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POSSIBLE SURGICAL APPROACHES IN CORNEAL ENDOTHELIAL FAILURE: A CRITICAL ANALYSIS OF THE CURRENT LITERATURE

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Abstract: Objective: To identify, through the current literature, the main surgical interventions for the treatment of corneal endothelial failure, their practical applications, technical aspects, indications and contraindications, as well as the challenges and limitations of each procedure. **Methodology**: Literature review carried out from April to May 2023, with searches in the Scielo and PubMed databases, where 370 articles were found and 15 were selected for analysis. **Results**: Data demonstrated a preference for Descemet's Automated Endothelial Keratoplasty with Stripping (DSAEK) or Descemet's Membrane Endothelial Keratoplasty (DMEK) compared to Deep Anterior Lamellar Keratoplasty (DALK). DSAEK showed a greater association with immunological rejection, as well as a longer period until full postoperative recovery and the need for more training to be performed properly, but showed better rehabilitation of early visual acuity. On the other hand, DMEK proved to be a more complex procedure for performing and preparing the graft, however, it presented better visual and refractive results, with less graft rejection, provided that patients were properly oriented regarding the signs of rejection and risk factors.
Final considerations: The different types of studies analyzed indicate that, in order to succeed in transplanting healthy cells, the choice of technique must be based on specific criteria related to the expertise and functional capacity of each service and location. Therefore, it is necessary to carry out comparative studies in controlled situations in order to obtain detailed data that allow a better elucidation of the ideal indications for each method.
Keywords: Corneal Endothelial Failure, Automated Endothelial Keratoplasty with Descemet Stripping (DSAEK), Descemet's Membrane Endothelial Keratoplasty (DMEK), Deep Anterior Lamellar Keratoplasty (DALK).

INTRODUCTION

The cornea, the anterior portion of the eyeball, is a clear, avascular structure that is composed of six distinct anatomical layers: the epithelium, Bowman's membrane, the stroma, Dua's layer, Descemet's membrane, and the endothelium. R. et al., 2019). This structure plays a key role in transmitting and refracting light, as well as providing protection to the eye. There are several pathological conditions, such as Fuchs endothelial dystrophy and damage to endothelial cells, which can impair corneal function. These disorders, which can result from intraocular inflammation, infections, local physical trauma, or intraocular surgical procedures, can affect corneal hydration, which must be maintained at approximately 78% humidity. When hydration is altered, endothelial failure may occur, leading to the production of corneal edema, loss of transparency and, consequently, visual impairment (ONG H.S. et al, 2021).

In the context of treating endothelial failure, there are three main strategies: redistribution of healthy corneal endothelial cells (CECs), repair of dysfunctional CECs, or use of an external source of CECs for replacement. The currently predominant approach is replacement, which involves the use of an exogenous source of healthy SCCs for corneal transplantation, which can be performed using several techniques (ONG H.S. et al, 2021).

Over the past decade, innovative lamellar keratoplasty techniques such as Deep Anterior Lamellar Keratoplasty (DALK) for anterior keratoplasty and Automated Endothelial Keratoplasty with Descemet's Stripping (DSAEK) / Descemet's Membrane Endothelial Keratoplasty (DMEK) for keratoplasty later, have been developed. These new techniques have significantly reduced endothelial graft rejection (HOS D. et al., 2019). Furthermore, corneal endothelial transplantation has become the gold standard in the treatment of corneal endothelial disorders, replacing full-thickness transplantation, known as penetrating keratoplasty. This can be performed using two main techniques: DMEK and DSAEK (STUART A.J. et al., 2018).

This study proposes to carry out a critical review of the current literature on the main surgical interventions for the treatment of corneal endothelial failure. Technical aspects, indications and contraindications will be addressed, as well as the challenges and limitations of each procedure, with the aim of contributing to its effective application in clinical practice.

METHODOLOGY

This article is a narrative review, carried out from April to May 2023 and developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. The guiding question was used for the elaboration of the research: "What are the possible surgical approaches currently available for the treatment of corneal endothelial failure, and how do these approaches compare in terms of efficacy, safety and long-term results?". searches were carried out in the Scientific Electronic Library Online (Scielo) and PubMed databases. Health Sciences Descriptors (DeCS) were used in different combinations with the Boolean operators "AND" and "OR": Descemet Membrane Endothelial Keratoplasty (DMEK), Descemet's stripping automated endothelial keratoplasty (DSAEK), Deep Anterior Lamellar Keratoplasty (DALK), Corneal Endothelial Failure and Surgical Treatment. Inclusion criteria were: articles in Portuguese, English and Spanish; published in the last 5 years, including observational studies, review studies, clinical trials and cohorts. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the studied proposal and which did not meet the other inclusion criteria. The search with the mentioned descriptors resulted in a total of 365 articles in the PubMed database and 5 articles in the SciELO database. After applying the mentioned inclusion and exclusion criteria, a total of 11 articles from the PubMed database and 4 articles from the SciELO database were selected, adding up to a total of 15 articles to compose the collection of this study.

