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Outcomes of Phacoemulsification in Patients with Chronic Ocular Graft-Versus-Host Disease

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Abstract

Purpose—To evaluate the outcomes of phacoemulsification in patients with ocular graft-versus-host disease (GVHD).

Methods—The occurrence of cataract, cataract surgery and its outcomes were analyzed in the medical records of 229 patients (458 eyes) with ocular GVHD. Outcome measures included pre- and postoperative corrected distance visual acuity (CDVA) and the rate of postoperative complications.

Results—From 458 eyes evaluated 58 were pseudophakic, from the 400 phakic eyes 238 (59%) presented with cataracts and 62 (26%) underwent cataract surgery. Analysis of postoperative complications and visual outcomes at one month was performed in 51 eyes in which detailed surgical and immediate postoperative records were available. Preoperatively, the mean CDVA was 0.67±0.57 LogMAR (Snellen 20/93) and improved postoperatively to 0.17±0.18 (Snellen 20/29) at one month (P<0.0001), and to 0.13±0.14 (Snellen 20/26) by the final follow-up visit (P<0.0001). Postoperative complications included: corneal epithelial defects (8%), filamentary keratitis (6%), worsening of corneal epitheliopathy (16%), posterior capsular opacification (18%), and cystoid macular edema (4%). A corrected distance visual acuity of 20/30 or better was achieved in 87% of the eyes; suboptimal CDVA improvement was accounted by severe ocular surface disease, pre-existing advanced glaucoma, and prior macular surgery.

Conclusions—Phacoemulsification in patients with chronic ocular GVHD is a safe and efficacious procedure resulting in significant visual improvement. Overall, postoperative adverse events responded well to timely management.

Keywords

graft-versus-host disease; cataract; phacoemulsification; ocular surface disease

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Introduction

Hematopoietic stem cell transplantation (HSCT) is an established treatment for various hematological disorders [1]. Advancements in transplantation techniques have led to an increase in the number of procedures performed annually and have contributed to the long-term survival of these patients [1,2]. Therefore, long-term complications after HSCT are becoming the main factor affecting patients' quality of life [3]. Chronic graft-versus-host disease (GVHD) has become a major cause of morbidity and mortality after allogeneic HSCT, this condition is originated by an immune response of donor T cells against the recipient's tissues [4]. Ocular manifestations in patients with chronic GVHD are present in 60–90% of cases [5]. Ocular GVHD commonly presents with eye discomfort, pain, grittiness, redness, light sensitivity, and blurred vision. Clinical signs include conjunctival hyperemia, corneal epitheliopathy, meibomian gland dysfunction, conjunctival and corneal scarring, and stromal ulceration, which negatively impact vision-related quality of life [4–6].

Posterior subcapsular (PSC) cataract is highly prevalent in patients undergoing HSCT, mostly due to irradiation and steroid treatment [7–9]. Furthermore, cataract has been reported as a major cause of decreased visual acuity in patients with systemic GVHD [10]. Consequently, a large number of patients are expected to undergo cataract surgery in the setting of ocular GVHD. Ocular surface manifestations of GVHD may affect the outcomes of cataract surgery and the postoperative course in these patients. Limited information regarding the outcomes of cataract surgery in patients with chronic ocular GVHD is available in the current literature [11–12]. The purpose of this study was to evaluate visual outcomes and post-operative complications of phacoemulsification in patients with chronic ocular GVHD.

Methods

We conducted a retrospective study that involved chart review of 229 patients with chronic ocular GVHD examined at the Cornea Service of the Massachusetts Eye and Ear Infirmary (MEEI) from May 2007 to December 2012. The study was approved by the Institutional Review Board and followed the tenets of the Declaration of Helsinki. Patients were selected according to the National Institutes of Health (NIH) diagnostic criteria for chronic ocular GVHD. These criteria are defined by a distinctive manifestation of systemic GVHD accompanied by: 1) new ocular sicca documented with a bilateral Schirmer test averaging ≤5 mm, or 2) new onset of ocular sicca by slit-lamp examination with a bilateral Schirmer test averaging 6–10 mm [13].

We evaluated the presence and type of cataract in patients with ocular GVHD and the surgical outcomes in those who underwent cataract surgery. Data collected included demographic information, slit-lamp and fundus exam, change between preoperative and postoperative visual acuity, and intraoperative and postoperative findings. The surgical outcomes included corrected distance visual acuity at one month and last follow-up visits, and the intraoperative and postoperative complications. All postoperative ocular surface events occurring within 4 weeks postoperatively were considered related to the surgical procedure.

