Real-World Outcomes of Descemet Membrane Endothelial Keratoplasty: 5 Years Single-Center Experience

Resultados de Vida Real da Queratoplastia de Membrana Endotelial Descemet: 5 Anos de Experiência em um Único Centro

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ABSTRACT

INTRODUCTION: Our objective was to evaluate the 5-year clinical outcomes of a case series after Descemet membrane endothelial keratoplasty (DMEK) in a tertiary hospital center.

METHODS: Retrospective, single-center, observational cohort revision of the DMEK surgeries performed between August 2016 and August 2022.

Main outcome parameters (survival graft, best-corrected visual acuity (BCVA) in logMAR scale, and central endothelial cell density (ECD) were recorded. Intra, postoperative complications, and the need for subsequent keratoplasties were considered secondary outcomes.

RESULTS: A total of 69 DMEKs, in 56 patients, were performed in our center between August 2016 and August 2022. The mean age of the patients at surgery was 65.91 ± 11.82 years. A percentage of 62.5% were female while 37.5% male. The leading indication for surgery was Fuchs dystrophy, followed by pseudophakic bullous keratopathy, corneal decompensation from previous keratoplasties, and bullous keratopathy associated with phakic lens. Mean BCVA improved from 0.75 ± 0.26 (LogMAR) to 0.24 ± 0.23 at 1 year follow-up (N=57, p<0.001)). At 5 years-follow-up (N= 9), mean BCVA was 0.44 ± 0.24 (range 0.1 – 0.7) and mean ECD was 854.75 ± 218.97 cells/mm^2. After the first year, an annual rate of ECD loss was calculated to be 12.9% (range, 8.7% to 16.1%).

Six eyes needed rebubbling. Allograft rejection was diagnosed in only one eye. Overall graft survival was 95.5 ± 2.5% at six months, 94.0 ± 2.9% at 1 year, 88.3 ± 4.2% at 2 years and 75.7 ± 7.9% at 5 years. Ten eyes underwent retransplantation.

CONCLUSION: Most eyes that underwent DMEK showed stable clinical outcomes with an early significant improvement in visual acuity. The overall results suggest that DMEK is a safe and effective treatment option for corneal endothelial diseases.

KEYWORDS: Corneal Transplantation; Descemet Stripping Endothelial Keratoplasty; Fuchs' Endothelial Dystrophy.

RESUMO

INTRODUÇÃO: OO nosso objetivo foi valiar os resultados clínicos de uma série de casos de *Descemet membrane endothelial keratoplasty* (DMEK) realizados num centro hospitalar terciário durante 5 anos.

MÉTODOS: Estudo de coorte retrospetivo de um único centro hospitalar. Foi efetuada a revisão dos registos clínicos de cirurgias DMEK realizadas entre Agosto de 2016 e Agosto de 2022. Os *outcomes* primários foram a sobrevida do enxerto, a melhor acuidade visual corrigida (MAVC) na escala logMAR, e a densidade central de células endoteliais (ECD). Como *outcomes* secundários foram consideradas as complicações intra e pós-operatórias, bem como a necessidade de queratoplastias subsequentes.

RESULTADOS: No período compreendido entre Agosto de 2016 e Agosto de 2022 foram realizados no nosso centro um total de 69 DMEKs, em 56 doentes. A idade média dos doentes à data da cirurgia foi de 65,9 ± 11,8 anos. Dos pacientes, 62,5% eram do sexo feminino e 37,5% do sexo masculino. A principal indicação para a realização da cirurgia foi a distrofia de Fuchs, seguida pela queratopatia bolhosa pseudofáquica, descompensação de queratoplastias prévias e queratopatia bolhosa associada a lentes fáquicas. A MAVC média melhorou de 0,75 ± 0,26 (LogMar) para 0,24 ± 0,23 após um ano de seguimento (N=57, p<0,001). Aos 5 anos de seguimento, a MAVC (N=9) é de 0,44 ± 0,24 (intervalo, 0,1 – 0,7) e a ECD média é de 854,75 ± 218,97 células/mm^2.

Seis olhos necessitaram da realização de procedimento de *rebubbling*. A rejeição do enxerto ocorreu em apenas um olho. A sobrevida global do enxerto foi de 95,5 ± 2,5% aos 6 meses, 94,0 ± 2,9% após um ano de *follow-up*, 88,3 ± 4,2% aos 2 anos e 75,7 ± 7,9% aos 5 anos de *follow-up*. Dez olhos foram submetidos a uma nova queratoplastia.

