Early Postoperative Effects of Uncomplicated Phacoemulsification Surgery on Corneal Endothelial Cells and Thickness in Patients with Pseudoexfoliation Syndrome

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Research Article

Keywords: Central corneal thickness, corneal endothelium, phacoemulsification, pseudoexfoliation syndrome

Posted Date: April 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-327802/v1

Abstract

Purpose: To compare early postoperative effects of uncomplicated phacoemulsification surgery on corneal endothelial cells and thickness in patients with pseudoexfoliation syndrome (PEX).

Methods: One eye each of 32 patients with PEX and 32 age-matched non-PEX subjects was evaluated preoperatively and on 1st, 7th, and 30th days after uncomplicated phacoemulsification surgery in this retrospective case-control study. Nuclear firmness, corneal edema (CE), anterior chamber reaction (ACR) intensity were graded by a slit-lamp microscope. Endothelial cell density (ECD), coefficient of variation in cell area (CV), hexagonal cell ratio (HEX), and central corneal thickness (CCT) were measured using a noncontact specular microscope.

Results: There was no significant group-difference in age, sex, corneal edema (CE), anterior chamber reaction (ACR), coefficient of variation in cell area (CV), and hexagonal cell ratio (HEX). Mean effective phaco time (EPT) was significantly lower intraoperatively ($p<0.001$) and logarithm of the minimum angle of resolution (logMAR) values of best-corrected visual acuity (BCVA) were significantly higher on both 1st ($p<0.001$), 7th ($p=0.011$), and 30th ($p=0.025$) days postoperatively in the PEX group than in the non-PEX group. Mean ECD was significantly lower in the PEX group than in the non-PEX group on 7th ($p=0.013$), and 30th ($p=0.037$) days postoperatively. The mean CCT significantly differed only on 1st ($p<0.001$) day postoperatively.

Conclusion: Eyes with PEX presented lower corneal ECD and decreased BCVA after uncomplicated phacoemulsification surgery. Further, there was no association between CCT and PEX existence preoperatively and in the early postoperative period.

Introduction

Pseudoexfoliation syndrome (PEX) is the widespread intraocular and systemic formation and accumulation of an anomalous flake-like fibrillar extracellular material. This age-related disorder is clinically diagnosed by slit-lamp examination, which allows the observation of pseudoexfoliative material (PEM) on the anterior segments of the globes [1]. It is now regarded as the most common identifiable reason of open-angle glaucoma all over the world and is related to development of cataract [2]. The prevalence of PEX which gets larger with increasing age differs broadly in racial and ethnic populations [3, 4]. In PEX, PEM fibrils are synthesized multifocally by numerous intraocular cell types including the preequatorial lens epithelium, nonpigmented ciliary epithelium, trabecular endothelium, corneal endothelium, vascular endothelial cells, and virtually all cell types of the iris. The resulting histopathological alterations can bring about many intraocular complications such as glaucoma, cataract, poor mydriasis, and zonular instability [5, 6]. The risk of complicated cataract surgery raises in patients with PEX due to the atrophy of the iris and pupillary ruff, with insufficient mydriasis, weak zonula and vitreous loss, and increased risk of capsule / zonular rupture [7]. Besides, the corneal endothelial involvement of PEM may potentiate complications of cataract surgery [8]. In recent years, specular and

electron microscopic studies have shed light on new clinical trials allowing both quantitative and qualitative corneal endothelial cell changes to occur in eyes with PEX. Along with lower endothelial cell density (ECD) [9], changes in the percentage of hexagonal cells (an index of pleomorphism) and the coefficient of variation of cell size (a measure of polymegathism) [10] have been shown in the eyes with PEX when compared to eyes without PEX. Furthermore, some studies have shown decreased [11] or increased [12] central corneal thickness (CCT) in eyes with PEX compared to without PEX.

This study was designed to evaluate the degree of corneal endothelial changes, ocular inflammation, and central corneal thickness between the eyes with and without PEX after uncomplicated phacoemulsification surgery.