Statistical Analysis

Mean corrected distance visual acuity values were calculated after converting recorded data from Snellen to LogMAR scale. Normality of the data was evaluated using the D'Agostino and Pearson omnibus test. The Wilcoxon signed-rank test was used to compare preoperative and postoperative corrected distance visual acuity and corneal fluorescein staining. A two-sided P value of <0.05 was considered statistically significant. We calculated the occurrence of postoperative complications and expressed it as the proportion from the total eyes intervened.

Results

A total of 458 eyes with a diagnosis of chronic ocular graft-versus host disease were included, from which 58 eyes (13%) were pseudophakic at the initial visit. From the 400 phakic eyes, 162 (40.5%) had a clear lens and 238 (59.5%) presented with one or more types of lens opacities as described in table 1. In total nuclear sclerosis was seen in 158 eyes (39.5%), posterior subcapsular cataract in 132 eyes (33%), and cortical cataract in 22 eyes (5.5%). Cataract surgery was performed in 62 eyes, representing 26% of all the eyes diagnosed with cataract. Posterior subcapsular cataract was present in all the operated eyes either alone (33 eyes) or in combination with nuclear sclerosis or cortical opacity (29 eyes). Analysis of postoperative complications and visual outcomes at one month was performed in 51 eyes with detailed surgical and immediate postoperative records. Six patients (11 eyes) who had the surgical procedure performed by their primary ophthalmologist but were followed at our ocular surface clinic were included in the visual acuity analyses for the preoperative and final visits.

At the time of cataract surgery the mean patient age was 50 ± 13 years (range: 22–72). The mean interval between HSCT and development of ocular GVHD in patients undergoing cataract surgery was 19 ± 28 months (median: 11, range: 1–159 months). All patients presented clinical features of chronic ocular GVHD, except one patient who first presented with acute ocular GVHD but later developed chronic ocular GVHD. Phacoemulsification was performed 42 ± 33 months (median: 32, range: 19–251) after HSCT and 23 ± 19 months (median: 19, range: 2–91) after the diagnosis of ocular GVHD. The mean patient follow-up after cataract surgery was 12 ± 13 months (1–50). The primary disorder for which HSCT was performed, conditioning regimens, and extraocular GVHD involvement are shown in Table 2; other concurrent pathological conditions in the eyes undergoing cataract surgery are shown in Table 3.

Surgical procedure

In all eyes undergoing cataract surgery adequate control of ocular surface disease was achieved preoperatively. Preoperative topical and systemic therapy for ocular GVHD and concurrent systemic GVHD are shown in Table 4. Treatment with topical autologous serum was discontinued three days prior and until one week after surgery since it is rich in protein and growth factors, and hence may increase the risk of microbial colonization and infection in the setting of intraocular surgery [14,15]. Scleral contact lenses were removed immediately before intraocular lens calculation to ensure an even ocular surface and accurate biometry, to subsequently resume their use until the day of surgery. Postoperatively, scleral contact lens wear was restarted after one week if the corneal wound was sutured or after three to four weeks otherwise. Phacoemulsification through a clear corneal incision with posterior chamber intraocular lens implantation was performed in all the eyes. Postoperatively, 1% topical prednisolone acetate was prescribed four times a day tapered over four weeks, and topical fluroquinolone four times a day for one week. Patients were examined postoperatively at day one, week one, and one month after the surgery unless otherwise required. After one month, the frequency of visits depended on the status of the ocular surface.

Visual outcomes

The mean preoperative CDVA was 0.67 ± 0.57 LogMAR (Snellen 20/93) and improved to 0.17 ± 0.18 (Snellen 20/29) at one month postoperatively ($P<0.0001$), and to 0.13 ± 0.14 (Snellen 20/26) at the final follow-up visit ($P<0.0001$). Table 5 shows the visual acuities at one-month and the final visits. By the final visit 54 eyes (87%) had achieved a visual acuity of 20/30 or better. From the eyes (8) that did not achieve a visual acuity of 20/30 or better, five eyes presented with concurrent pathologies such as advanced glaucoma (4) and prior macular surgery (1), while three eyes had severe dry eye with corneal epitheliopathy, some of which required management with scleral contact lens.

Intraoperative findings

There were no severe intraoperative complications. One eye required limited anterior vitrectomy with intraocular lens implantation in the sulcus due to a posterior capsular tear.

