Phacoemulsification Alone or Combined with Descemet's Stripping Without Endothelial Keratoplasty in Patients with Cataract and Early-Stage Central Fuchs Endothelial Dystrophy: A Comparative Study

Facoemulsificação Isolada ou Combinada com Stripping da Descemet Sem Queratoplastia Endotelial em Doentes com Catarata e Distrofia de Fuchs em Estadios Iniciais: Um Estudo Comparativo

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ABSTRACT

INTRODUCTION: To compare the efficacy of Descemet stripping without endothelial keratoplasty (DWEK) associated with phacoemulsification versus phacoemulsification alone in patients with moderate cataract and early-stage central Fuchs endothelial corneal dystrophy (FECD).

METHODS: Retrospective, comparative, non-randomized study, including all patients with early-stage central FECD who were proposed to cataract surgery alone (group 1) or associated with a Descemet's stripping only (group 2) at our ophthalmology department. Early-stage central FECD was defined as having central confluent guttae, confirmed with specular microscopy, a clear peripheral endothelium (with a peripheral endothelial count >1500 cells/mm^2), a central pachymetry < 600 µm and absence of corneal edema. Best-corrected visual acuity (logMAR BCVA), endothelial cell central count (ECC), central pachymetry, vision quality (Ocular Scatter Index-OSI- and Modular Transfer Function-MTF, HD Analyzer™) were evaluated 12 months after surgery. Time to achieve corneal transparency and the need for a corneal transplant were also compared.

RESULTS: Fourty-four eyes were included: 21 were submitted to phacoemulsification alone (group 1) and 23 to cataract surgery associated with DWEK (group 2). Patients from group 1 were older (76.4±5.4 *vs* 68.7±9.1 years old, p=0.001). Although all patients had central confluent guttae, fifteen eyes from group 1 (71.4%) and 7 eyes from group 2 (30.4%) had countable central endothelial cells at baseline (p=0.007).

Four eyes from group 1 (19%) and 2 eyes from group 2 (8.7%) did not achieve corneal transparency and were submitted to an endothelial keratoplasty (p=0.403). Among those who achieve transparency, eyes from group 2 took longer to get a clear cornea (3.20±1.15 *vs* 0.97±0.96 months, p<0.001).

BCVA was significantly improved in both groups 12 months after surgery, but final BCVA was higher in group 1 (logMAR 0.07±0.07 *vs* 0.17±0.13, p=0.007). ECC was similar in both groups (1388.8±337.7 and 1445.1±321.1 cells/mm^2, respectively- p=0.614). Three out of 17 eyes (17.6%) from group 1 did not have countable endothelial cells, while all patients from group 2 had countable

cells (p=0.081). There was no difference regarding pachymetry (516.1±55.7 and 528.8±36.8, respectively-p=0.419). OSI and MTF values were similar between groups (p>0.05).

CONCLUSION: Although the results were not statistically significant, the need for an endothelial transplant was higher when cataract surgery was performed alone. In the other hand, eyes submitted to phacoemulsification achieved faster corneal transparency and better BCVA, which may be explained by the better endothelial cell count at baseline in this group. In addition, no differences were found regarding final ECC, pachymetry and vision quality parameters.

In conclusion, both procedures are suitable and effective for selected patients with cataract and early-stage central FECD, delaying or avoiding corneal transplant in eyes with central FECD.

KEYWORDS: Cataract Extraction; Descemet Membrane; Descemet Stripping Endothelial Keratoplasty; Fuchs' Endothelial Dystrophy.

RESUMO

INTRODUÇÃO: O nosso objetivo foi comparar a eficácia do *stripping* da Descemet sem queratoplastia endotelial (DWEK) associado a cirurgia de catarata versus cirurgia de catarata em pacientes com distrofia de Fuchs em estadio precoce de atingimento central e catarata ligeira a moderada.

MÉTODOS: Trata-se de um estudo retrospetivo, comparativo, não randomizado, que incluiu todos os pacientes com Fuchs ligeiro e central que foram propostos para cirurgia de catarata (grupo 1) ou cirurgia de catarata associada a DWEK (grupo 2) no Serviço de Oftalmologia do CHUPorto. Distrofia de Fuchs ligeira e central foi definida como: presença de gutatas confluentes centrais, confirmado com microscopia especular; endotélio periférico saudável, com uma densidade celular >1500 células/mm^2; uma paquimetria central < 600 µm e ausência de edema de córnea.