CONCLUSÃO: A maioria dos olhos submetidos a cirurgia DMEK demonstraram resultados clínicos estáveis, com uma melhoria significativa precoce da MAVC. Os resultados obtidos sugerem que a DMEK é uma opção terapêutica efetiva e segura para o tratamento de doenças endoteliais da córnea.

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

INTRODUCTION

The last decades have revolutionized the surgical approach to corneal diseases.[1] Recent advances in the understanding of corneal microanatomy and microsurgery have allowed the development of lamellar keratoplasties for both stromal and endothelial pathology, with considerable success.[1-3]

In 2006, Melles *et al* introduced the Descemet membrane endothelial keratoplasty (DMEK),[4] which uses a manually prepared partial-thickness donor cornea containing only endothelium and Descemet membrane.[3]

DMEK requires higher expertise than the previously described technique Descemet stripping automated endothelial keratoplasty (DSAEK). Longer surgical learning curve, complex graft preparation and handling, higher susceptibility to endothelial surgical trauma, and longer intraoperative time justify larger technical difficulties.[3]

However, evidence suggests superior visual outcomes and a shorter rehabilitation period. Furthermore, reduced hyperopic shift, induction of visual distortions and high-order aberrations as well as lower graft rejection are also advantages of this technique.[3]

DMEK is reported to achieve excellent visual outcomes with relatively low complication rates in specialized centers.[5] The purpose of this work was to review the clinical outcomes of DMEK surgeries performed in our center during a 5-year period.

MATERIAL AND METHODS

SUBJECTS

This study was completed according to the tenets of the Declaration of Helsinki.

The medical records of DMEK cases performed at our center between 2016 and August 2022 were retrospectively reviewed.

Demographics and previous medical history were collected as well as surgery indications.

Preoperatively, all patients underwent best corrected visual acuity (BCVA) testing using the Snellen chart, slit-lamp evaluation, lens status, intraocular pressure (IOP) measurement, dilated fundoscopy, and endothelial cell counts, if possible.

DONORS

The donor corneoscleral buttons, preserved in a specific corneal chamber (CTC 001-01, Alchimia®), were provided by the internal institutional eye bank, a nonprofit organization situated within the hospital premises.

Corneas from donors over 50 years old were considered due to the easier extraction and manipulation of lenticules from older donors. Only good-grade optical quality donor tissue with an endothelial cell count ≥ 2000/mm^2 was used. The baseline donor central endothelial cell density (ECD) was measured by an eye bank specular microscope (Konan Eye Bank KeratoAnalyzer EKA-04).

GRAFT PREPARATION AND SURGERY

Lenticule preparation was directly performed by the surgeon in the operating room prior to donor insertion during the surgical procedure. Three differentiated surgeons from the Section of Cornea of our institution performed the procedures. The applied DMEK technique that was previously described by our team,[6] was based on the standard "No-Touch" technique for Descemet membrane described in 2011 by Melles *et al*.[7]

OUTCOME MEASUREMENTS

During each visit, BCVA was measured using the Snellen chart. A detailed slit-lamp examination was performed to check the graft transparency and IOP was measured. Postoperative ECD was measured with the clinical specular microscope (Topcon SP 3000P) for all patients after 6 months, and then yearly by an experienced technician. The main outcomes were graft survival, BCVA and ECD, considered at 6 months, and yearly until 5 years. Secondary outcomes were intra and postoperative complications, and the need for subsequent surgeries or keratoplasties.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS Statistics 26.0 (IBM, Armonk, NY).

Snellen BCVA was converted to logarithms of the minimum angle of resolution (LogMAR) for statistical analysis and graphical representation. Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as numbers (percentage, %). Normality data was accessed with Kolmogorov–Smirnov test. The chi-squared test or Fisher's exact test was used to compare the two categorical variables, and Student's t-test was applied to compare the means of continuous variables between two groups. The Kaplan-Meier curves were used to analyze the corneal graft survival after a successful DMEK. A p value of < 0.05 was considered statistically significant.

RESULTS

PATIENTS' DEMOGRAPHICS

Sixty-nine eyes from 56 patients were included in this study, 37.5% male and 62.5% female. The mean age of the patients at surgery was 65.91 ± 11.82 years.

