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Delivering endothelial keratoplasty grafts: modern day transplant devices

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Running title

Transplant devices for endothelial keratoplasty

ABSTRACT

For over a decade, endothelial keratoplasty (EK) has been popularized as a standard of care for treating endothelial dysfunction. New techniques and devices have been introduced and implemented to prepare, load, transport and transplant the grafts for EK. The advantages are not only limited to the surgical theatre but also widely spread across the eye banking field. Investigation of advanced materials and designs have been rapidly growing with continuous evolution in the field of eye banking and corneal transplantation. Innovative techniques and modern devices have been evaluated to reduce the endothelial cell loss and increase the precision of the transplant in order to benefit both surgeons and patients. In addition, due to limited availability of healthy cadaveric donor corneas required for such transplants, it becomes extremely important to reduce any potential wastage and optimize the use of every donor cornea. As a result, the use of pre-cut and pre-loaded grafts supplied by the eye banks in calibrated devices have been gaining momentum. Innovation in the field of bioengineering for the development of new devices that facilitate excellent clinical outcomes along with reduction in learning curve has shown promising results. The review thus aims to summarize and compare the popular devices that have been used for delivering EK grafts in recent times.

KEYWORDS

Cornea; endothelial keratoplasty; DSAEK; DMEK; devices; glides; injectors

INTRODUCTION

Penetrating keratoplasty (PK) has been refined due to the occurrence of substantial post-operative complications, most notably; poor wound healing from the vertical stromal wound, immunological rejection, astigmatism and microbial keratitis, which all increase the risk of long-term vision loss.^{1,2} Advanced procedures involve replacement of only the recipient dysfunctional corneal endothelium and underlying Descemet's membrane with a healthy donor tissue known as endothelial keratoplasty (EK). EK has shown an early rehabilitation rate, better visual outcomes and reduced post-operative complication rates. Currently there are three types of endothelial transplantation techniques in use; 1) Descemet's stripping automated endothelial keratoplasty (DSAEK) in which the host's affected corneal endothelium and Descemet's membrane (DM) is replaced by the donor's posterior corneal stroma, DM and corneal endothelium, 2) Ultrathin DSAEK, a relatively thin graft with intended central graft thickness of 100 microns containing a small portion of stroma, DM and corneal endothelium; and 3) Descemet's membrane endothelial keratoplasty (DMEK) which replaces the DM and corneal endothelium only, without the presence of stroma, following descemetorhexis.³

Despite the evolution of these surgical techniques, each technique has its own limitations and challenges that may affect graft survival. Although attempts have been made to standardize the procedures, ongoing research, and development for DSAEK and DMEK continues to optimize the surgical outcomes. Attention has been given to the devices and techniques that are used to deliver the graft to the anterior chamber, with the goal of developing a method of delivery that limits corneal endothelial cell damage. These procedures have evolved from insertion of the tissue by simple folding and pulling techniques (using forceps) further towards utilizing glides to support the graft^{4,5} and adoption of cartridge-based injection devices.⁶ Notable improvements post-operatively, although not fully attributable to the device used, include risk reduction of wound-induced astigmatism, decreased numbers of grafts rejected, faster visual recovery^{2,7} and improved visual acuity.^{8,9}

DSAEK has showed an improvement over PK in terms of early visual rehabilitation, gaining 20/20 visual acuity, and reduced endothelial cell loss (ECL), however, access to the procedure is limited in low volume centers and developing countries due to immediate economic barriers.⁶ Introduction of procedures like ultrathin DSAEK and DMEK³ led to improvements in visual outcomes compared to DSAEK.¹⁰ Faster visual restoration was observed with some patients reaching a visual acuity of 20/40 post-DMEK on the first postoperative day with the equivalent visual acuity seen with DSAEK occurring usually after weeks or even months.⁶ However, some challenges such as increased learning curve during graft preparation¹¹ and higher post-operative complications such as graft detachment and re-

bubbling rates¹² have been identified following DMEK compared to DSAEK surgery. Unfortunately, the rate of ECL still remains a challenge with DMEK with cell loss of approximately 30-40% reported within 12 months.¹² The post-operative outcome cannot be attributed only to the delivery device used. Donor or tissue characteristics, learning curve of the technician or a surgeon, pre-operative diagnosis, follow-up period etc. also play an important role in determining the success of a transplant.

Analysis of potential causes of ECL damage during EK surgery has helped to identify the delivery methods of the donor corneal graft into the anterior chamber as one of the challenging steps leading to tissue damage during the procedure.⁶ In order to minimize this damage, a number of novel delivery devices have been developed. A range of devices utilize different methods to load and deliver the graft, making some features more suitable for specific types of transplant. Here we summarize the devices that have been used for delivering EK grafts.