Os *outcomes* primários, avaliados aos 12 meses após a cirurgia, incluíram: avaliação da melhor acuidade visual corrigida (logMAR MAVC); paquimetria central; qualidade de visão medida pelo HD Analyzer™(*Ocular Scatter Index-OSI- e Modular Transfer Function-MTF*). Foi também avaliado o tempo necessário até obter transparência corneana e a necessidade de queratoplastia endotelial.

RESULTADOS: Quarenta quatro olhos foram incluídos- 21 submetidos a cirurgia de catarata (grupo 1) e 23 submetidos a cirurgia de catarata+DWEK (grupo 2). A idade média no grupo 1 foi superior (76,4±5,4 *vs* 68,7±9,1 anos, p=0,001). Apesar de todos os pacientes apresentarem gutatas centrais confluentes, 15 olhos do grupo 1 (71,4%) e 7 olhos do grupo 2 (30,4%) apresentavam células centrais contabilizáveis na *baseline* (p=0,007). Quatro olhos do grupo 1 (19%) e 2 olhos do grupo 2 (8,7%) não atingiram uma transparência corneana adequada e foram submetidos a uma queratoplastia endotelial (p=0,403). Entre os olhos que atingiram transparência corneana adequada, no grupo 2 o período foi mais longo (3,20±1,15 *vs* 0,97±0,96 meses, p<0,001).

A MAVC melhorou significativamente em ambos os grupos, mas foi superior no grupo 1 (logMAR 0,07±0,07 *vs* 0,17±0,13, p=0,007). A densidade endotelial foi semelhante em ambos os grupos (1388,8±337,7 *vs* 1445,1±321,1 células/mm^2, respetivamente- p=0,614). Três em 17 olhos do grupo 1 (17,6%) não possuíam células centrais contabilizáveis, enquanto que todos os pacientes do grupo 2 apresentavam células centrais (p=0,081). Não se verificaram diferenças na paquimetria central (516,1±55,7 e 528,8±36,8 µm, respectivamente-p=0,419). Os valores de qualidade de visão (OSI e MTF) foram semelhantes (p>0,05).

CONCLUSÃO: Apesar de os resultados não terem mostrado diferenças estatísticas, a necessidade de transplante endotelial foi superior no grupo submetido apenas a cirurgia de catarata. Por outro lado, os pacientes submetidos apenas a cirurgia de catarata apresentaram uma MAVC superior, o que pode ser explicado pela melhor contagem de células endoteliais na *baseline*. Em adição, não se encontraram diferenças na paquimetria e na qualidade de visão. Concluindo, ambos os procedimentos são adequados e eficazes em pacientes bem selecionados, atrasando ou mesmo evitando a necessidade de transplante endotelial.

PALAVRAS-CHAVE: Distrofia Endotelial de Fuchs; Extração de Catarata; Lâmina Limitante Posterior; Queratoplastia Endotelial com Remoção da Lâmina Limitante Posterior.

INTRODUCTION

Fuchs endothelial corneal dystrophy (FECD) is the most common primary corneal endothelial dystrophy and the leading indication for corneal transplantation worldwide. It typically manifests in the fifth or sixth decades of life and is three times more common in women. It is estimated that 9%-11% of women and 3.5%-7% of men are affected.[1]

The presence of endothelial guttae, which is a pathognomonic sign of FECD, correlates with loss of endothelial cells and the appearance of polymegatism and pleiomorphism, with consequent development of corneal edema and decreased visual acuity and quality.[2] Loss of visual acuity and quality are not only due to the presence of corneal edema, which usually develops in more advanced stages of the disease, but also to the presence of central endothelial guttae itself.[3,4]

The progressive development of posterior lamellar keratoplasty techniques- DSAEK (Descemet stripping endothelial keratoplasty) and DMEK (Descemet membrane endothelial keratoplasty)- had significantly improve the outcomes of corneal transplantation in patients with corneal endothelial diseases.[1,5]

While endothelial keratoplasty has become the standard treatment for FECD, the strategy for first-line surgery in patients with associated cataract is still debated.