Methods

This retrospective, cross-sectional case-control study was conducted in a tertiary eye care referral centre. The study was approved by the regional committee for medical and health research ethics (E-18-2407/2019) and conducted per the Declaration of Helsinki and legal regulations. Informed written consent was obtained from all patients before receiving the examinations. One eye each of 32 patients with PEX and 32 without PEX as control subjects that both groups underwent uncomplicated phacoemulsification surgery were studied. The diagnosis of the syndrome was based on the typical slit-lamp appearance of pseudoexfoliative material at the anterior lens capsule and/or at the pupillary margin. A complete ophthalmological examination including best-corrected visual acuity (BCVA), non-contact tonometry, and a non-contact specular microscope was performed preoperatively and on 1st, 7th and 30th days after the cataract surgery for all patients. Visual acuity results were converted to the logarithm of the minimal angle of resolution (logMAR) units from the Snellen chart. Noncontact specular microscope (EM-4000, TOMEY; Nagoya, Japan) measurements via an automated method of all patients were performed by the same technician. All measurements were performed at least 3 times using the “center” method and at least 110 cells were included in each measurement. Endothelial cell density (ECD) (cells/mm2), coefficient of variation in cell area (CV) (%), hexagonal cell ratio (HEX) (%), and central corneal thickness (CCT) (μm) were noted. Polymegethism was assessed using the CV, which is independent of cell area or density, and pleomorphism was assessed by the HEX.

The exclusion criteria of the study were as follows: the presence of active intraocular infection; previous ocular surgery or ocular trauma; the history of uveitis and glaucoma; pathology of vitreus or macula; ocular surface disease including any corneal pathology (such as cornea guttata, any type of corneal scar, keratoconus) and contact lens use. According to the Emery-Little classification, the nuclear firmness was preoperatively assigned to groups as grade I (very soft nuclear) (transparent and nonnuclear), grade II (soft nuclear) (yellow or yellow-white), grade III (medium-hard nuclear) (dark yellow), grade IV (hard nuclear) (brown or amber) and grade V (extremely hard nuclear) (dark brown or black).

A single surgeon (SKK) performed all cataract surgeries. The standardized phacoemulsification technique was used for all surgical procedures. The pupils were dilated using topical cyclopentolate hydrochloride

1% (Sikloplejin®, Abdi İbrahim, İstanbul, Turkey) and tropicamide 1% (Tropamid®, Bilim İlaç, İstanbul, Turkey) preoperatively. After topical anesthesia application (Proparakain HCl 0.5%), two side ports were opened and anterior chamber stabilization was achieved by injected viscoelastic material (Healon GV®, AMO). A 2.75 mm clear corneal incision was created between the 10 and 12 o'clock meridians. Perioperative adrenaline as an adjunct to preoperative topical mydriatics was injected intracamerally in all patients for the maintenance of mydriasis. Iris retractor hooks were rarely (one in eight patients) used only in eyes with PEX in which adequate mydriasis was not achieved intraoperatively. Following capsulorhexis with a diameter of about 5.5 mm, the nucleus was emulsified with bimanual phacoemulsification (WhiteStar® Signature, Abbott Medical Optics [AMO], Santa Ana, CA, USA) using the divide-and-conquer or phaco-chop nuclear fracturing technique. Irrigation/aspiration of cortical material was semiautomatic and bimanual. In pursuit of cortex cleaning, foldable hydrophobic acrylic intraocular lens (Acrysof SA60AT®, Alcon) was implanted into the capsular bag. The viscoelastic material was then removed and the anterior chamber reformed with balanced salt solution (BSS®). 0.5%/0.1 mL cefuroxime (1 mg/0.1 ml) was injected into the anterior chamber following the corneal wound and side port hydration with BSS. In the postoperative period, patients were treated with topical moxifloxacin hydrochloride (Vigamox® 0.5% ophthalmic solution, Alcon) four times a day for one week and topical prednisolone acetate (Predforte® 1% ophthalmic solution, Allergan) four times a day for one month. At the end of the surgery, ultrasound time (UST) (seconds), average ultrasound power (AVG) (%), and effective phaco time (EPT) (seconds) were recorded. EPT was calculated by multiplying the total phaco time by the percentage power used and represents how long the phaco time would have been if 100% power, continuous mode had been utilized [13].

Anterior chamber reaction (ACR) intensity was graded according to the Standardization of Uveitis Nomenclature (SUN) criteria postoperatively. The SUN criteria normalized scoring for these measures: Cells are counted in a field size of 1 × 1 mm slit-beam and scored based on the number of cells observed (0 [<1 cell], 0.5+ [1–5 cells], 1+ [6–15 cells], 2+ [16–25 cells], 3+ [26–50 cells], and 4+ [>50 cells]). The grading for flare is less quantitative, based on 0 (none), 1+ (faint), 2+ (moderate, iris, and lens details clear), 3+ (marked, iris, and lens details hazy), and 4+ (intense, fibrin, or plastic aqueous) [14]. Corneal edema grading according to the Oxford Cataract Treatment and Evaluation Team (OCTET) was noted. Corneal edema defined as an increase in central corneal thickness with or without Descemet folds was graded as transient corneal edema(+) (grade I); transient corneal edema with Descemet membrane folds of <10 (++) (grade II); and transient corneal edema with Descemet membrane folds of >10 (+++) (grade III).