RESULTS

DSAEK X DMEK X DALK

To ensure adequate corneal hydration, a healthy corneal endothelium is crucial. The distance between collagen lamellae plays a key role in maintaining satisfactory corneal transparency. Although the density of corneal epithelial cells suffers a continuous and variable decline throughout life, this phenomenon, when physiological, does not usually cause damage to the normal structure and function of the cornea. However, specific pathological conditions, such as Fuchs' corneal endothelial dystrophy or other mechanisms of injury to the corneal endothelium, such as surgical or direct trauma, intraocular inflammation or infection, can cause an accelerated decline of corneal endothelial cells beyond the normal. This, when it reaches a pathological level, can result in visual loss (ONG H.S. et al, 2021).

Currently, the treatment of corneal endothelial dysfunction is based on the transplantation of healthy cells, performed using various surgical techniques (ONG H.S. et al, 2021). According to Nanavaty M.A. et al. (2018), corneal endothelial transplantation has become the gold standard in the treatment of corneal endothelial dysfunctions, such as Fuchs endothelial dystrophy and pseudophakic bullous keratopathy. Performing this transplant involves removing the affected part of the cornea and replacing it with a healthy donor cornea through different techniques, such as DALK, DMEK and DSAEK, each with its advantages and disadvantages (SINGH R. et al., 2019).

The treatment of corneal endothelial failure can vary according to the severity of the disease, ranging from the use of hypertonic saline drops to surgical intervention (NANAVATY M. A. et al., 2018). The most popular techniques are automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK). However, not all transplants can be performed lamellarly, since these techniques are not available worldwide and there are still pathologies that require the replacement of all layers of the cornea (ONG H.S. et al, 2022). As exposed by Singh R. et al. (2019), Deep Anterior Lamellar Keratoplasty (DALK) is performed for deep anterior corneal opacities with good endothelial function, such as in cases of keratitis scars, keratoconus and stromal dystrophies. This technique is associated with superior visual results and graft rejection rarely occurs.

In a comparative study between DMEK and Ultrathin DSAEK (UT-DSAEK) techniques in patients with corneal endothelial dysfunction due to Fuchs dystrophy and bullous keratopathy, Dimtsas G.S. and Moschos M.M. (2023) found that the DMEK technique requires a longer learning period to be performed and tends to provide greater surgical trauma to the endothelium, in addition to a greater frequency of need for reapproach due to graft detachment, and is therefore less used. However, better visual results, less graft rejection and superiority in vision rehabilitation up to 12 months after surgery were observed when using the DMEK technique (DIMTSAS G.S.; MOSCHOS M.M., 2023),(MARQUES R.E. et al., 2019). Patients who underwent the DSAEK technique had more frequent graft rejection. This is probably due to the lower implantation of antigenic load in DMEK, as indicated by Marques R.E. et al. (2019).

In DSAEK, only the posterior lamella is replaced, which leads to faster visual recovery. The problems linked to the suture, astigmatism and risk of rejection are smaller. The most common complication in this technique is graft displacement (SINGH R. et al., 2019). DMEK, in turn, consists of a selective transplantation of the corneal endothelium and Descemet's membrane, which has low graft rejection rates, rapid visual recovery and little technical equipment required. However, it is considered a more difficult intervention and requires a more accurate technique (ONG H.S. et al., 2022).

Both DMEK and DSAEK aim to transplant a layer of healthy endothelial cells that will restore corneal clarity with improved vision. Some studies suggest that rehabilitation and final visual acuity after DMEK may be superior to DSAEK (NANAVATY M. A. et al., 2018). Furthermore, visual recovery after DMEK is faster than after DSAEK, and DMEK provides better long-term visual acuity result compared to DSAEK (ONG H.S. et al.,2022).

DSAEK

Descemet Stripping Automated Endothelial Keratoplasty (DSAEK) is a surgical approach option in which the surgeon uses an automated machine called a microkeratome to separate a thin layer from the back of the donor cornea, which will be transplanted into the recipient, applied to his posterior cornea. This thin layer measures 50 to 150 microns thick and must contain the Descemet membrane, corneal stroma, and endothelial cells. The preparation of the donor button can be done manually, as in the technique developed in 2005 of Endothelial Keratoplasty by Endothelial Stripping (DSEK), from the English "Descemet stripping endothelial keratoplasty", or also by femtosecond laser (FLEK), from the English "Femtosecond laser". assisted endothelial keratoplasty" (MOURA G. et al., 2013).