For patients with cataract and early-stage central Fuchs, cataract surgery may be performed alone. A special care must be taken considering the risks of endothelial cell loss during surgery and to minimize the risk of corneal decompensation. A preoperative management should evaluate the severity of the FECD and other factors such as cataract density, thickness of the cornea and the anterior chamber depth.[6]

In early stages of FECD, central cornea is typically affected with variable involvement of peripheral cornea, which typically occurs later in the disease. Furthermore, in at least a subgroup of patients with FECD, the disease appears to be limited to the central cornea with slow or even absent progression to the peripheral cornea.[5]

The concept of descemetorhexis or intentional removal of Descemet membrane and endothelium without endothelial keratoplasty was derived from multiple observations of spontaneous resolution of corneal edema after detached DMEK graft or after iatrogenic removal of Descemet membrane during cataract surgery.[7-12] Suggested mechanisms have been studied, including the migratory and regenerative capacity of the host endothelial corneal cells or even the transfer of cells from the donor endothelial detached graft.[13-15] A few studies shown that DWEK is an efficient and safe procedure in selected cases of FECD.[5,16,17] However, as far as we know, there is not any published study comparing the efficacy of DWEK associated with phacoemulsification versus phacoemulsification alone in patients with moderate cataract and early-stage central FECD.

Thus, the purpose of this study was to report our results of DWEK associated with phacoemulsification versus phacoemulsification alone in patients with moderate cataract and FECD, comparing the efficacy of both procedures.

METHODS

Retrospective, comparative, non-randomized study, including all patients with early-stage central FECD who were proposed to cataract surgery alone (group 1) or associated with a Descemet's stripping only (group 2) at our ophthalmology department at Centro Hospitalar Universitário do Porto, Oporto, Portugal

This study was conducted in accordance to the Declaration of Helsinki (as revised in 2013). All patients provided a verbal and written consent to participate in the study. This study complies with the requirements of the institute's committee on human research ("Departamento de Ensino, Formação e Investigação") of Centro Hospitalar Universitário do Porto (CHUPorto).

SURGICAL TECHNIQUE

All patients underwent standard phacoemulsification cataract surgery with insertion of a posterior chamber intraocular lens. In the combined procedure with DWEK, cataract surgery was followed by a central circular 4 mm descemetorhexis, performed under viscoelastic using a reverse Sinskey hook followed by a descemetorhexis forceps. All the surgeries were performed by three experienced surgeons (LO, MG and MMN). Topical rho-kinase inhibitors were not used.

Postoperative regimens included: topical ofloxacin eye drops (1.5 mg/0.5 mL) five times a day for two weeks, topical flurbiprofen eye drops (0.3 mg/mL) five times a day for 4 weeks, topical dexamethasone eye drops (1 mg/mL) five times a day for at least 4 weeks and topical sodium chloride eye drops (5%) five times a day for at least two weeks, in both groups. Topical dexamethasone and sodium chloride eye drops were tapered after the initial treatment cycle, depending on clinical evolution of corneal edema.

INCLUSION AND EXCLUSION CRITERIA

All eyes had central confluent guttae at slit-lamp examination that was confirmed by specular microscopy in addition to a visually significant moderate cataract. All eyes had clinically healthy peripheral endothelium, with a peripheral endothelial count greater than 1500 cells/mm^2 and central pachymetry lower than 600 μm. Patients with corneal edema, Descemet's membrane folds, leukomas, significant peripheral guttae, peripheral endothelial count <1500 cells/mm^2 or other corneal comorbidities were excluded.

Surgical options, such as cataract surgery alone, combined with DWEK or with posterior endothelial keratoplasty were discussed with the patients before obtaining the written consent to the surgery. All patients understood that endothelial keratoplasty might be necessary in the future. The surgical technique was individualized and decided in accordance to patient's clinical data and preference. The presence of blurred vision upon waking was one of the main criteria, along with patient's age and need for a faster recovery.

MAIN OUTCOMES

Baseline characteristics were collected, including demographic data (age, gender), best corrected visual acuity (BCVA) in logMAR scale, central endothelial cell count (ECC) by Specular Microscope (EM-3000™ Tomey, Germany) and central corneal thickness (CCT).

