital inflammation), acromegaly, vascular and infectious causes, and metastatic malignancy.[9,18,19] Accurate diagnosis can be difficult; some reports describe the clinical picture of extraocular muscle metastases as being very similar to that of thyroid eye disease with imaging demonstrating selective enlargement of the medial and lateral rectus muscles.[7,10,11,20] In the case described here, diagnosis was based on clinical findings of weakness of the affected muscle and atypical extraocular muscle enlargement in the context of previously metastatic choroidal melanoma.

Choroidal melanoma may infiltrate the extraocular muscles following metastasis, as in the case described here. In a review of 1842 cases of choroidal melanoma, there was recurrence of tumor in the orbit following simple enucleation in 55 cases (3%).[21] Forty-three of these occurred in the group of 235 patients in which the original histopathological sections revealed evidence of extrascleral extension, while only 12 of the 1607 patients without evidence of the same developed orbital recurrence. Put another way, the chance of a patient having orbital recurrence was 26 times greater if extrascleral extension of the initial tumor was noted.[21] The orbital recurrence rate was 65% for those cases in which the extraocular tumor had a cross-sectional area of 100 mm^2, and one-fifth of that rate when the extrascleral extension of the tumor was smaller than this.[21] In cases showing no evidence of encapsulation or in which there was evidence that the surgeon had cut into the epibulbar tumor, the recurrence rate was 6 times greater than when there was no evidence of the same.[21]

In the 12 cases with recurrence in the orbit without demonstrable extrascleral extension at the time of enucleation, it is worth noting that 2 patients had had surgery for retinal detachment, 1 for glaucoma, and another had experienced traumatic rupture of the globe. It is thought that approximately 2 of every 5 cases of choroidal melanoma have extraocular extension when enucleation is preceded by retinal detachment surgery.[22] Tumor cells may be released into the orbit during drainage of subretinal fluid or there may be gross extension of tumor through the scleral wound to the orbit. Inadvertent seeding during other intraocular surgeries or following globe rupture might also be expected to occur.

At least 2 cases of choroidal melanoma treated with evisceration because of an erroneous preoperative diagnosis of panophthalmitis have been described.[21] Both patients experienced recurrence of tumor within the scleral shell and subsequent extrascleral extension to the orbit. One patient underwent exenteration 4.3 years after evisceration and survived 4 months while the second underwent exenteration 5 years after evisceration and died 2 years later.[21] Ten percent of blind, painful eyes with opaque media were found to contain unsuspected malignant neoplasms, usually uveal melanomas, on pathological examination.[23,24] Consequently, the presence of a malignant intraocular neoplasm should be excluded prior to evisceration of any eye, particularly those with opaque media, and if this cannot be done confidently, enucleation should be performed.[25]

Orbital metastases are rarely the first sign of metastatic melanoma but generally occur in patients already having multiple metastases.[2] It is much less common for ocular metastases to be the first evidence of disease spread.[26] In one study, 68 of 76 patients (89%) with primary cutaneous melanoma had at least one other non-ophthalmic distant metastasis at the time of presentation with ophthalmic metastasis.[5] These were cutaneous and/or subcutaneous in 45%, lymph nodes in 38%, central nervous system in 34%, lungs in 27%, and liver in 25%. The remaining 8 patients with negative metastatic evaluations were all later diagnosed with non-ophthalmic systemic metastases.[5]

The median survival times of those with hepatic metastases from choroidal melanoma is typically less than a year, but patients with only extrahepatic metastases appear to have longer median survival times of 19-28 months.[27,28] In one study, patients with orbital metastases from cutaneous melanoma survived an average of 7.5 months, whereas those with intraocular metastases survived 6.6 months.[5] Zografos et al.[2] reviewed 14 cases of melanoma metastatic from various sites (cutaneous in 5 cases, uveal in 3 cases, mucosal in 1 case, and unknown primary in 2 cases) and found that patients with orbital metastases still had better survival times than those with intraocular metastases, at 19.7 (range 5-48 months) and 8.8. months, respectively.

Ninety percent of patients with any ophthalmic metastasis from melanoma do not survive beyond 12 months.[2]

Symptom palliation is, consequently, often the main goal of the management of orbital metastatic melanoma and aims to maximize ocular function while minimizing discomfort. The correction of bothersome diplopia, reduction of proptosis that may be unsightly and/or prevent eyelid closure and thus lead to exposure keratopathy, or treatment of optic nerve compression to maintain or restore visual function must often be considered.[2] The choice of treatment modality (surgery, chemotherapy, or radiotherapy) will depend on the symptomatology, treatment toxicities, and the patient's general health and life expectancy.

Solitary orbital metastases can be treated with surgery and radiation with or without chemotherapy or immunotherapy. The goal of surgery is to decrease tumor volume, though significant debulking of extraocular muscle metastases is often not possible. In our case, complete local control would not have been possible given the extent of muscle involvement. Radiation may be the primary mode of treatment in the absence of other effective options or may be used to address residual microscopic disease, but is generally not the treatment modality of choice for choroidal melanoma. In a review of patients with exclusively extraocular muscle metastases, the most common treatment was excision of the tumor mass, which was conducted in 11 of 19 patients (58%). Radiation was used in 9 (47%) of these patients. The treatment advances that have improved survival in patients with cutaneous melanoma have unfortunately not provided similar benefits in those with advanced choroidal melanoma.

This unique case highlights the possibility of recurrence of uveal melanoma metastases in unusual locations in survivors, particularly survivors of metastatic disease elsewhere.[8] Proptosis, diplopia, pain, and eyelid changes are the most common presenting symptoms of orbital metastases. At the time of their presentation with ophthalmic metastatic disease, most patients either have previously diagnosed widespread systemic disease or disseminated disease is discovered upon work up for metastatic disease. Patient survival largely depends on the extent of systemic disease and is generally not very long, rarely over one year.[2]

Ethics

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Elizabeth McElnea, Louis J. Stevenson, Cesae Salinas La Rosa, Sem Liew, Thomas G. Hardy, Concept: Elizabeth McElnea, Thomas G. Hardy, Design: Elizabeth McElnea, Thomas G. Hardy, Data Collection or Processing: Elizabeth McElnea, Louis J. Stevenson, Cesae Salinas La Rosa, Sem Liew, Thomas G. Hardy, Analysis or Interpretation Elizabeth McElnea, Louis J. Stevenson, Cesae Salinas La Rosa, Sem Liew, Thomas G. Hardy, Literature Search: Elizabeth McElnea, Louis J. Stevenson, Thomas G. Hardy, Writing: Elizabeth McElnea, Louis J. Stevenson, Cesae Salinas La Rosa, Sem Liew, Thomas G. Hardy.

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