Statistical Analysis

Statistical analyses were performed with SPSS program version 15.0 (SPSS Inc., Chicago, Illinois, USA). Results were expressed as the mean ± standard deviation. Kolmogorov-Smirnov (K-S) test was used to determine whether the data showed normal distribution or not. It was determined that there was no normal distribution because the p values of the distributions whose normality was tested by using the K-S test were less than .05. Accordingly, non-parametric tests were used in the analysis of the data.

Differences between the PEX group and the non-PEX group in ECD, CV, HEX, CCT, ACR intensity, corneal edema, BCVA, operative factors, and other continuous variables were compared using the Mann-Whitney U test (intergroup differences). Wilcoxon signed-rank test for paired samples was used to test the significance of the difference between the scores of two associated measurement sets (preop-30 day postop BCVA). Discrete variables between the 2 groups were compared using the chi-square test. Differences with a P value less than. 05 were considered statistically significant.

Results

Data for 32 eyes of 32 patients in the PEX group and 32 eyes of 32 patients in the non-PEX group were analyzed. The mean age was 72.68±5.61 years in the PEX group and 69.84±7.98 years in the control group (p=0.093). There were 14 women and 18 men in the PEX group and 13 women and 19 men in the non-PEX group (p=0.800). There was no statistically significant difference in age and sex between the groups **(Table 1)**. Intraocular pressure readings were between normal range preoperatively and postoperatively in both the PEX and non-PEX groups. Mean cataract firmness was 2.96±0.54 (grade) in the PEX group and 2.65±0.86 (grade) in the non-PEX group (p=0.087). Differences between two groups in mean nuclear firmness, BCVA, ECD, CV (polymegathism), HEX (pleomorphism), CCT preoperatively; UST, AVG (except EPT) intraoperatively; and corneal edema (CE), anterior chamber reaction (ACR) intensity **(Table 2)**, CV, HEX postoperatively were not statistically significant.

Mean EPT was significantly lower in the PEX group than in the non-PEX group (p<0.001) **(Table 1)**. Despite both groups had significant improvement in mean BCVA postoperatively (p<0.001), BCVA values (logMAR) were significantly higher (worse) in the PEX group than in the non-PEX group on both 1st (p<0.001), 7th (p=0.011), and 30th (p=0.025) days postoperatively. Although there was no statistically significant difference between groups in mean ECD values preoperatively and on 1st day postoperatively; mean ECD was significantly lower in the PEX group than in the non-PEX group on 7th (p=0.013), and 30th (p=0.037) days postoperatively. None of the eyes with or without PEM had clinical signs of corneal endothelial decompensation postoperatively. The mean CCT significantly differed only on 1st (p<0.001) day postoperatively between the 2 groups throughout the follow-up period **(Table 3)**.

Discussion

PEX is a systemic disorder and a frequent clinical feature seen in patients with cataracts because the prevalence increases with age [15]. It is also presumed that patients with PEX are more pronounced to intraoperative complications [16] and endothelial decompensation [9, 17] after intraocular procedures. It is crucial to prevent corneal endothelial cell damage during phacoemulsification surgery. The use of ultrasonic energy during nuclear emulsification is nearly always associated with endothelial cell loss [18]. Despite Wirbelauer and colleagues [19] not finding any significant group-difference in phaco time and power; Kaljurand and colleagues [20] found phaco time significantly higher in PEX group than in non-PEX. However in our study, although differences between two groups in mean nuclear firmness, UST, AVG were not significant; mean EPT was significantly lower in the PEX group than in the non-PEX group (p<0.001).

Significantly lower EPT values in the PEX group might be explained with the surgeon's conservative approach initially and diligence to lower EPT in patients with PEX due to the reality of its preoperatively well-known clinical risks. Together with, to effectively introduce ultrasound (US) energy into the eye while eliminating or limiting its negative influence on tissue other than the lens [21, 22] at the time that surgical conditions are difficult or the cataract is severe as well as in eyes that have disorders other than cataract [23] is particularly important. Therefore as much as possible reduced phacoemulsification energy might have been administered by the surgeon.