Best-corrected visual acuity (logMAR BCVA), refraction (spherical equivalent and cylinder values), endothelial cell central count (ECC), central pachymetry and vision quality parameters (Ocular Scatter Index-OSI- and Modular Transfer Function-MTF, measured by the HD Analyzer™) were evaluated 12 months after surgery. The need for a corneal transplant and time to achieve corneal transparency were also compared.

Patients who did not achieve corneal transparency in the first 4 months were offered an endothelial keratoplasty and were excluded from the final endpoint analysis descripted above.

Statistical analysis was performed using SPSS®, version 27 (IBM Statistical Package for Social Sciences, USA). A normality test was performed to all continuous variables (Shapiro-Wilk test). A significance value of 0.05 was accepted as statistically significant.

RESULTS

BASELINE

Fourty-four eyes from 29 subjects were included, 21 subjects were female (77.3%) and 8 were male (22.7%). Twenty-one eyes (47.7%) were submitted to cataract surgery alone (group 1) and 23 (52.3%) to cataract surgery associated with DWEK (group 2).

Patients submitted to cataract surgery alone were older (76.4±5.4 *vs* 68.7±9.1 years old, p=0.001). Although all patients had central confluent guttae, some still had countable endothelial central cells, being more frequent in group 1 (15 eyes, 71.4%) than in group 2 (7 eyes, 30.4%), p=0.007. From those eyes, ECC count was higher in group 1 (1503.2±393.4 *vs* 1102.9±274.4, p=0.025). Central pachymetry was similar in both groups (527.1±41.8 and 530.2±39.7 µm, respectively, p=0.808). Although not statistically significant, baseline LogMAR BCVA tended to be superior in group 1 (0.35±0.15 *vs* 0.49±0.24, p=0.077). Baseline data is represented in Table 1.

Table 1. Baseline data.

Number of eyes (n)	n= 44 eyes; 29 subjects Group 1: 21 eyes | Group 2: 23 eyes
Gender	21 female (77.3%); 8 male (22.7%)
Age	Group 1: 76.4±5.4 years-old Group 2: 68.7±9.1 years-old p=0.001
BCVA (logMAR)	Group 1: 0.35±0.15 Group 2: 0.49±0.24. p=0.077
Central corneal thickness (CCT)	Group 1: 527.1±41.8 Group 2: 530.2±39.7 µm p=0.808
Countable endothelial cells	Group 1: 15 eyes (71.4%) Group 2: 7 eyes (30.4%). p=0.007
Endothelium cell count (ECC)	Group 1: 1503.2±393.4 Group 2: 1102.9±272.4 cells/mm^2 p=0.025

ENDPOINTS

Four eyes from group 1 (19%) and 2 eyes from group 2 (8.7%) did not achieve corneal transparency and were submitted to an endothelial keratoplasty (p=0.403). From those who achieved transparency, eyes from group 2 took longer to get a clear cornea (3.20±1.15 *vs* 0.97±0.96 months, p<0.001).

BCVA was significantly improved in both groups 12 months after surgery, but final BCVA was better in group 1 (logMAR 0.07±0.07 *vs* 0.17±0.13, p=0.007). These results are presented in Fig. 1. Spherical equivalent was similar in both groups (-0.53±0.69 and -0.58±0.63 diopters, respectively, p=0.887), as well as astigmatism (1.06±1.05 and 0.83±0.51 diopters, respectively, p=0.386). There were no differences regarding pachymetry (516.1±55.7 and 528.8±36.8, respectively-p=0.419).

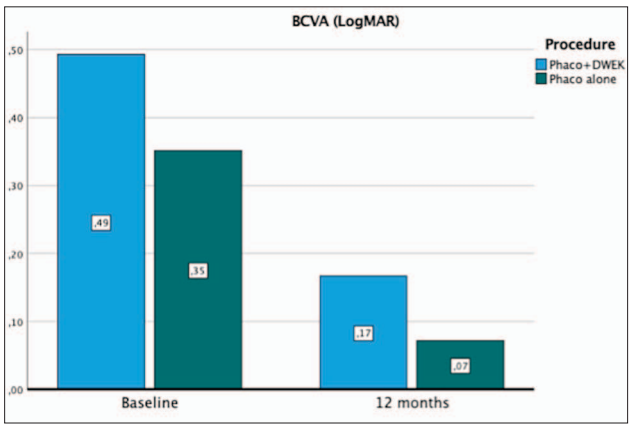

Figure 1. LogMAR BCVA evolution.