Compared to the standard Penetrating Keratoplasty, these operative techniques present an improvement in safety and rapid rehabilitation of visual acuity, contain less records of complications related to intraoperative hemorrhage and suture. The learning curve for these approaches is more complex and requires more experience from the surgeon. Hospital centers that started changing the technique from Penetrating Surgery to Endothelial Keratoplasty show higher rates of primary failure of endothelial cells (MOURA G. et al., 2013). Most tissue losses are reported within the first year of using the new approach. These show a decrease with the adjustment of experience related to the use of the microkeratome (MADI S. et al., 2019).

Some operative complications can be observed in DSAEK, such as early graft failure (less than 3 months after transplantation). According to a study carried out by Gurnani B. et al.(2023), such failure was found in 11.1% of patients after DSAEK due to endothelial insufficiency secondary to phakic intraocular lenses. In this same study, cases of post-surgical glaucoma (22.2%) were also recorded, with 50% of them requiring trabeculectomy to control intraocular pressure (HIPOLITO-FERNANDES D. et al, 2021). There are also additional records of endothelial loss even when handling the button for the anterior chamber, displacement of the donor endothelial button, immunological rejection of the graft by the recipient, retinal displacement, macular edema, epithelial growth, endophthalmitis and pupillary block (MOURA G. et al., 2013).

Sabe-se que o período de recuperação da DSAEK é mais prolongado em relação a DMEK. This factor raises doubts about the technique to be used, when prioritizing the best quality of vision in the postoperative period. DSAEK shows stable long-term visual performance, but is still inferior to DMEK when compared 12 months postoperatively (HIPÓLITO-FERNANDES D. et al, 2021). The aim of both techniques is to transplant a layer of endothelial cells that will provide hydration out of the cornea, however the stromal layers present in DSAEK can still cause optical irregularities. Some studies also show that the thickness of the endothelial layer transplanted in DSAEK directly influences its results, since thinner grafts show faster visual recovery and better long-term results (STUART A.J. et al., 2018).

With the aim of improving the results found in the DSAEK, in 2009, a "middle ground" approach was proposed between these two mentioned techniques, the Ultrathin DSAEK (UT-DSAEK). Microkeratome dissection was modified in this technique, producing thinner grafts, with an average thickness of 101 microns and also with a decrease in the stromal component, when compared to traditional DSAEK, which had an average thickness of 209 microns. UT-DSAEK shows better interface transparency and faster visual recovery than DSAEK in a year of comparison. When the results were observed for 2 years, they did not differ from DMEK in terms of visual acuity, except for a higher rate of immunological rejection presented by UT-DSAEK and slower visual recovery. Patients can benefit from UT-DSAEK by reducing surgical manipulation, lower complication rates after the procedure, vision recovery rate to 20/20 increasing over time and which can exceed 50% at 5 years postoperatively (MADI S. et al., 2019).

DMEK

Descemet's Membrane Endothelial Keratoplasty (DMEK) represents another surgical technique in the treatment of corneal endothelial failure. This technique, first described in 2006, replaces only the corneal endothelium and Descemet's membrane. SUCH a procedure differs from alternative techniques, such as DSAEK, in which a stromal layer is also transplanted along with Descemet's membrane and the corneal endothelium (KOÇLUK Y. et al., 2018). Studies indicate that DMEK provides more satisfactory visual and refractive results, with faster visual rehabilitation and lower risks of graft rejection compared to DSAEK. However, DMEK presents greater complexity in the preparation of the donor material and requires greater surgical skill compared to DSAEK. These peculiarities justify the resistance of many surgeons to adopt DMEK as the technique of choice in the treatment of corneal endothelial failure (ONG H.S. et al, 2022).

The complexity of DMEK is evident, mainly due to the tendency of Descemet's membrane to adopt a rolled-up configuration with the outer endothelial surface when separated from the stromal surface of the cornea. This fact is more pronounced when the graft comes from young donors. Therefore, the introduction and unrolling of the graft, inside the recipient's anterior chamber, constitutes a complex step in DMEK, requiring great technical mastery by the surgeon and a careful methodology to unroll the graft (ONG H.S. et al, 2022). However, in addition to the technical difficulties in preparing the donor material and the greater surgical technical requirement, DMEK has increased risks of primary graft failures, which occur within 2 to 3 months after surgery, compared to PKP, DALK and DSAEK (GURNANI B. et al., 2023; TRINDADE B. L. et al., 2022). Failures can be attributed to graft detachment, iatrogenic failure due to its inadvertent upside-down position (ONG H.S. et al, 2022), poor graft quality (endothelial cell density less than

2300 cells/mm 2), and poor manipulation. excessive during graft preparation or surgery (GURNANI B. et al., 2023).