Postoperative findings

Corneal epithelial defects—Corneal epithelial defects ≥ 1 mm were noted in four eyes (8%) at postoperative days two (2 eyes), seven (1) and 14 (1). Epithelial defects were located centrally in all the eyes and resolved within a week after treatment with lubrication, antibiotic ointment, and bandage contact lens (3 eyes).

Filamentary keratitis—Filamentary keratitis was noted in three eyes (6%) at postoperative days one (1 eye) and 14 (2).

Corneal punctate keratitis—Worsening of corneal epitheliopathy was noted in eight eyes (16%) at postoperative weeks one (6 eyes) and four (2). We were not able to compare the pre and postoperative corneal fluorescein staining in all patients due to lack of consistent data recorded in the same scheme for all visits (e.g., NEI or Oxford scheme). Nonetheless, in 45% of the cases the preoperative and postoperative (one week and one month) corneal fluorescein staining values were available in the modified Oxford scheme. In this subgroup of patients, the mean corneal fluorescein staining increased from 1.02 ± 0.77 Oxford units preoperatively to 1.65 ± 1.29 units at one week postoperatively ($P=0.04$), and subsequently decreased to 1.30 ± 1.05 units at one month postoperatively ($P=0.23$, compared to the preoperative score). From eight eyes with exacerbated punctate keratitis after surgery, two eyes had been treated preoperatively with autologous serum. After restarting the preoperative topical therapy, including autologous serum, both eyes reached preoperative punctate keratitis levels by eight weeks. Exacerbation of punctate keratitis after surgery responded to treatment with one or more of the following: preservative-free lubricant eye drops, topical corticosteroids, punctal plugs, resumption of topical autologous serum, and scleral or bandage contact lenses.

Posterior capsular opacification (PCO)—Vision impairing posterior capsular opacification (PCO) where laser capsulotomy was indicated was present in nine eyes (18%) and was noted between one to eight months after surgery.

Cystoid macular edema (CME)—Cystoid macular edema was diagnosed when cystic changes were evident either by fundoscopy or by optical coherence tomography, and when the vision acuity was ≤ 20/40. CME was noted in the two eyes (4%) of the same patient at months five and seven postoperatively. Both eyes underwent uneventful phacoemulsification, and were treated with YAG laser capsulotomy three months after the surgery due to PCO. After unsatisfactory visual acuity improvement, a macular comprehensive evaluation revealed the presence of CME. However, fundus examination also revealed retinal microaneurysms and microhemorrhages in both eyes, while the fluorescein angiography revealed perifoveal telengiectatic vessels; a diagnosis of radiation retinopathy was made by the MEEI Retina Service. The CME responded to topical non-steroidal anti-inflammatory treatment only in one eye but required subtenonian triamcinolone and intravitreal bevacizumab in the fellow eye. At the final follow-up visit both eyes showed improvement with visual acuity of 20/25 and 20/30, respectively.

Discussion

In this retrospective study cataract was present in 59% of the eyes of patients with chronic ocular GVHD. Twenty-six percent of these eyes underwent cataract surgery with good visual outcomes, represented by a postoperative corrected distance visual acuity of 20/30 or better in 87% of the eyes. From eight eyes (13%) that did not achieve visual acuity of 20/30, three eyes (5%) presented severe ocular surface disease, four eyes (6%) advanced glaucoma, and one eye (2%) previous macular surgery (Table 3).

We observed nuclear sclerosis in 39.5% of the eyes with ocular GVHD, which is in concordance with the prevalence of nuclear sclerosis reported in the general population (19 to 51%), most likely reflecting the aging changes in the lens [16,17]. However, the prevalence of posterior subcapsular cataract noted in our cohort (33%) is 5 times higher than reported in the general population [16,17]. Our study is consistent with other studies reporting a high prevalence of up to 48% of PSC cataract in patients with systemic GVHD [8,10]. This can be explained, to a large degree, by the known association between exposure to radiation and systemic corticosteroids and the development of posterior subcapsular cataract in patients receiving hematopoietic stem cell transplants [8, 18–20]. In the present study, 47% of the eyes diagnosed with PSC cataract underwent cataract surgery at a mean age of 50 years, a considerably younger age when compared to the mean age of individuals undergoing cataract surgery in the general population [21,22].