DSAEK

FORCEPS

The first technique established while undertaking EK was the insertion of the graft into the anterior chamber via a small incision through the use of two types of forceps; 1) compression forceps; where the donor tissue was only compressed at a single point and 2) non-compression forceps; where the compression occurred across the whole length of the graft. The most common technique used is the taco-folded insertion technique. This involves the insertion of the donor lenticule through 3 mm - 5 mm corneal or scleral incision by folding the lenticule, followed by gripping the folded tissue with either compressing forceps (i.e Kelman-Mcpherson) or non-compressing (i.e Goosey) forceps.^{13,14} In comparison to PK, EK led to a noticeable improvement in patients' functional outcome; with significant improvements seen in patient recovery time [(1.5 week in the DSAEK vs 5.3 weeks in the PK operation (P = 0.01)], and improved visual acuity [(BCVA logMAR)- PK-0.33± 0.19 (20/43) vs EK 0.22 ± 0.18 (20/33)].⁸ It must be noted that although EK was performed using insertion forceps, the visual outcomes cannot be fully attributable to the surgical instrument or technique. One study directly comparing different types of forceps in DSAEK showed mean ECL being greater than 30% at 6 months [Goosey 33±18% (n=170), Kelman 38±17% (n=93)].¹⁴ This is believed to occur as a result of folding and compression of the tissue during insertion.^{13,15,16,17}

GLIDES

Busin Glide

Moving on from the forceps technique, Busin et al¹⁸ developed a glide device to aid in transfer of the graft from the donor to the recipient and delivery to the anterior chamber. Busin glide is the most commonly used device for the pull-through technique. It is a 2-part reusable metallic device with important features like the elliptical tip that prevents both the folding of the donor endothelium as well as reducing the incision compression pressure (ICP).^{5,16} In comparison to forceps insertion, the glide shows slightly lower levels of ECL with several studies reporting mean ECL between 20-30% (n=10-68).^{4,9,19} A study⁸ that directly compared forceps and the Busin glide delivery method showed a greater improvement at 6-month follow-up for Busin glide (BSCVA 0.27 ± 0.14) compared to forceps technique (BSCVA 0.32 ± 0.27) however, it was not found to be significantly different (n=24; p=0.39). Similar results were also observed for Busin glide in a 12-month follow-up study undertaken by Ang et al. in 2011 in an Asian population showing ECL of 40.9% in PK (n=173) compared with 22.4% following DSAEK (n=68).¹⁹ Atraumatic insertion of the donor lenticule can be technically challenging especially for young surgeons leading to the anterior chamber (AC) collapse.^{20,21} However, AC collapse can be avoided by creating an adequately sized incision and inserting the device without pressing on the posterior lip with continuous irrigation during graft delivery. A modified technique of placing the Busin glide outside the incision to avoid anterior chamber (AC) collapse has also been reported, however, ECL levels still remain a concern.^{20,21}

I-Glide

Although the number of requests for pre-cut tissue from eye banks is rising, there has also been an increasing interest in pre-loaded DSAEK tissues in the last few years as reported by the Veneto Eye Bank Foundation, Italy.¹² An early investigation using I-Glide (Eurobio, France) showed reduction of surgical time avoiding possible complications related to the donor preparation in operating room.²² The device is designed to carry the tissue for transportation and also serve as an implantation device. I-Glide is cylindrically shaped to integrate a pre-cut DSAEK tissue with storage media that maintains corneal endothelial cell (CEC) viability during the transportation phase. The spillage of the storage media or the tissue is prevented with a glide cap. This glide comes with two diameter options for DSAEK and ultrathin DSAEK.

I-Glide for DSAEK: Laboratory investigations (n=20) showed ECL of $2.30 \pm 3.21\%$ with tissue swelling of $30.8 \pm 20.85\%$ after 7 days of preservation. The cells displayed an active metabolism by utilizing approximately 33% of the available glucose during the preservation period. A single-center single-surgeon clinical study (n=14) showed 25% ECL after 6 months post-op with improvement of BSCVA to 20/25 or better within the first 3 months. In this study, the surgery time did not exceed 21 minutes.²³

For clinical grade tissues, I-Glide provides several advantages when using pre-loaded tissues with less tissue wastage and preparation errors in theatre, reduced overall surgical costs considering the overall reduction of the surgical time and the same device for both transportation and implantation of the graft, further cutting down additional expenses.

*I-Glide for Ultrathin DSAEK: A study from Parekh et al.*²⁴ demonstrated preloaded large diameter (9.5 mm) ultrathin DSAEK grafts using I-Glide (iGlide, Eurobio, Les Ulis, France). Laboratory and clinical studies were performed to evaluate the ECL. In the laboratory study, endothelial cell density (ECD) was analyzed before graft preparation. The graft was then gently folded in an endothelium-inward configuration and placed into the I-Glide followed by preservation of the graft in transport medium at room temperature. On day 4 after preservation, the graft was released, and the ECD was measured. The ECD change between before graft preparation and post-preservation did not show any statistical significance ($p=0.8$). ECL after 4 days of preservation was 1.7%. The clinical study was performed on 39 eyes of 39 patients. At 6 months post-operation, ECL was 28% with 23% of patients requiring rebubbling.²⁴