The leading indication for surgery was Fuchs dystrophy in 63.8%, followed by pseudophakic bullous keratopathy in 18.8%, and decompensation from previous keratoplasties in 7.2% (Table 1). Surgery was combined with phacoemulsifi-

Table 1. Demographic characterization of the patients.

Number of eyes / Patients	69/56
Sex (n, %)	
Males	21, 37.5%
Females	35, 62.5%
Age at surgery (mean ± SD)	65.91 ±11.82 years
Eye	
Right eye (n, %)	36, 52.2%
Left eye (n, %)	33, 47.8%
Indication for DMEK (n, %)	
Fuchs dystrophy	44, 63.8%
Pseudophakic bullous keratopathy	13, 18.8%
Failed PK/DSAEK	5, 7.2%
Phakic lenses bullous keratopathy	2, 2.9%
Bullous keratopathy associated to other surgeries	2, 2.9%
Other	3, 4.3%
Combined surgery with phacoemulsification (n, %)	23, 33.3%
Mean Follow-up Time (months)	20.35 ± 21.32

SD, standard deviation; DMEK, Descemet membrane endothelial keratoplasty; PK, penetrating keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty.

cation and IOL implantation in 33.3%. The mean follow-up time of the patients was 20.35 ± 21.32 months, ranging from 1 month to 73 months. Sixty three eyes completed a follow-up of 6 months, 57 of 1 year, 45 of 2 years, 33 of 3 years, 15 of 4 years and 9 of 5 years. Four patients dropped out of the follow-up, mainly during the SARS-CoV-2 pandemic.

Table 1 summarizes the baseline characteristics of the population. The number of surgeries performed by year is present in Fig. 1.

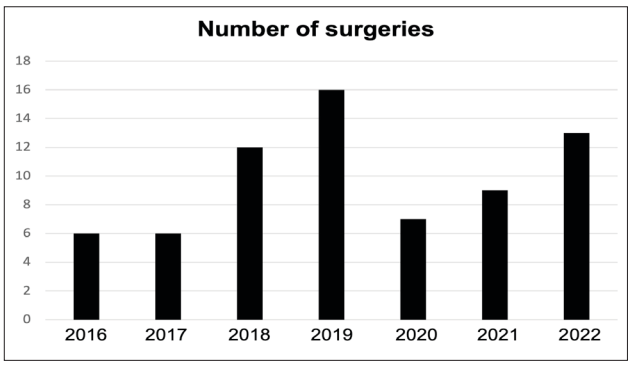


Figure 1. Number of surgeries performed by year.

In 2016, 6 DMEKs were performed in our center, as well as in 2017. In the following years we assisted to a peak in the technique performance (12 in 2018 and 16 in 2019), followed by a decrease due to SARS-CoV-2 pandemic. Only seven surgeries were performed during 2020 and 9 in 2021. In 2022 we assisted to a regrowth of the technique' implementation with 13 surgeries already performed in the first 8 months of the year.

VISUAL OUTCOMES

Mean BCVA improved from 0.75 ± 0.26 (LogMAR) to 0.38 ± 0.29 at 6 months (N= 63; p<0.001) and to 0.4 ± 0.23 at 1 year follow-up (N=57; p<0.001, Table 2).

At 2 years-follow-up (N=45), mean BCVA was 0.28 ± 0.25 (LogMAR). At 5 years-follow-up (N= 9), mean BCVA was 0.44 ± 0.24 (range, 0.1 – 0.7).

Additional analysis of visual acuity outcomes was performed after excluding 9 of 69 eyes (13.0%) with significant retinal pathology or advanced optic nerve disease.

Among the remaining 60 eyes, the median BCVA increased from 0.74 ± 0.25 (logMAR) before surgery to 0.34 ± 0.27 at 6 months postoperatively (p<0.001) and 0.23 ± 0.21 at 1 year (p<0.001). A percentage of 78.6% of the patients presented BVCA between 20/20 and 20/40 (0.0 to 0.3 logMAR) at 1 year follow-up.

After two years of follow-up, BCVA starts to decrease, with statistical differences between BCVA at 1 and 4 years and 1 and 5 years (p=0024 and p=0.038, respectively, Table 2).

ENDOTHELIAL CELL DENSITY

The mean ECD of donor grafts was 2638.84 ± 428.33 cells / mm2. Pre-operative mean ECD was not available in almost all the patients due to severe corneal edema.