This study, in common with many former similar studies, assessed endothelial parameters of the central cornea and did not take into consideration regional differences of endothelial cell density, which might be significant [24-26]. The corneal endothelium plays an important role in maintaining normal corneal hydration, thickness, and transparency. This cellular monolayer is highly vulnerable because when some corneal endothelial cells die, the remaining cells cannot divide fast enough to replace the dead cells. In lieu, they become larger and outstretch to cover dead cells to sustain the intact monolayer mosaic [27]. The integrity of the corneal endothelium is substantial for successful visual results after cataract surgery as well as cataract surgery itself is among the factors that can cause endothelial cell damage [28]. It was also reported that ultrastructural evidence suggested focal in situ production of PEM by corneal endothelial cells is associated with focal degeneration, melanin pigment deposition and abnormal extracellular matrix production in the endothelial cell layer resulting in dysfunctioning [9, 29]. Even though the structural deformity of endothelial cells and difficult surgical techniques necessary for eyes with PEX, there were some previous studies in the literature showing that there is no significant difference in endothelial cell loss after cataract surgery between eyes with PEX and those without PEX [30, 20, 19]. However in the current study, despite the similarities in preoperative corneal morphology, nuclear firmness, and intraoperative parameters; mean ECD values were significantly lower in the PEX group than in the non-PEX group on post-operative 7th and 30th days. Hayashi and colleagues observed similar outcomes in the mean ECD after cataract surgery that supports ours [17]. This finding shows that corneal endothelial cells are more susceptible and prone to be damaged in the eyes with PEX than in the eyes without PEX after uncomplicated phacoemulsification surgery in the early postoperative period. We did not find any significant difference preoperatively and postoperatively in the measurements of pleomorphism and polymegathism between PEX and non-PEX group. This finding was in agreement with that of previous studies [11, 30, 31].

Although there were no cystoid macular edema on postoperative clinical examination or significant group-difference in corneal edema and ACR intensity; BCVA was significantly worse on the 1st, 7th and 30th days postoperatively in PEX group than the non-PEX group. This loss in BCVA at 1 month may be attributed to weakening of the ciliary zonules in eyes with PEX which may be a reason in postoperative unexpected worse refractive outcomes following intraocular IOL implantation [32]. Presumed decreased blood-aqueous barrier seen with PEX or possible iris contacts in the PEX group which could have resulted in postoperative inflammation may be other reasons. Fibrillin deposition around the microvasculature in eyes with PEX could have increased the leakage of proteins into the aqueous humor and thus compromised the blood-aqueous barrier [33]. Besides, this result also implies that the vulnerability of the

corneal endothelial cells in eyes with PEX can affect visual acuity in the early postoperative period. We are unable to comment on longer-term visual outcomes in this study, but it is possible that BCVA may improve in eyes with PEX after the first month.

On the first postoperative day, the CCT was significantly increased in both groups indicating edema. CCT had returned to the preoperative state one month after the operation. Our data revealed that CCT returns the preoperative values soon after irrespective of the degree of the corneal ECD. No association existed between central corneal thickness and corneal endothelial cell numerical density. This result confirmed the findings of previous studies [34, 28, 20].

There were some limitations to this study. First, the surgeon responsible for all study operations was aware of PEX presence or absence preoperatively. However, not knowing the presence of this condition could increase the risk of surgical complications. In case any complications occurred, the surgeon would have the appropriate tools during surgery for excellent outcomes. Along with these, the postoperative examiner wasn't made blinded to which study group each subject belonged to. Because after surgery, frequent and thorough follow-up visits were vital for early detection and treatment of complications such as an increase of IOP, formation of synechiae, or development of fibrin. Secondly, the study groups had small sample sizes. However, the sample sizes of our report are comparable with those of similar studies in the literature. Another limitation was the evaluation of ACR intensity carried out via slit-lamp biomicroscope instead of a flare meter.

In conclusion; despite the similarities in preoperative and intraoperative parameters, corneal endothelial cell density and best-corrected visual acuity after uncomplicated phacoemulsification surgery in eyes with PEX were significantly lower than that in eyes without PEX in the early postoperative period which indicates the susceptibility of corneal endothelial cells to phacoemulsification surgery. There was no association between central corneal thickness and PEX existence preoperatively and in the early postoperative period. Due to reduced endothelial cell counts and a decreased functional reserve; caution, experienced surgeon, and careful techniques are required during cataract surgery in PEX eyes. Additional studies are needed to evaluate corneal endothelial cell density after surgery in eyes with PEX.