Complications that occur after the three-month period are classified as secondary. In DMEK, these complications are usually caused by the gradual loss of corneal endothelial cells (ECL) over time, possibly related to an immune reaction. However, it is important to note that other common risk factors also affect ECL, including patient and donor age, donor source, occurrence of iatrogenic trauma, bubbling, type of gas tamponade, culture medium, graft diameter and the type of surgery - either DMEK only or triple DMEK, when DMEK is combined with cataract surgery (GURNANI B. et al., 2023).

Additionally, eyes that have had prior trabeculectomy or placement of glaucoma drainage devices tend to lose air from the anterior chamber (AC) more rapidly than normal eyes, which increases the risk of graft detachment and ECL. In addition, the tubes in AC can rub against the endothelium in normal state or when there is friction in the eyes, leading to increased ECL. Success with bubbling is also lower in these eyes, as achieving good air filling is usually more challenging (GURNANI B. et al., 2023). It must also be mentioned that anterior segment diseases such as anhydria and aphakia carry a high risk of large detachments and very low graft survival (44% at one year and 17% at two years), which can cause complications more often than not. than in cases of hyphema (GURNANI B. et al., 2023).

It is noteworthy that DMEK has an incidence rate of rejection considered low among the types of corneal transplants, ranging from 0 to 21%. The reasons for this relatively low bounce rate are still not fully understood. Therefore, it is essential to know the risk factors to plan adequate preventive strategies (GURNANI B. et al., 2023). Risk factors for rejection include corneal vascularity, anterior penetrating keratoplasty, previous glaucoma surgery, pre-existing glaucoma, and steroid responders. Furthermore, African-Americans are at a higher risk of rejection of both DMEK and DSEK (GURNANI B. et al., 2023).

It is imperative that the recognition of the rejection situation be immediate for the rapid initiation of treatment. Therefore, patients who underwent DMEK must be properly instructed to recognize the symptoms of graft rejection, such as worsening visual acuity, redness, pain and photophobia, as well as the need to immediately notify the surgeon in case of occurrence of these symptoms (GURNANI B. et al., 2023).

In cases of graft failure or rejection, redoing the DMEK implies a greater risk of secondary surgery failure and exposes the patient to a greater chance of having to undergo a penetrating keratoplasty, which has many risks. In addition, repeating DMEK in cases of failure has shown a failure rate greater than 20% in one year and up to 30% in 6 months, according to different studies (GURNANI B. et al., 2023; TRINDADE, B. L. et al. 2022).

In conclusion, it is of fundamental importance that the corneal surgeon is familiar with the strategies to avoid and predict DMEK rejection (GURNANI B. et al., 2023). In addition, considering that both intra- and postoperative complications and the time for Descemet's membrane deployment may decrease as surgeons gain experience, a great mastery of the technique is necessary for better results to be achieved with DMEK (KOÇLUK Y. et al., 2018).

Given the existing limitations for currently available endothelial keratoplasty techniques, such as DMEK, which include graft availability, preservation, and preparation, new future perspectives must be explored. Among them, we highlight the use of cultured human corneal endothelial cells and the use of stem

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cells, including induced pluripotent stem cells and mesenchymal stem cells for application in corneal endothelial failure (GURNANI B. et al., 2023).

DALK

Lamellar keratoplasty (LK) is a surgical technique used since the 19th century, mainly in the treatment of opacities in the anterior layer of the cornea, but the technique has been losing ground as others have shown more promise. The technique that had the greatest rise at the time was full-thickness penetrating keratoplasty (PKP), associated with better visual quality, in addition to being considered a relatively easier procedure to perform. However, PKP was associated with several complications, such as prolonged recovery time, astigmatism, suture dehiscence and consequently risks of infiltration and loose donor-recipient junction, in addition to graft rejection and loss of endothelial cells. Faced with these problems, KL was reintegrated into the techniques used for the treatment of corneal opacities, as it proved capable of resolving most of the complications associated with PKP (SINGH R. et al., 2019).