Endoglide

When introduced, Endoglide was the first disposable inserter. It comprised a 3-part disposable device (preparation base, glide cartridge and glide introducer)⁴ with a standout feature of a double coil tip. This aimed at reducing the trauma on the graft, and more specifically, the endothelial lining as the graft takes the shape of the tip, fitting the graft into a smaller space, reducing the incision compression pressure (ICP) and hence attempting to reduce ECL. A study undertaken²⁰ in the UK on 52 eyes of 52 patients showed a direct comparison between the Endoglide and Busin glide technique. The study noted a significantly lower rate of ECL postoperatively at 6 months after using the Endoglide (25.76%) compared to Busin glide (47.46%) ($p<0.0001$), however, it is worth noting that the ECL for Busin glide reported here is greater than it has previously been described elsewhere in the literature. Focusing on ECL using the Endoglide device, a study undertaken by Khor et al.²⁵ on 20 Asian patients reported a mean ECL of 13.1% (95% CI, 8.4%–17.8%). This is particularly impressive given that large studies utilizing optical coherence tomography (OCT) have shown the anterior chamber depth (ACD) is significantly shallower in American Chinese populations (2.77 ± 0.30 mm) than in Caucasians (3.04 ± 0.33 mm, $p < 0.0001$) leading to an increased frequency of both AC collapse and ECL amongst the Asian population.²⁵⁻²⁷ No significant difference was noticed in terms of BCVA logMAR ($p=0.34$) between Busin and Endoglide.²⁰ However, a case series of 100 eyes undergoing DSAEK for FECD and PBK using the EndoGlide device presented by Khor et al.²⁸ showed an average BSCVA of 20/40 consistently at 3,

6 and 12 months in 61, 55 and 48 eyes respectively. ECL was 13.7%, 13.5% and 14.9% at 3, 6 and 12 months respectively. Complications were due to prior glaucoma with 2.6% showing endothelial rejection and 1.3% that failed. Overall, EndoGlide demonstrated good clinical outcomes with low ECL at one year. A retrospective case series comparing long-term graft survival and ECL following DSAEK using EndoGlide (100 eyes) and Sheets glide (119 eyes) technique showed significantly lower ECL in the EndoGlide (16% at 1 year; 23% at 2 years and; 29% at 3 years) group vs Sheets glide technique (29% at 1 year; 35% at 2 years and; 38% at 3 years). The study also reported that EndoGlide had lower ECL in eyes with FECD and superior graft survival in eyes with pseudophakic bullous keratopathy (PBK) compared to the Sheets glide. Long-term graft survival and endothelial cell maintenance was found to be higher when the grafts were inserted using EndoGlide.²⁹ Yokogawa et al. showed ECL of 22% at 6 months and 24% at 12 months following DSAEK using the EndoGlide on 6 eyes of 6 patients. VA of 20/63 or better at 12 months with four patients reaching 20/32 has also been reported.³⁰ Balidis et al. reported 25% ECL after 6 months following DSAEK surgery using the EndoGlide with BCVA of 20/40, no episodes of graft failure and 2 partial graft dislocations.³¹ EndoGlides have been used extensively for DSAEK with acceptable ECL and good short and long-term clinical outcomes.

INJECTORS

Many injectors are commercially available but only three have been reported with clinical data; EndoSerter (Ocular Systems Inc., Winston-Salem, North Carolina), Neusidl Corneal Inserter (Fischer Surgical, Imperial, Montana) and NS Endo-inserter (HOYA Surgical Optics, Tokyo, Japan).

EndoSerter

The Endoserter is a disposable, non-transparent corneal inserter device.^{17,32} It is designed to protect the allograft from ICP during insertion with an irrigation system to ensure a deep chamber, which is particularly important in the Asian population. Looking at the rate of ECL, a large (n=175) non-randomized control study undertaken by Foster et al.³³ showed 28.3% ECL with EndoSerter (n=70) compared to 44.1% with forceps delivery (n=105). However, a study showed that Endoserter did not have any statistical improvement in terms of BCVA compared to Endoglide.³²

Neusidl Corneal Inserter

The Neusidl corneal inserter¹⁷ has a pointed elliptical opening to match the shape of the allograft, with the aim of preventing the endothelium from folding. Terry et al.³⁴ undertook a large randomized controlled study looking at 100 eyes comparing the inserter to forceps delivery. The mean ECL was significantly higher in the Neusidl group (33%; n=50) compared to the forceps group (25%; n=50) at 6

months ($p=0.017$) however, the visual outcomes were not recorded. Kobayashi et al. showed ECL of 22% at 6 months and 31% at 12 months following DSAEK in 6 eyes of 6 patients using Neusidl Inserter with no intra- or post-operative complications.³⁵ The result suggests that perhaps alternative methods are more suitable, however, a greater number of studies are required to arrive at a definitive conclusion.