After keratoplasty, the mean ECD was 1592.38 ± 483.22 at 6 months (N=63) and 1487.61 ± 461.62 at 1 year (N=57). Subsequently, the mean ECD decreased to 1303.90 ± 541.65 at 2 years (N=45), 936.50 ± 257.33 at 4 years (N=15), and 854.75 ± 218.97 at 5 years (N=9).

The major rate of endothelial cell loss occurred during the first year after DMEK (34.6%). During the following four years of follow-up, the average annual rate of endothelial cell loss was 12.9% (range, 8.7% to 16.1%). Fig. 2 illustrates endothelial cell loss during the follow-up.

Table 2. BCVA before and after DMEK.

	Pre-Operative	6 months	1 year FU	2 years FU	3 years FU	4 years FU	5 years FU
	N =69	N = 63	N = 57	N= 45	N=33	N=15	N=9
BCVA, Snellen (%)							
< 20/40	100%	42.1%	22.2%	29%	36.4%	36.4%	60%
≥ 20/40	0%	57.9% (61,5%)1	77.8% (78,6%)1	71.0% (69.9%)1	63.6% (70.0%)1	63.6 (63,6%)1	40% (40%)1
≥ 20/25	0%	28.1%	42.2%	45.2%	36.4%	36.4%	20%
≥ 20/20	0%	5.3%	20.0%	9,7%	9.1%	9.1%	0%
Mean ± SD (LogMAR)	0.75 ± 0.26	0.38 ± 0.29 *	0.24 ± 0.23 * **	0.28 ± 0.25 *	0.34 ± 0.29 *	0.30 ± 0.23 * ++	0.44 ± 0.24 * +++

1 After exclusion of eyes with retinal or optic nerve pathologies, pre-operative N=60
* p<0.001 *vs* BCVA pre-operative
** p = 0.08 *vs* BCVA at 6 months
++ p = 0.024 *vs* BCVA at 1y FU and p= 0.038 *vs* BCVA at 2y FU
+++ p 0.038 *vs* BCVA at 1y FU and p= 0.099 *vs* BVCA at 2y FU
BCVA, best corrected visual acuity
DMEK, Descemet membrane endothelial keratoplasty
FU, follow-up

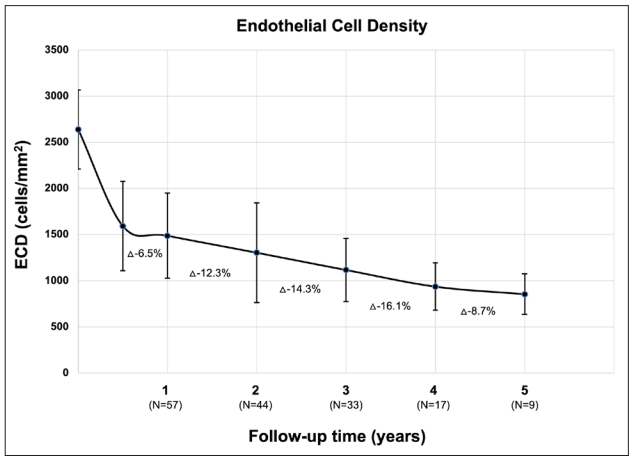


Figure 2. Endothelial cell density up to 5 years after DMEK.

Mean ECD values are displayed, vertical bars represent standard deviations, and delta represents the percentage of ECD decrease between time points. Time 0 represents donors' ECD. Number of eyes available per follow-up is given underneath the follow-up time points.

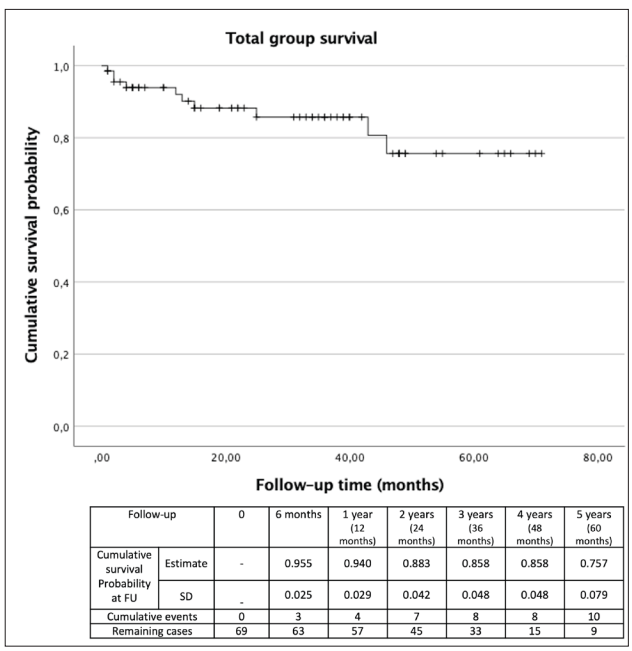
ECD, endothelial cell density; DMEK, Descemet membrane endothelial keratoplasty.