Baseline p=0.077; 12 meses: P=0.007.

ECC was similar in both groups (1388.8±337.7 and 1445.1±321.1 cells/mm^2, respectively- p=0.614). Three out of 17 eyes (17.6%) from group 1 did not have countable endothelial cells, while all patients from group 2 had countable cells (p=0.081). Fig. 2 shows a graph that represents endothelial cell count evolution. The existence of corneal endothelial central cells at baseline did not influence the need for a corneal transplant (Fisher exact test, p=0.664).

Ocular Scatter Index (OSI) showed values of 2.68±1.99 in group 1 and 2.67±1.65 in group 2 (p=0.985). In the same way, modular transfer function (MTF) was similar between groups (22.86±10.02 *vs* 23.72±11.70, p=0.825). Endothelial cell central count did not correlate with OSI (Pearson's cor-

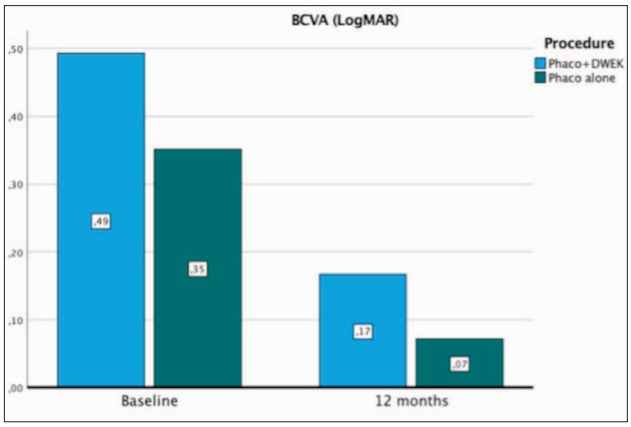

Figure 2. Endothelial cell count evolution (baseline versus 12 months).

relation, R=0.062, *p*=0.736) nor with MTF (Pearson's correlation, R=-0.068, *p*=0.713).

Data concerning endpoint's evaluation is presented in Table 2.

Table 2. Endpoints.

Need for a posterior transplant	Group 1: 4 eyes (19%) Group 2: 2 eyes (8.7%). *p*=0.403
Time to clear cornea after DWEK	Group 1: 0.97±0.96 Group 2: 3.20±1.15 months. *p*<0.001
BCVA (logMAR)	Group 1: 0.07±0.07 Group 2: 0.17±0.13. *p*=0.007
Spherical equivalent	Group 1: -0.53±0.68 Group 2: -0.58±0.63 diopters. *p*=0.887
Cylinder	Group 1: 1.06±1.05 Group 2: 0.83±0.51 diopters *p*=0.386
Central corneal thickness (CCT)	Group 1: 516.1±55.7 Group 2: 528.8±36.8 µm. *p*=0.419
Countable endothelial cells	Group 1: 14 eyes (82.4%) Group 2: 21 eyes (100%) *p*=0.081
Endothelium cell count (ECC)	Group 1: 1388.8±337.7 Group 2: 1445.1±321.1 cells/mm^2 *p*=0.614
Ocular Scatter Index (OSI)	Group 1: 2.68±1.99 Group 2: 2.67±1.65 *p*=0.985
Modular Transfer Function (MTF)	Group 1: 22.86±10.02 Group 2: 23.72±11.70 *p*=0.825

DISCUSSION

Although the endothelial keratoplasty has been the mainstay of treatment of FECD, worldwide lack of available donor corneas limits the access to this treatment. Thus, the search for newer effective and tissue saving treatments is extremely important.

In selected cases, DWEK associated with phacoemulsification or phacoemulsification alone are possible approaches. The purpose of this study was to compare the efficacy of these 2 procedures.

Despite both procedures showed excellent outcomes avoiding corneal transplant in the majority of patients (38 eyes, 86.4%), there were some differences that should be emphasized.

First of all, the samples were not exactly homogeneous, since the presence of endothelial countable central cells and central cell density itself was significantly higher in the group submitted to cataract surgery alone. Also, the BCVA tended to be superior in this group, probably as a consequence of a better endothelium and a less advanced status of FECD. The fact that this study was not randomized justifies these differences at baseline, once the decision of surgical technique was made case by case, in accordance with patients' clinical data. Hence, eyes with better endothelium tended to be more proposed to phacoemulsification alone and eyes with worse endothelium to phacoemulsification combined with DWEK.