Cataract surgery can induce or aggravate preexisting dry eye disease [23]. Ocular surface complications such as punctate keratitis, recurrent epithelial defects, filamentary keratitis and corneal melting have been reported after cataract surgery in patients with dry eye disease, especially in those associated with systemic disorders such as Sjogrens syndrome and rheumatoid arthritis [24–26]. In patients with preexisting aqueous deficiency and an unstable tear film undergoing cataract surgery the inflicted insult due to incision (nerve damage), ocular surface exposure and toxicity from eye drops may pose the cornea in a vulnerable situation for epithelial breakdown [23,27]. In our series, the incidence of epithelial defects after cataract surgery was 8%. Other studies on cataract surgery in patients with dry eyes after bone marrow transplantation have reported epithelial defects in 0–3% of the eyes [11,12] and one study in patients with dry eye secondary to connective tissue disorders and older age reported epithelial defects in 32% of cases [26]. In the current study, three of the four eyes that developed epithelial defects were being treated with scleral contact lenses and two with topical autologous serum prior to the surgery, which is indicative of severe ocular surface disease. Additionally, cessation of treatment with scleral lenses and topical autologous serum in the early postoperative period might have contributed to the development of epithelial defects. However, all the epithelial defects responded satisfactorily to adequate treatment and resolved within one week. Based on the observations of the current and other studies, the evidence suggests that the severity of dry eye disease at the time of surgery can largely influence the occurrence of postoperative epithelial breakdown. Ocular inflammation triggers mucus production and adherence of the mucus strands to the compromised epithelium leads to filamentary keratitis, which was noted in 6% of the cases in the early postoperative period.

We noticed worsening of corneal epitheliopathy in 16% of the eyes in the early postoperative period. The comparison between the pre and postoperative corneal fluorescein staining scores revealed that the mean corneal fluorescein staining increased statistically significantly one week after the cataract surgery but subsequently decreased at one month postoperatively, showing at this later point no statistically significant difference with the preoperative scores. This pattern is similar to that described in the general population after phacoemulsification [28].

Vision impairing PCO that required YAG laser capsulotomy developed in 18% of the operated eyes and was noted between one and eight months after surgery. The general incidence of PCO reported within one year of cataract surgery varies from 2–11% [29,30,31]. A meta-analysis by Schaumberg et al. reported an estimate of PCO incidence of 11.8% after one year of surgery and 20.7% after three years [32]. PCO development is influenced by several factors such as patient age, type of surgery, materials and designs of intraocular lenses, and the follow-up period making it difficult to compare the incidence among different studies. In the current study a higher incidence of PCO, when compared to the incidence reported for the general population, is likely related to the high prevalence of PSC cataract, treatment with systemic corticosteroids, and to a younger mean age, all of which have been linked to posterior capsular opacification [33,34,35]. Interestingly, the 18% PCO incidence noted in this study is much lower than the 44% PCO incidence reported by our group in 2001 in recipients of bone marrow transplants that underwent cataract surgery, this reduction in the incidence of PCO may be influenced by advancement in surgical techniques and intraocular lenses as reported for the general population. [11,36]

The patient who presented with bilateral cystoid macular edema several months after cataract surgery was ultimately diagnosed with bilateral radiation retinopathy. This patient had history of standard treatment with fractionated total body irradiation as a part of pre-transplant conditioning regimen but additionally received cranial radiation. Penn et al. reported a similar case with bilateral CME in one patient with ocular GVHD after cataract surgery, however the CME in that patient was noted within two months of cataract surgery and there is no mention of radiation retinopathy [12]. It is unlikely that the occurrence of bilateral CME in this case was related to the cataract surgery given the delayed appearance after six months and the concurrent diagnosis of associated radiation retinopathy. Radiation is a well-known factor that inflicts damage to the retinal vascular endothelium and leads to capillary occlusion, microaneurysm formation, and telengiectatic vessels, ultimately leading to leakage and macular edema [37]. However, it is possible that radiation-induced retinal compromise may predispose to macular edema development in the setting of otherwise uncomplicated cataract surgery. Awareness of this potential risk and assessment of the macular condition in previously irradiated patients undergoing cataract surgery (e.g., by optical coherence tomography) may be of help to better understand the patient’s ocular condition, and to implement the right procedures to improve the ultimate visual prognosis.