Graft insertion device

Soma et al. described a new device made of polypropylene with a hydrophilically coated, flexible polyethylene platform to place the graft lenticule. The system also comprised of a movable polypropylene cartridge fitted to the main body supplemented with a valved conduit made of silicon rubber. The syringe is filled with BSS and the plunger is partially depressed to lubricate the surface of the hydrophilic platform on which the DSAEK graft is placed. The platform along with the graft are partially rolled and drawn within the main body. Following the generation of negative pressure to keep the graft in position, the device is turned 180 degrees to allow the endothelial side to appear in face down position. The graft is delivered by depressing the plunger. All 12 eyes showed successful and uneventful surgery. No post-operative graft complications, failure or detachments were observed. ECL was not reported in this study.³⁶

NS Endo-inserter

The NS Endo-inserter was proposed to prevent endothelial cell damage caused by mechanical trauma during surgery and collapsing of the anterior chamber during graft delivery. The hydrophilic platform surface was connected to a 2.5 mL syringe containing balanced salt solution (BSS). For loading of the DSAEK graft, the graft was placed with endothelial cells facing upwards and then the cartridge was gently moved forward. The valve at the inner tube inside the cartridge was used to create a negative pressure allowing the graft to be drawn into the inserter body. The DSAEK graft was delivered to the recipient anterior chamber with the use of BSS flow. The early and late postoperative results were observed and compared with Busin glide. At 3 months post-operation, ECL was 9.1% and 44% and; 18.2% and 46.5% at 6 months, which was found to be significantly lower in NS Endo-inserter ($n=13$) group compared to Busin glide ($n=10$) respectively ($p=0.024$ and 0.016).³⁷

The NS Endoserter has also been reviewed by Yokogawa et al.³⁸ The study evaluated the use of a suture pull-through technique using NS Endoserter (NSI, Hoya Co. Ltd, Tokyo, Japan) to treat bullous keratopathy (BK). DSAEK tissues were loaded in the NSI device and pulled into the anterior chamber using a lifeline suture in 6 aphakic eyes. Intraoperative complications, graft dislocation, or primary graft failures were not observed. ECL at 6 months was 27%. The aim of this study was to show the

efficacy of the technique for complicated eyes using the NS Endoserter device, which allowed safe insertion of DSAEK without donor tissue migration into the vitreous cavity. However, in another study,³⁹ the outcomes of NS Endoserter were investigated for DSAEK on BK secondary to argon laser iridotomy. The donor tissue was pushed using pressure flow unlike the one described by Yokogawa et al.³⁸ where the authors used a pull-through technique. No intraoperative or postoperative complications were observed. A mean ECL of 14% was recorded thus showing comparable results with conventional DSAEK insertion techniques.

Endosaver

The Endosaver device (Endosaver, Ocular Systems Inc., Winston-Salem, North Carolina, USA) described by Tsatsos et al. has shown significant difference in ECL compared to non-injector (forceps) devices in DSEK procedures. The device requires connection to irrigation and requires a temporal clear corneal or scleral tunnel incision of 4 mm. In a retrospective case series including 43 eyes, the mean post-operative ECL recorded was 21% and 29% at 6 and 12 months respectively for the Endosaver group, whereas 43% and 50% ECL was recorded in the forceps group for the same period respectively. This difference indicates a less traumatic insertion of the graft and probably a more stable system during surgery due to a smaller incision.⁴⁰

Macaluso inserter

The Macaluso inserter (e.Janach, Como, Italy) is a metallic reusable glide with a closed chamber that helps in AC maintenance. The DSAEK graft is placed in the concave winglet, which has a circular marked region that allows centration of the graft. The graft is pulled towards the tip of the device, which allows the graft to roll and form the shape of the device. The graft is sealed with a plunger along with the media. The device has a peripheral opening with a tapered elliptical shape with a 'V' shaped opening. A 4.2 mm incision is recommended for an 8-8.5 mm graft. The graft can be injected using a plunger. The advantage of this device is that it is reusable following sterilization. The device was used successfully on 72 consecutive cases with no complications. ECL and visual outcomes are not available for this inserter.^{41,42}

SUMMARY

Looking at the established clinical options available, it seems that there was big improvement in reducing ECL from the forceps 'pull-through' technique when using the Busin glide. Only the EndoSerter and EndoGlide have shown a slight improvement in terms of reduced ECL with no difference in visual outcomes, and this may be due to a number of reasons. One could be the ethnicity

of the patients requiring surgery, with one example that the Asian population tend to have shallower anterior chambers and hence are more prone to AC collapse,²¹ which perhaps suggests that different techniques and devices may be preferable for different populations. Surgical skill and experience of an eye bank technician or a surgeon also plays an important role, but this can be subjective and should be taken into account when assessing the post-operative complications or ECL with these delicate procedures. The aim of using simpler devices and techniques is to reduce the challenges and a practical example is the advent of a 3D printed smart storage glide described in literature.²³ The pre-cut, pre-loaded tissue, similar to those preserved and delivered using iGlide aimed at eliminating the potential complications arising from the operating room related to the preparation of the donor tissue. The technique of pre-loading has been shown to reduce the overall surgical time.

A summary of all the devices used for DSAEK and UT-DSAEK with their characteristic features have been included in table 1.