The successful cases of cataract surgery alone achieved faster visual recovery and better visual acuity. All patients submitted to DWEK experienced corneal edema in the immediate post op (Fig. 3).

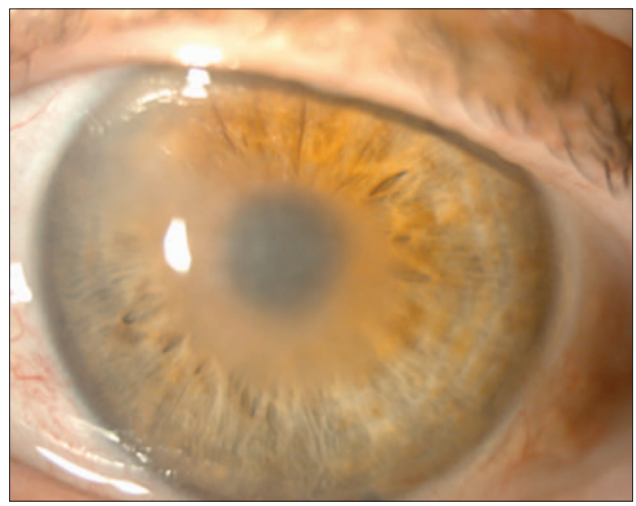

Figure 3. Central corneal edema at the 1st day after DWEK.

In the other hand, although non statistically significant results were found, endothelial transplant rate was higher in eyes submitted to cataract surgery alone (4 eyes- 19% *vs* 2 eyes-8.7%), even with a better endothelium at baseline. In addition, the existence of corneal endothelial central cells at baseline did not influence corneal decompensation and the need for a corneal transplant. Twelve months after surgery, endothelial cell density was similar between groups, but less eyes had countable cells after cataract surgery alone. These results may be explained by the migration and re-

generative capacity of the host endothelial cells in regenerating the central endothelium that only happens in DWEK, after the diseased endothelium is removed.

HD AnalyzerTM measures vision quality using a double-pass technology optical quality system. Both groups presented a similar objective scatter index (OSI) and modular transfer function frequency, which means that descemetorhexis did not create significant haze to disturb vision quality. It is important to remember that OSI and MTF measurements are performed under artificial conditions, with a pupil-based diameter of 4 mm, which may not relate to real-life vision complaints. Hence, more parameters should be evaluated in order to better characterize vision quality, including contrast sensivity and glare. Fig. 4 shows a case of DWEK with 56 months of follow-up, with sustained corneal clearance; the central corneal stripping is demonstrated.

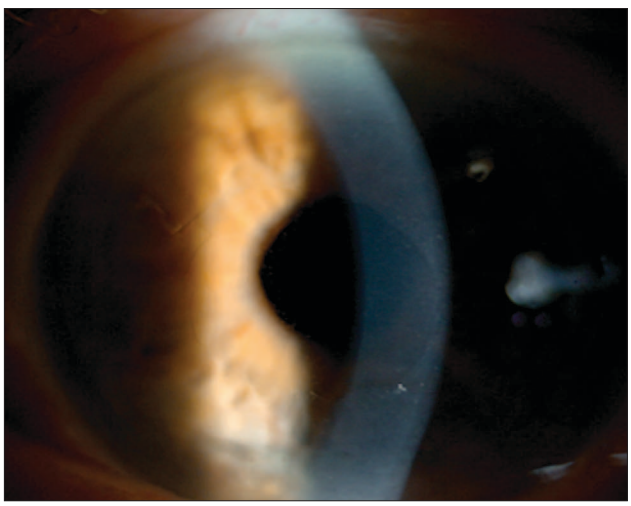

Figure 4. Sustained corneal clearance 56 months after DWEK. Image demonstrates corneal central stripping.