GRAFT SURVIVAL

Overall graft survival measured 99.5 ± 2.5% at 6 months, 94.0 ± 2.9% at 1 year, 88.3 ± 4.2% at 2 years and 75.7 ± 7.9% at 5 years (Fig. 3). Only one patient presented graft rejection. The patient in question presented a history of congenital glaucoma and had been submitted to several surgeries before. No other graft rejections were noted. Three patients presented primary failure grafts, two of them with persistent corneal edema following surgery and another with central lenticule detachment not reversible with rebubbling procedures.

Other six patients presented late graft failures presenting with progressive corneal edema.

A total of ten patients underwent re-transplantation, three patients performed a re-DMEK, three patients proceeded to DSAEK, and four patients performed penetrating keratoplasty (PK).



Follow-up		0	6 months	1 year (12 months)	2 years (24 months)	3 years (36 months)	4 years (48 months)	5 years (60 months)
Cumulative survival Probability at FU	Estimate	-	0.955	0.940	0.883	0.858	0.858	0.757
	SD	-	0.025	0.029	0.042	0.048	0.048	0.079
Cumulative events		0	3	4	7	8	8	10
Remaining cases		69	63	57	45	33	15	9

Figure 3. Kaplan-Meier curve of cumulative graft survival probabilities after DMEK.

Survival probabilities and number of eyes at risk per follow-up moments are presented in the table below the graph.

DMEK, Descemet membrane endothelial keratoplasty; FU, follow-up.

INTRA AND POSTOPERATIVE COMPLICATIONS

No lenticule loss or other intra-operative complications were recorded.

The most common post-operative complication was rebubbling, registered in 6 patients (8.7%), with subsequent rebubbling in only one patient. All the rebbubling procedures were performed in the first 3 months post-surgery, having been effective in all but one patient who required a re-DMEK, which was successful.

One patient developed Urrets-Zavalia syndrome. However, no intra-ocular hypertension was noted during the post operative period. Mydriasis progressively improved, with complete spontaneous resolution after 6 months of follow-up. One patient developed cystoid macular edema (CME) during post-surgery follow-up. However, he presented retinal pathology and had performed a previous vitrectomy for a retinal detachment.

DISCUSSION

In the last years, we have assisted to a shift from penetrating keratoplasties towards lamellar and endothelial keratoplasties, given its lower rejection rates and faster visual rehabilitation.[1,3,8]

Among endothelial procedures, DMEK has gained relevance since it allows anatomic restoration of the cornea avoiding interface irregularities.[1,3] Comparative studies with DSAEK have shown superior visual outcomes and a shorter rehabilitation period, allied to reduced hyperopic shift, reduced visual distortions and high-order aberrations, as well as lower graft rejection in DMEK patients.[3,8]

These observations have led to an increase in this procedure's performance around the world.[1,2] The experience of our center overlaps the previous literature with increasing surgeries performed with time, with a peak in 2019, and a subsequent decrease in 2020 and 2021 related to SARS-CoV-2 pandemic. However, after the control of the sanitary problem, the number of surgeries has also increased with a proportion of surgeries performed in the half of 2022 superior to the previous years.

In specialized centers, this technique is reported to achieve excellent visual outcomes with relatively low complication rates.[9-11] The main indication for DMEK in the literature is Fuchs dystrophy,[9-12] in line with our cohort.

Regarding visual outcomes, our center results revealed a significant improvement of BCVA early after DMEK surgery, with 77.8% of the eyes presenting a BCVA better than 20/40 after one year and 71% after two years. Previous studies reporting early outcomes of DMEK surgeries show that more than 90% of eyes improve vision at 6 months.[9,12] After two years of follow-up, BCVA in our cohort presented a slight but significant decrease. Long-term studies report that gains in vision remained stable at 5 years[11,13] and 7 years.[14] In our cohort, BVCA improvements are similar in the first years but seem to have a decrease in the subsequent follow-up. The lower number of patients included in our study at 4 and 5 years of follow-up compared with these larger reports may justify our results. Furthermore, these few cases correspond to the first DMEK surgeries performed in our institution. It is known that there is a learning curve in the DMEK technique that may potentially influence our results. Additionally, phakic status was not considered in visual outcomes. It is possible that some of the patients with longer follow-ups may have developed cataracts, decreasing their visual capacity. Notwithstanding, visual acuities in our cohort at 5 years follow-up are still significantly better than before the keratoplasty.