DMEK

As discussed earlier, EK offers distinct advantages over PK in terms of visual outcomes and early visual rehabilitation. However often, it is noted that graft preparation from the donor tissue is challenging, requires skills and has a learning curve to achieve.¹¹ It has been observed that if the DMEK graft is not excised precisely then it may result in high ECL or tissue wastage due to tearing of the graft therefore constant attempts are made to standardize this process.⁴³ However, although a higher ECL might be expected following DMEK, comparable ECL has been found when compared with DSAEK.^{44,45} Both, DSEK and DMEK have shown linear decline in ECD from 6 months to 10 years. Intraoperative and postoperative complications have been noted with DMEK surgery. Difficult graft unfolding/positioning, high vitreous pressure, iris root hemorrhage, and Descemet's membrane remnants remain the main possible intraoperative complications accounting for 16%. Significant graft detachment rates from as low as 4% to as high as over 60%, have been noted as main postoperative complications.⁴⁶ Graft failure remains a rare but possible complication and inverse grafting can be minimized after marking the DMEK graft with 'S' or 'F' stamp. Other postoperative complications such as increase in intraocular pressure, allograft rejection, cystoid macular edema and microbial keratitis have also been reported.⁴⁷ Although rare, calcification of a hydrophilic intraocular lens (IOL) is reported as a possible complication in DMEK.⁴⁸ It has also been noted that triple procedure i.e. DMEK combined with phacoemulsification and cataract could lead to possible graft detachment.⁴⁹ Thus, indicating that early or late post-operative complications can arise due to multiple factors and the device may only play a partial role in surgical success.

ECL in DMEK

ECL from previous DSEK and PKP cases after up to 5 years of follow up has been recorded at 53% and 70% respectively.⁵⁰ It has been observed that ECL following DMEK has ranged between 31-40% at 3 months and 36-40% at 6 months and; for long-term studies of 1 year, between 19-36% .⁵¹⁻⁵⁸ A steep reduction (approximate rate of 7%) of the endothelial cells during the first 6 months has been observed with DMEK compared to that of DSEK that has an initial high ECL but then maintains at 3-6% after the first year.⁵⁹ It has been speculated from the studies that although the early cell loss is higher in DMEK compared with PKP, long-term ECL rate with DMEK and DSEK could be relatively lower.^{12,19}

DMEK INJECTORS

Apart from DMEK graft preparation, one of the important challenges that still remain in DMEK surgery is graft implantation. There are two important graft implantation techniques based on the orientation of the endothelium, i.e., endothelium inwards or endothelium outwards. Recently, in an ex vivo study, Parekh et al. showed that there was no significant difference in ECL when the tissues were implanted with endothelium inwards (10.53%; n=9) or outwards (7.56%; n=9). However, the preparation time for endo-in was significantly higher but the unfolding time was significantly lower compared to the endo-out technique thus indicating that either techniques could be used for implantation.⁶⁰ Clinically, at 6 months Busin et al. have reported similar outcomes with endo-in pull through technique (29.5%; n=24)⁶¹ to the endo-in injection method (28%; n=172) by Price et al.⁶² and injection technique with endo-out by Newman et al. (30.9%; n=67).⁶³ The second important parameter for graft implantation is the selection of the injector for holding and delivering the graft. The very first DMEK tissues were transplanted using custom-made injectors (Hippocratech, Rotterdam, The Netherlands) that helped to insert the donor DM scroll with endothelium rolled outwards in the anterior chamber.³ ECL was not reported, however, ECD averaged at 2350 cells/mm². This device has been out of commercial use in the recent times for DMEK implantation. For the endo-out technique, a modified Jones tube has been amongst the favorites. It is a glass injector that is useful for aspirating the naturally rolled endo-out DMEK tissue and implanting it in the recipient eye.⁶⁴ Another injector that has been used is the Geuder AG DMEK shooter from Heidelberg, Germany, or the DORC injector (DORC, Zuidland, the Netherlands). A double-roll form can be aspirated and injected in the recipient⁶⁵ eye using these devices. The listed injectors are for the endo-out technique. However, for endo-in, the IOL cartridge has been favoured as it maintains the architecture of the graft as a taco fold.^{61,66}

DORC injector

Downes et al. conducted an ex vivo study on DMEK procedures, comparing the DORC injector and modified Jones tube. ECL was not found to be statistically significantly different (p=0.17) between the

DORC injector (29.2%; n=9) and modified Jones tube (23%; n=9), but there was a different pattern of cell loss between injectors. The modified Jones tube data showed patterns of cell loss from the graft scraping against the injector as it travels into and out of the injector, in the DORC group the graft scraping occurs when it funnels down from wider opening to the narrower opening, showing a central wide band.⁶⁷ This was observed using calcein AM staining for cell viability analysis.