The present study has limitations inherent to its retrospective design, including the variability of postoperative follow-up within the cohort. It is important to emphasize that it is difficult for the ophthalmologist to follow-up patients with ocular GVHD, these patients are usually followed up in oncology or internal medicine departments, have multiple serious systemic conditions that frequently result in hospitalization or mortality, thus leading to variable follow-ups to an eye clinic. However, we believe that despite the limitations, the evidence from this large cohort provides valuable clinical data regarding the visual potential and expected complications of cataract surgery in patients with ocular surface disease secondary to GVHD. To overcome the most common limitations we face with these patients, we propose the creation of a multicentric registry that facilitates accessibility to accurate and continuously updated data from large cohorts, hence improving our understanding of ocular GVHD, its natural history, and the impact of cataract surgery and other interventions.

In summary, visual outcomes of phacoemulsification in patients with chronic ocular graft-versus-host disease are excellent, resulting in visual acuities of 20/30 or better in 95% of eyes without any concurrent pathological condition other than GVHD. No serious adverse events occurred and ocular surface complications responded well to appropriate management. Awareness of concurrent co-morbidities, such as severe ocular surface impairment or posterior segment conditions, may help to identify cases with a more reserved visual prognosis. Herein, we show that optimal preoperative stabilization of the ocular surface and timely identification and management of complications proves phacoemulsification an efficacious procedure in patients with ocular graft-versus-host disease.

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Table 1

Summary of the lens opacities in patients with ocular GVHD

Lens condition	Total number of eyes (%) (N= 400)
Clear lens	162 (40.5)
Nuclear sclerotic cataract	90 (22.5)
Posterior subcapsular cataract	78 (19.5)
Cortical cataract	2 (0.5)
Nuclear sclerotic + Posterior subcapsular cataract	48 (12)
Nuclear sclerotic +Cortical cataract	14 (3.5)
Nuclear sclerotic + Posterior subcapsular + Cortical cataract	6 (1.5)

Table 2

Transplant details in patients undergoing cataract surgery

Parameter	N=36 (%)
Primary disorder	
Acute Myeloid Leukemia	17 (47)
Chronic Lymphoid Leukemia	6 (17)
Acute Lymphoid Leukemia	4 (11)
Non-Hodgkin's Lymphoma	5 (14)
Chronic Myeloid Leukemia	2 (5.5)
Myelodysplastic syndrome	2 (5.5)
Conditioning regimen	
Total body irradiation + Chemotherapy	16 (44)
Chemotherapy alone	20 (56)
Systemic graft-versus-host disease	
Skin	26 (72)
Mouth	25 (69)
Liver	13 (36)
Gastrointestinal tract	7 (19)
Lung	3 (8)

Table 3

Concurrent pathological findings in the eyes undergoing cataract surgery

Preoperative findings	No. of eyes (%) N=62
Meibomian gland dysfunction	62 (100)
Superficial punctate keratopathy	61 (98)
Conjunctival hyperemia	36 (58)
Lid margin scarring	10 (16)
Subconjunctival fibrosis	9 (14.5)
Conjunctivochalasis	9 (14.5)
Filamentary keratitis†	9 (14.5)
Glaucoma	4 (6)
Healed adherent leucoma	1 (2)
Corneal scar post healed corneal ulcer	1(2)
Previous corneal perforation requiring PKP	1 (2)
Resolved central serous chorioretinopathy	1 (2)
Post macular hole surgery	1 (2)

†Filamentary keratitis was resolved prior to cataract surgery in all eyes. PKP: Penetrating keratoplasty

Table 4

Patients' preoperative topical and systemic therapy for ocular and systemic GVHD.

Local treatments for ocular GVHD	No. of cases (%)
Topical lubricants	62 (100)
Punctal occlusion	42 (67.7)
Topical anakinra	27 (43.5)
Topical autologous serum	23 (37)
Antibiotic ointment	20 (32)
Topical cyclosporine	17 (27)
Topical corticosteroids	9 (14.5)
Scleral lens	9 (14.5)
Mucolytic (10% N-acetylcysteine) therapy	5 (8)
Systemic treatments for ocular and concurrent systemic GVHD	
Corticosteroids	47 (76)
Mycophenolate mofetil	29 (47)
Doxycycline	21 (34)
Sirolimus	21 (34)
Tacrolimus	18 (29)

Table 5

Preoperative and postoperative corrected distance visual acuity

Visual acuity Snellen	Preoperative eyes (%) N=62 eyes	Postoperative	
		1 month N=51 eyes (%)	Final visit N=62 eyes (%)
<20/200	7 (11)	0 (0)	0 (0)
<20/80–20/200	18 (29)	0 (0)	0 (0)
<20/30–20/80	28 (45)	16 (31)	8 (13)
≥20/30	9 (15)	35 (69)	52 (87)