Within the classification of lamellar keratoplasty there are a variety of techniques that approach different layers of the cornea according to the depth of the opacity, which can be divided into anterior and posterior. Among the former are superficial anterior lamellar keratoplasty (SALK), automated therapeutic lamellar keratoplasty (ALTK) and deep anterior lamellar keratoplasty (DALK). SALK is indicated in the presence of superficial scars, such as those that occur in trauma, trachoma and keratitis. ALTK is indicated in the approach to opacities in the anterior or middle stroma. There are several indications for DALK, the main ones being: keratoconus, deep stromal scars and stromal dystrophies. (SINGH R. et al., 2019). This procedure must be performed in the presence of deep opacities in the cornea as long as the endothelial function is preserved (NANAVATY M. A. et al., 2018).

In DALK, the recipient corneal tissue is removed in layers, leaving only Descemet's Membrane (MD) and the corneal endothelium, then the donor corneal button, devoid of MD, is sutured to the host (NANAVATY M. A. et al., 2018). This technique can be subdivided into pre-descemetic, in which the high risk of perforation caused by the thin thickness of the cornea requires that part of the posterior stroma be preserved along with the endothelium, and descemetic, in which the entire stroma is removed, preserving only the membrane. by Descemet (SINGH R. et al., 2019).

Lamellar procedures must be compared in terms of visual acuity and the ability to maintain/preservation of the graft, including the risks of rejection, drop in endothelial cell counts and susceptibility to trauma. DALK has shown good results over the years due to the reduction in rejection episodes (NANAVATY M. A. et al., 2018).

This is due to the fact that it is an extraocular surgery in which the endothelium is not replaced, and the anterior chamber is not violated, so that immunological rejection becomes insignificant, as the antigenic load was reduced during the procedure. (CARLOS L. et al., 2022). In addition, it is believed that DALK allows the number of endothelial cells to be preserved for a longer period of time, allowing for better refractive results and lower complication rates (NANAVATY M. A. et al., 2018).

Surgical time in DALK is longer compared to other techniques, due to corneal stripping being performed in layers, therefore, the surgical procedure becomes more complex. Thus, the surgeon's skill has a direct influence on the results obtained from the surgery, since the irregularities created at the graft interface can reduce visual acuity after the procedure. (NANAVATY M.A. et al., 2018).

There are adverse events that can occur during the procedure that must be addressed correctly to achieve success in DALK, these complications will be covered in detail below. (NANAVATY M.A. et al., 2018).

1. Difficulty separating the Dua and MD layers – multiple attempts with air or viscoelastic or manual dissection are required (SINGH N. P. et al., 2018).
2. Double bubble formation – occurs when the air injector cannula is positioned improperly in the MD, forming a type 1 and type 2 bubble. DALK can be completed if flaps are made on the posterior lamella and removed one by one before the positioning of the donor button (NANAVATY M. A. et al., 2018).
3. Perforations – microperforations affect less than a quarter of the cornea and can be solved by simple tamponade with air or fibrin glue, whereas macroperforations affect more than a quarter of the cornea and may reach MD, in these cases it is better to convert for PKP (NANAVATY M.A. et al., 2018).
4. Formation of two anterior chambers – appears as a result of a microperforation or double bubble, the first case requires tamponade, in the second case the type 2 bubble must be drained (SINGH N. P. et al., 2018).
5. Urrets-Zavalia syndrome - if there is air trapped in the anterior chamber after surgery, it can cause an increase in intraocular pressure, which must be drained after surgery (SINGH N. P. et al., 2018).
6. Wrinkled interface – occurs when the donor bud does not adhere properly to the host MD, it can be solved by increasing the size of the donor bud (SINGH N. P. et al., 2018).
7. Suture laxity – common in very superficial sutures, and can be corrected by deepening the suture by 80-90% (SINGH N. P. et al., 2018).
8. Vascularization – formation of vessels at the interface, may indicate stromal rejection, must be treated with corticosteroids (SINGH N. P. et al., 2018).
9. Rejection – epithelial or stromal rejection may occur, but not endothelial rejection as in PKP. They can be treated with corticosteroids or cyclosporine drops (SINGH N. P. et al., 2018).

FINAL CONSIDERATIONS

Corneal endothelial failure is a condition that currently can only be treated with corneal transplantation, through keratoplasty, which can be of the lamellar or penetrating type, the first being the gold standard. It was observed that lamellar keratoplasty has a lower rate of graft rejection. This modality can be performed using three different techniques, all of which, however, present challenges due to the need for expertise and prolonged time, increasing the risk of poor graft implantation and surgeon fatigue. Therefore, the authors of this article argue that these issues must be addressed with greater emphasis, in order to improve the postoperative period for patients. In this sense, the need to develop more research in areas such as genetic engineering and the creation of new equipment and tools is highlighted, in order to make surgeries less invasive and complex. The objective is to reduce dependence on the surgeon's skill and minimize the most common problems in surgeries.

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