A comparative retrospective case series conducted from 2010 to 2013 analyzed three different injectors: The DORC (n=16) and Geuder injectors (n=24), and the Pasteur pipette (n=26) on 66 consecutive DMEK procedures. All three injector systems demonstrated similar outcomes in terms of surgical complications and ECL. DORC injector demonstrated the lowest, whereas the Pasteur pipette showed the highest ECL among the groups which was found to be statistically significant at 3 months after surgery. ECL post DORC at 12 months was 39% with Geuder injector was 43% and 47% with Pasteur pipette. This is probably due to the fact that with the Pasteur pipette, the DMEK roll is aspirated through a narrow opening with a vertical edge profile causing friction and cell damage compared to the other injectors. There was no significant difference in the rate of injector-related complications and re-interventions.⁶⁸

Double port injector device

Arnalich-Montiel et al. proposed an injector made of glass. It consists of a pipette with a separate asymmetric double port with a large diameter (3–4 mm) and a small diameter (0.8–1.3 mm) lumen that does not require disassembling. The proximal end (3 mm diameter lumen) is where all the tubing and syringe that allows suction and ejection of air/fluid are connected; the distal 0.8 mm diameter end is the tip where the graft exits the injector into the eye. An accessory conical-shaped port has a lumen diameter of 4 mm and forms an angle of 70° with respect to the main trunk/pipette. The graft is loaded by a suction force through the large port while occluding the small port and the graft is pushed along the small port allowing the double roll to face up inside the anterior chamber. Endothelial survival following single port pipette was 78.8±20.9% (n=8) compared with 96.8±8.4% (n=8) following double port injector, which was significantly different. ECL at 3 months was 26.1%.⁶⁹

Endoject

ENDOJECT™, described by Rossler et al. (Medicel AG, Wolfhalden, Switzerland), is a cartridge with a thinner wall-thickness compared to glass tubes, with the same inner diameter of glass tubes. The suitable incision size for ENDOJECT™ is 2.5 mm which makes the characteristics very similar to a Viscoject 2.2 mm (Medicel) injector.⁷⁰ The ENDOJECT™ is not designed to store preloaded DMEK grafts.

EndoGlide

EndoGlide, as described for DSAEK, has also been used for inserting DMEK grafts following modifications in the technique. Recently, a surgical device and technique, EndoGlide-DMEK (E-DMEK), was evaluated for pull-through using the endothelium-inwards method. An ex-vivo study on 9 human donor corneas showed ECL of 15%, however, clinically, on 69 eyes, the method resulted in 33% ECL after 6 months follow-up. Rebubbling and primary graft failure accounted for 11% and 1.5% respectively.⁷¹ A hybrid DMEK (H-DMEK) has also been proposed where the DMEK tissue is implanted using a bimanual pull-through technique using DSAEK-prepared donor stroma as a carrier and the EndoGlide UT-DSAEK donor insertion device. 85 eyes of 79 patients out of which 43.5% with BK and 28.2% with FECD were evaluated. 4.7% required rebubbling. BCVA of 20/25 or better was attained in 44.7% and 57.1% of eyes at 6 and 12 months with an ECL of 32.2% at 6 months. The results indicated that hybrid DMEK can be used for a controlled pull-through technique of donor insertion in the 'endothelium-in' configuration.⁷² In a prospective, interventional case series, Ang M et al. evaluated the use of the EndoGlide pull-through prototype device (Descemet Mat, or D-Mat). This study was carried out on 30 eyes of 30 patients. Partial detachment was observed in 10% and rebubbling was required in 3% of the eyes. Six-month ECL reduced from 65% to 48% however, it was still much higher than the conventional DMEK. The study suggested that the device can be used for controlled insertion with correct orientation i.e. endothelium-inwards. Long-term ECL and graft survival needs to be evaluated further.⁷³

Coronet DMEK EndoGlide

This EndoGlide (Network Medical Products, North Yorkshire, UK) is adapted from Descemet-stripping endothelial keratoplasty Tan EndoGlide (AngioTech, Reading, PA/Network Medical Products, North Yorkshire, UK). The tissue is stored within a cylindrical chamber using an endothelium-in method. The cartridge size is 2.65 mm hence, a small clear corneal incision can be applied. A retrospective clinical study showed a significant improvement of BCVA at 9 months post-operation ($p=0.03$) using EndoGlide. ECL at 6 months post-operation was 26.6% ($p=0.008$), which is in the acceptable range of DMEK.⁷⁴

Custom built device

Kim et al. reported a DMEK graft injector which was made from the supplies available in the theatre. A standard intravenous tube was cut 2 inches from the Luer lock end, leaving a steep bevel. The cut end of the tubing was firmly wedged bevel up and advanced into the back of an Alcon intra ocular lens (IOL) B cartridge. The Luer lock end of the tubing was then attached to a 5- or 10-mL syringe filled with

BSS Plus. The DMEK was peeled and placed in BSS before drawing it in the injector with the bevel-side up followed by insertion into the AC. All seven eyes of the seven patients with FECD showed corneal clarity and improved visual acuity in this pilot study.⁷⁵

More recently, with increasing popularity of pre-loaded DMEK grafts, modifications and use of innovative devices and techniques have been observed.