Besides visual outcomes, ECD is a major concern of all endothelial procedures. In endothelial keratoplasties, most endothelial cell death commonly occurs early after transplantation.[5] In our cohort, the biggest drop in ECD also occurred during the first 6 months, with a more stable loss in the following years of follow-up. An annual rate loss of 12.9%, with a range from 8.7% to 16.1% was calculated in our sample between the first and 5 years of follow-up. This represents a slightly higher value compared to the available studies.[10,11,14,15] The small sample size and the consequent high standard deviation may also contribute to the bigger loss found in our cohort.

Concerning DMEK technique, intra-operative complications comprise lenticule loss during preparation, difficulties in inserting, unfolding, or positioning the graft, intraoperative hemorrhage, high vitreous pressure, iris root hemorrhage, and Descemet membrane remnants.[12,16] None of these complications were noted in our cohort. Regarding postoperative complications, lenticule detachment is the most common complication reported in the literature.[16] Only 8.7% of our patients needed rebubbling procedures. Among previous studies, the percentage of eyes requiring rebubbling ranges from 2% to 84%, with most authors reporting values between 10% and 30%.[5,9,16-18] Other reported complications in the post-operative period comprise an increase in intraocular pressure, significant cataracts in phakic eyes, CME, microbial keratitis, and retinal detachment, besides graft failure or rejection.[16,19] One patient from our cohort developed CME during the follow-up, although this condition was likely related to other ocular pathologies rather than keratoplasty. Also, an isolated patient developed Urrets-Zavalia syndrome. However, no predisposing factors to the occurrence were identified, and the condition resolved itself spontaneously.

The risk of an immunological rejection after DMEK is lower compared to previous keratoplasty techniques and rarely leads to graft failure.[20,21] In our cohort, only one patient presented graft rejection. This was a particular patient with a severe and complex past ophthalmologic history of congenial glaucoma, several glaucoma surgeries, and intensive use of anti-hypertensive topical medications. No other patients presented rejection during the follow-up. Graft rejection prophylaxis is recommended with topical corticosteroid therapy for at least the end of the second-year post keratoplasty.[21] In our cohort, all the patients received a tapered topical corticosteroid regimen during the first six months, followed by persistent low-dose maintenance. The continuous low-dose corticotherapy, allied to a technique less prone to rejection, may justify the good results obtained.

Considering graft survival, our cohort presented an overall graft survival of 94.0± 2.9% at 1 year, 88.3 ± 4.2% at 2 years and 75.7 ± 7.9% at 5 years. Previous reports present similar results, with consistent overall graft survival above 85% in the first two years.[5,11,14,15] Factors contributing to graft failure include significant lenticule manipulation during keratoplasty, which seems to be related to surgical experience.[22] The graft failures found in our cohort correspond mainly to surgeries performed in the first years of the technique's implementation in our hospital, which may be related to a learning curve effect.[10] Furthermore, it is possible that undetected corneal pathology was present in corneal donors, compromising the graft outcomes.[22] Notwithstanding, our overall graft survival is in line with the previous reports.[5,11,23]

In conclusion, our findings provide real-world support that DMEK is an effective treatment for patients with corneal endothelial decompensation, allowing a significant and fast improvement in vision, good graft survival at 5 years, and rare complications.

A few limitations of this work need to be considered. First, this is a single-center study with a limited cohort. Second, it is a retrospective review with the consequent missing data and losses to follow-up. On the other hand, this is a real-world revision, that demonstrates good outcomes, reasonably comparable to previous bigger multicentric studies. The achievement of good outcomes in our center reinforces the safety and efficacy of DMEK surgery even in lower and not-so experienced centers.

APRESENTAÇÕES PRÉVIAS / PRESENTATIONS:

Dados preliminares foram apresentados no Congresso ESCRS 2021.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

AFM, RVM and MR prepared the material and collected data.

AFM analysed data and wrote the first draft of the manuscript.

All authors contributed to the study conception and design, commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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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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