Declarations

Funding:

The authors did not receive support from any organization for the submitted work. The authors have no relevant financial or non-financial interests to disclose.

Conflicts of interest/Competing interests:

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Eren Ekici, Ali Keleş, and Süleyman Korhan Kahraman. The first draft of the manuscript was written by Eren Ekici and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval:

All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol and study documents were approved by the local ethics committee (E-18-2407/2019).

Consent to participate:

Informed consent was obtained from all individual participants included in the study.

Consent to publish:

The participant has consented to having their data published in a journal article.

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Tables

Table 1. Patient characteristics and intraoperative factors by group.

Parameter	PEX Group (n=32)	Non-PEX Group (n=32)	*P* Value
Mean age (y)	72.68±5.61	69.84±7.98	0.093
Male/female sex (n)	18/14	19/13	0.800
Mean nuclear firmness	2.93±0.56	2.71±0.77	0.139
Mean EPT (s)	12.67±10.27	35.78±26.86	0.000*
Mean UST (s)	96.59±44.24	108.65±62.16	0.537
Mean AVG (%)	6.98±3.55	7.56±5.57	0.845

Data are presented as mean ± standard deviation.

PEX: pseudoexfoliation syndrome, EPT: effective phaco time, UST: ultrasound time, AVG: average ultrasound power

*Statistically significant difference.

Table 2. Comparison of mean corneal edema and ACR intensity.

Parameter		PEX Group (n=32)	Non-PEX Group (n=32)	*P* Value
Corneal Edema	1 day postop	0.67±0.77	0.62±0.75	0.775
	7 day postop	0.07±0.27	0.09±0.39	0.859
	30 day postop	0.04±0.20	0.03±0.17	0.813
ACR Intensity	1 day postop	0.71±0.46	0.84±0.62	0.458
	7 day postop	0.03±0.19	0.15±0.36	0.146
	30 day postop	0.04±0.20	0.03±0.17	0.813

Data are presented as mean ± standard deviation.

PEX: pseudoexfoliation syndrome, ACR: anterior chamber reaction

*Statistically significant difference.

Table 3. Comparison of mean BCVA, ECD, CV, HEX, and CCT.

Parameter		PEX Group (n=32)	Non-PEX Group (n=32)	*P* Value
BCVA (logMAR)	Preop	0.83±0.37	0.95±0.65	0.989
	1 day postop	0.43±0.27	0.17±0.13	0.000*
	7 day postop	0.17±0.16	0.08±0.09	0.011*
	30 day postop	0.10±0.13	0.04±0.09	0.034*
p-value (Pre- vs. Postoperative30th Day BCVA)		<0.0001†	<0.0001†	
ECD (cells/mm^2)	Preop	2329.93±333.29	2411.75±298.63	0.398
	1 day postop	1944.40±535.29	2099.27±395.59	0.323
	7 day postop	1730.84±568.84	2072.00±481.57	0.022*
	30 day postop	1709.26±591.65	2048.00±471.93	0.029*
CV (%)	Preop	39.12±5.28	41.96±7.92	0.228
	1 day postop	46.03±8.51	49.55±10.31	0.234
	7 day postop	47.65±7.82	44.87±7.87	0.183
	30 day postop	45.34±6.83	45.18±6.95	0.851
HEX (%)	Preop	45.06±7.62	43.21±6.13	0.199
	1 day postop	39.61±8.33	37.62±8.60	0.269
	7 day postop	35.30±7.47	37.87±5.49	0.100
	30 day postop	39.13±6.44	37.84±6.75	0.533
CCT (µm)	Preop	517.90±27.50	532.06±39.81	0.113
	1 day postop	535.50±28.85	576.13±35.95	0.000*
	7 day postop	540.00±33.96	551.56±37.26	0.267
	30 day postop	521.04±23.49	533.96±32.89	0.189

Data are presented as mean ± standard deviation.

PEX: pseudoexfoliation syndrome, BCVA: best-corrected visual acuity, ECD: endothelial cell density, CV: coefficient of variation in cell area, HEX: hexagonal cell ratio, CCT: central corneal thickness.

*Statistically significant difference.

† Wilcoxon signed-rank test for paired samples.