Straiko modified Jones tube

One of the most commonly used injectors is a modified Jones tube, which consists of a glass cartridge to aspirate and deliver the DMEK tissue that is rolled outwards. A study by Newman et al. showed that DMEK tissues can be preloaded in a Straiko modified Jones tube and delivered to the recipient eye using the same device. No primary graft failure was reported but a 14.4% re-bubble rate was noted. ECL at 3 and 6 months was 26.7% and 30.9% respectively.⁶³ ECL was found in the range of conventional DMEK procedures and therefore preloading DMEK tissues using such devices could be of interest for those surgeons willing to graft DMEK using the endo-out technique. However, this injector is limited only to endo-out as the internal diameter of the preservation chamber is wide and does not have a capacity to maintain the architecture of the endo-in grafts.

Intra ocular lens cartridge

For endo-in, a standard IOL cartridge has been used to reduce the friction between the endothelial cells and the wall of the cartridge, which is an added feature of the endo-in technique.⁶⁶ The DMEK tissue is manually tri-folded and inserted in a standard 2.2 IOL cartridge (Medical AG, Thal, Switzerland) also used for implantation in the recipient eye.⁶¹⁻⁶⁶ However, with recent advances, pre-loaded DMEK grafts with specific injectors⁷⁶ or IOL cartridges⁶⁶ have preliminarily shown significant advantage for the surgeons and the eye banks. Storage of tri-folded DMEK grafts in Viscoject 2.2 cartridges (Wolfhalden, Switzerland), sealed and preserved in a sterile flask with transport media at room temperature was studied by Parekh et al.⁶⁶ The results showed an ECL (n=20) of 4.35% after preservation with 3.55% mortality and 7.80% uncovered areas after 4 days of storage. Busin et al. reported 29.5% ECL (rebubbling 19.6%)⁶¹ using this device with endo-in format whereas Price et al. reported 28% ECL (rebubbling 10%)⁶² using a similar device but the same orientation of the graft. This indicates that the IOL cartridge can be used successfully for loading and transplanting a DMEK tissue. One of the most commonly used IOL cartridges is ALCON B. The clinical outcomes of using ALCON B IOL cartridge have been evaluated by Ighani et al.⁷⁷, they retrospectively reviewed medical charts of 23 patients. However, it is unclear if this cartridge could be used for pre-loading DMEK grafts, but results showed it was a safe and effective device for traditional DMEK. The Bonfadini-Todd injector is

a modified ALCON B cartridge. It is assembled using standard IV tubing (part number MX451FL; Smiths Medical, Inc., Dublin, OH, USA) and ALCON B IOL cartridge and cut with a bevel approximately 1.91 cm from the Luer-lock leaving a steep bevel. This is further advanced into the back of ALCON B IOL cartridge. It comes with disposable parts and it is easy to assemble.

So far, one published study compared an IOL cartridge to a tube injector: Schallhorn et al. compared the Jones tube injector (Gunther Weiss Scientific Glass) and intraocular lens injector (Viscoject 2.2; Mediceal). These are both closed systems meaning that any movement of the plunger directly translates into a movement of the fluid within the injector chamber. In this in vitro study there was no significant difference in the cell loss associated with the injector method.⁷⁸ In Europe, the DORC glass injector, the Geuder glass injector (Geuder AC, Heidelberg, Germany), and the ENDOJECT TM (Mediceal, Wolfhalden, Switzerland), are all in use.⁷⁸

Shen et al. investigated three different injectors in a laboratory setting: the modified Jones tube, the STAAR IOL injector and the Geuder glass cannula. Eight human donor corneas were used for each arm and loaded in the injectors. The percentage of endothelial damage was analyzed after ejections, the mean ECL was 37.8% for the Jones Tube, 37.0% for the STAAR IOL cartridge and 23.5% for the Geuder cannula. The study concluded that the Geuder cannula may offer a significant reduction in tissue damage.⁷⁹

DMEK Rapid device

DMEK Rapid, a relatively new Geuder system, has an aperture diameter of 1.6 mm, a posterior loading orifice of 4.29 mm and a smooth opening edge profile. In a laboratory investigation, DMEK Rapid compared with conventional flask showed 9.15% and 10.35% ECL respectively.⁸⁰ However, another study compared the media inside the DMEK Rapid device and found 20.8% and 19.5% ECL after preserving the tissues for 4 days at RT in tissue culture medium and transport medium respectively. An ECL of 12.9% has also been reported when the tissues were shipped from Italy to the UK using the same device.⁸¹ A laboratory study confirmed that grafts stored for 24-48h in the pre-loaded cartridge show similar ECL compared to pre-cut graft in a conventional viewing chamber.⁸² Rickmann et al. conducted a retrospective clinical study on 254 patients undergoing DMEK surgery using the Geuder glass injector. After 6 weeks of DMEK, endothelial cell count decreased by 28.6%. After 6 months, endothelial cell count remained stable at 1735 cells/mm², resulting in a statistically significant increase in mean BCVA from preoperative 0.84 logMAR to 0.27 logMAR after 6 months.⁸³

A summary of all the devices used for conventional DMEK and pre-loaded DMEKs with their characteristic features has been included in table 2.