Based on the results of the present study and on published literature, initially the attending physician must distinguish how the vision loss is due to the cataract itself versus to FECD, before determining the best surgical approach, either cataract surgery alone or cataract surgery combined with a lamellar keratoplasty or with a DWEK.[18] A meticulous preoperative assessment is required, including endothelial cell size, density and morphology, corneal thickness, cataract density and other factors such as anterior chamber depth, which was not evaluated in the present paper.[6]

In fact, a study conducted by Malandain *et al*,[19] showed that the absence of morning blur and CCT below 630 µm are preoperative factors that influence visual outcomes after cataract surgery alone in FECD.[19] In our study all patients had central pachymetry lower than 600 µm but some patients complained of morning blur, and this factor was not analyzed or used as an exclusion criteria.

Some considerations must be caried out regarding endothelial cell loss during surgery, such as type of viscoelastic and phacoemulsification technique, in order to minimize the effects on endothelium. Although it was not the subject of the presented study, femtosecond laser assisted cataract surgery (FLACS) may be beneficial in FECD, since it uses less energy and requires less phacoemulsification time, theoretically resulting in less corneal damage compared to conventional surgery.[20] However, the results are not consistent.[20-22]

A retrospective study with long-term follow-up showed that changes in endothelial density did not significantly decrease over at least 4 years in middle-aged FECD patients and enhanced that cataract surgery would be a preferable option in FECD compared to keratoplasty combined with cataract surgery.[23] Thus, according to evidence and our data, cataract surgery alone is a viable option for selected cases of FECD.

As previously referred, the ability of self-repair from corneal endothelium in patients with FECD is the basis of DWEK. The repopulation of the central cornea after descemetorhexis involves the migration from the periphery, proliferation of the remaining endothelium stem cells or a combination of both.[24,25] Hence, based on these apparent migratory and regenerative capacities of the unaffected endothelial cells, surgical removal of the central guttae with consequent repopulation of the central cornea could, theoretically, be a viable option for some of the patients with FECD.

A few studies were published in this field, with inconsistent results. This variability of results after DWEK has been attributed to several potential factors that can be due to the surgical technique itself or patient's selection criteria.[24]

Patient's age could be a prognostic factor for disease severity and response to treatment, with better outcomes reported in younger patients after DWEK.[24,26,27] In fact, proliferative endothelial capacity in vitro correlates negatively with age.[27,28] However, in most of the published studies, this association is not always present and is difficult to prove. Indeed, in our study, age did not correlate with disease severity nor with decompensation after surgery. Patients that were submitted to cataract surgery alone were older but had higher rate of eyes with countable endothelial cells and a better endothelial cell count itself.

Other genetic and environmental factors, such as tobacco and diabetes, polymorphisms in the TCF4 gene on chromosome 18 are already recognized as factors that affect the severity and response to treatment in FECD.[28,29]

Beyond the cataract status itself, it was identified a trend toward better outcomes with smaller central descemetorhexis and lower preoperative pachymetry.[16,17] In our study, a central descemetorhexis of 4 mm was performed in all patients and only patients with preoperative pachymetry inferior to 600 µm were included.

Another concern about DWEK is the haze on the edges of descemetorhexis that may lead to the appearance of opacities at the margins of descemetorhexis.[16,17] These may be associated with irregular astigmatism and decreased vision quality, which was not noticed in our study, since values of astigmatism and quality of vision parameters measured by HD Analyzer™ (OSI and MTF) were similar in both groups.

Although patients with advanced cataracts were not studied in the present paper, they might be at higher risk of endothelial cell loss during cataract surgery. For this reason, instead of a cataract surgery alone or combined with DWEK, an endothelial keratoplasty combined with cataract surgery was offered to those patients.

In conclusion, both procedures are suitable and effective for selected patients with moderate cataract and early-stage central FECD, delaying or avoiding corneal transplant. With this study we aimed to highlight that DWEK may be an option for patients who have indication for endothelial keratoplasty and does not yet have corneal edema. Prospective, randomized studies with larger samples are needed to strength these results and to better select patients for each procedure.

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CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

RV, CC and JC: Responsible for gathering the data, presenting the results, and creating the manuscript. RV was the main author and assumed the main responsibility for these assigned tasks.

LMN, MG and LO: Supervised this project and contributed with their expertise to its conclusion; and all authors read and approved the final manuscript.

All the authors had full access to all the data and take full responsibility for the integrity of the data and the accuracy of the data analysis; all were responsible for conceiving this research.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Miguel Mesquita Neves é consultor Alcon Portugal – Produtos e Equipamentos,Lda. Os restantes autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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ETHICAL DISCLOSURES

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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