SUMMARY

One of the unfavorable aspects of the DMEK procedure, is that the isolated membrane is prone to curling, making the tissue difficult to handle even by experienced surgeons and so often leads to ECL. Multiple factors have been observed that leads to graft scrolling and unscrolling in the anterior chamber.⁸⁴ However, this challenge has been significantly reduced with the endothelium-inwards method. The new techniques like pre-loading DMEK grafts could be useful in such cases.⁶⁶ Both, the endothelium inwards and the outwards techniques have shown ECL in the acceptable range without any significant complication rate.⁸⁵ The Straiko modified Jones tube⁶³ and IOL cartridge^{5,61,62} have been in clinical use with promising data, however, the relatively new and emerging devices such as DMEK Rapid⁸⁰⁻⁸³ may increase the interest for preloaded DMEK tissues in the future.

CONCLUSIONS AND FUTURE DIRECTIONS

EK has evolved significantly over the years clearly demonstrating the advantages over conventional PK techniques. With better clinical outcomes, EK has become a popular choice for treating endothelial dysfunction. Although there are unmet challenges, continuous development in eye banking, surgical care and bioengineering has enabled great outcomes. The growth and learning curves have been extensive from forceps and manual cutting to standardized instruments and pre-loaded grafts that not only reduce a surgeon's efforts but can also deliver optimal clinical outcomes in terms of visual acuity and endothelial cell maintenance. However, the primary restriction with regards to the donor corneal supply remains a challenge, necessitating alternatives to reduce the current burden on the requirement of human donor corneas. Recently, research has focused on the challenges of culturing human corneal endothelial cells successfully, which allows transplantation of the cultured cells to many recipients. However, standard culture methods and techniques of transplantation of cultured cells have not yet been well established for routine clinical purposes.

The rate of postoperative ECL following EK has shown a gradual improvement over the last 10 years. Despite the constant attempt for improvement, the recent plateau is of concern and whilst different devices are still being manufactured with the aim of reducing the known issues, it may be important to note that a number of these patients have corneal endothelial end-stage disease, which in itself may be an unsurmountable limiting factor. In addition, we must take into consideration the cost and availability of equipment and tissue, which is important as it means that the use of certain devices is

based on a balance of surgical cost and effectiveness. Having a larger number of corneal tissues available would aim to reduce the surgical cost as the overall cost of the tissue would reduce, allowing greater sums to be spent on ensuring the best possible device. It would also allow a larger number of devices to be clinically trialed extensively, leading to wider clinical applications.

It must be noted that the use of surgical devices is not only limited to the DSAEK or DMEK transplantations but can also be utilised in the preservation and transplantation of tissue engineered grafts in the future. If these devices, in particular I-Glide or Endoglide (as they have preservation chambers large enough for preserving the tissue engineered grafts and a pore opening for transplantation), are fully validated for EK then it will be relatively easier to adopt them for alternative procedures. With advances in the field of carrier materials and the success of tissue engineering strategies for corneal endothelial replacement, the use of such devices seems to be inevitable. The transfer of cell sheet into the anterior chamber and its stable fixation to the posterior cornea remains a surgical challenge that has not yet been met so far. I-Glide could offer advantages because the graft can be loaded, shipped and transplanted using the same device. It will also limit the contact time the surgeon has with a potentially unfamiliar graft material and likely reduce the cell loss as manipulation would be reduced to minimum. Endoglide may also prove useful for the insertion of tissue engineered grafts as its usefulness has already been demonstrated by Levis et al.⁸⁶ as a delivery device for tissue engineered corneal endothelial grafts made using plastic compressed collagen.

More recently, there has been an effort towards thinner tissues in DSAEK, Cheung et al. coined the term Nano-Thin DSAEK (NT-DSAEK) referring to a graft thinner than 50 μm .⁸⁷ These changes have clinical and surgical implications, because EK thickness involves different manipulation and insertion devices, leading to continuous evolution in this field. A rising interest has been noted for potential hybrid techniques between descemetorhexis only or Descemet membrane endothelial transfer (DMET) and conventional circular DMEK. Techniques like quarter-Descemet membrane endothelial keratoplasty (quarter-DMEK), and hemi Descemet membrane endothelial keratoplasty (hemi DMEK) have been recently introduced, potentially harvesting two grafts from a single donor corneoscleral rim.^{88,89} This would further reduce the need of human donor corneas, however, these types of tissues would require special devices to consistently prepare and load the grafts due to their specific sizes and shapes.

As there is a limited supply of donor corneas, techniques like Descemet stripping only (DSO) are becoming popular as it reduces the use of donor tissues completely, which may in turn reduce the use

of device altogether. However, although early postoperative results from DSO technique have been promising, its longevity still needs to be determined.⁹⁰

Regeneration of human corneal endothelial cells and corneal bioengineering have been studied and reviewed extensively⁹¹⁻⁹⁵ with one successful clinical trial been completed.⁹⁶ If the clinical application of cultured cells on scaffolds or bioengineered grafts are successful, it may significantly reduce the requirement of corneal tissues and in turn the use of devices for tissue transplantation. However, new and advanced devices may be required to store, transport and transplant bioengineered tissues in the future.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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