

Review Article

Descemet's Stripping Automated Endothelial Keratoplasty Tissue Insertion Devices

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Abstract

This review study provides information regarding the construction, design, and use of six commercially available endothelial allograft insertion devices applied for Descemet's stripping automated endothelial keratoplasty (DSAEK). We also highlight issues being faced in DSAEK and discuss the methods through which medical devices such as corneal inserters may alleviate these issues. Inserter selection is of high importance in the DSAEK procedure since overcoming the learning curve associated with the use of an insertion device is a time and energy consuming process. In the present review, allograft insertion devices were compared in terms of design, construction material, insertion technique, dimensions, incision requirements and endothelial cell loss to show their relative merits and capabilities based on available data in the literature. Moreover, the advantages/disadvantages of various insertion devices used for allograft insertion in DSAEK are reviewed and compared. The information presented in this review can be utilized for better selection of an insertion device for DSAEK.

Keywords: Allograft Inserter; Allograft Insertion Device; Corneal Injectors; Descemet's Stripping Automated Endothelial Keratoplasty; Descemet's Stripping Endothelial Keratoplasty

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INTRODUCTION

The cornea is the outermost transparent part of the eye which covers the iris, pupil and anterior chamber (AC). The cornea is transparent and comprises of five layers, namely, epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium.^[1,2] The endothelium, the innermost layer, is an extremely thin layer responsible for keeping the cornea in its dehydrated state, which is vital for maintaining corneal transparency.^[3,4] The endothelial cells (ECs) act as small pumps, which suck fluid from the corneal stroma and pump it back to the AC hence preserving corneal transparency. These cells regenerate at an extremely slow rate as compared to cell decay, since they are arrested in the G1 cell cycle.^[5,6] Therefore cell counts rapidly decrease until the age of 25 after which the rate of decay slows down.^[7,8] For clear vision, the EC count should stay above a certain critical

amount; however diseases such as Fuchs' dystrophy, pseudophakic or aphakic bullous keratopathy, posterior polymorphous dystrophy, iridocorneal endothelial syndrome, endothelial decompensation and failed penetrating keratoplasty (PK), result in a decrease in EC count and eventually, an endothelial layer transplant becomes necessary.^[9] Numerous surgeries have been developed in the past for endothelial layer transplant such as PK, deep lamellar endothelial keratoplasty, Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty. PK and DSAEK are the most popular choices among surgeons.^[10,11]

In 2013, the number of corneal tissues used for transplant/keratoplasty in the US alone was 72,736.^[12] This number was largely shared between PK (36,998)

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and endothelial keratoplasty (EK) (27,298) procedures with with larger share for PK. However, EK is quickly improving showing approximately 12% increase from previous years, and this number is expected to increase every year along with improvements in health care and life expectancy.^[10,13] DSAEK is a type of keratoplasty that has become the gold standard in EK in recent years. This procedure is effective, fairly reliable and shows low rates of complications, however, it is evolving towards achievement of more acceptable results.^[14]

With DSAEK the diseased endothelium and Descemet's membrane are replaced with an excised posterior allograft approximately 130-240 μm in thickness. This allograft comprises of posterior corneal stroma, healthy Descemet's membrane and endothelium. This donor allograft once trephined, is inserted into the AC through a side incision created in the cornea, limbus or sclera. The advantages of EK are small incision size, a structurally stronger cornea, requirement of few to no sutures, reduced operative time, lower risk of allograft rejection, cost effectiveness, stability of refraction, and swift visual rehabilitation^[15-25] However, the demerits of DSAEK are a significant initial loss in endothelial cells density (ECD) as well as AC collapse, intraoperative ECD loss particularly in Asian patients with shallow ACs and in eyes with high vitreous pressures, and ECD reduction during microkeratome cutting of donor allografts, handling of corneal allograft and air bubble insertion into the AC.^[26,27] The major ECD loss occurs during allograft insertion and subsequent unfolding in the AC,^[9] which can potentially lead to problems such as primary allograft failure and corneal opacity.^[22,27-29] AC collapse depends on incision size, allograft insertion mechanism, and AC maintainer.^[30] The majority of issues affecting DSAEK outcomes stem from the allograft insertion technique. In this regard, great attention has recently been directed toward developing allograft insertion devices to minimize trauma to the allograft tissue during insertion and unfolding, hence diminishing EC loss and AC collapse.

This review aims to compare the designs of various corneal inserters and discusses the performance of these insertion devices by reviewing their construction/design and the results of related clinical studies. Performance factors are considered taking into account ECD loss percentage, AC collapse, ease of use, number of hands required by the surgeon for use, required incision size, reusability and cost. Clinical studies conducted on the injectors are also compared. Although these studies were performed by different surgeons, the comparison is still valid as ECD loss or successful surgery is more dependent on technique and devices rather than surgeon's expertise.^[31] Another factor of variability was the difference in storage times of the donor allografts which are utilized in different clinical studies. However,

a recent study proved that allograft storage time was of little consequence in terms of ECD loss or the success of the DSAEK surgery.^[32] This review will provide helpful information regarding the current market of DSAEK inserter for surgeons and medical device professionals.

ENDOTHELIAL ALLOGRAFT INSERTION DEVICES

Forceps have traditionally been utilized for allograft insertion; however, corneal inserters seem a necessity because corneal allografts inserted using forceps experience more trauma resulting in greater ECD loss. All available inserters have been designed with the primary objective to protect the allograft from folding and reduce incision compression pressure (ICP). Almost all inserters have shown better ECD results in clinical trials as compared to forceps.^[33-38] Allografts inserted with forceps display a definite pattern of trauma such as parallel bands and orthogonal wrinkles due to folding and compression of the tissue during insertion through the incision.^[22] The initial trauma experienced by the allograft is even greater in Asian patients as they have shallow ACs, making allograft insertion and unfolding more challenging.^[39] Reduction in initial endothelial allograft trauma was mainly considered while developing a secure method in which the allograft is protected from ICP and folding effects. The developed insertion devices may broadly be categorized into two groups based on their injection mechanism; namely pull through designs (glides) and push in designs (injectors). Most of these devices require an incision size in the range of 3-5 mm to inject a lamellar allograft with a diameter >8 mm and thickness of 130-240 μm .^[10] This paper will compare the design of three glides and three injectors which are commercially available and extensively used. The glides discussed are Endoglide (Angiotech, Vancouver, BC, Canada), Macaluso inserter (E. Janach, Como, Italy) and Busin glide (Asico, Westmont, IL, USA). The reviewed injectors include Endoserter (Ocular Systems, Winston-Salem, NC, USA), Endoshield/Endoinjector (Keramed, San Jose, CA, USA), and Neusidl injector (Fischer Surgical, Arnold, MO, USA) [Table 1].

ENDOTHELIAL GLIDES

To operate endothelial glides, a corneal allograft is pulled inside the AC from the far side using forceps. This is a two hand technique with the inherent advantage of correct allograft unfolding and orientation inside the AC. The allograft undergoes considerably less trauma during insertion as compared with insertion using forceps. Allograft displacement, however, may occur due to AC maintainer interference. Conditions with high intraocular

Table 1. Characteristics of corneal inserters

Name	Company	Inventor	FDA approved	Incision size (mm)	Disposable/ Reusable	Allograft insertion technique	AC maintainer required	ECD loss (%) (6 months postoperative)
Kobayashi-Busin glide	Asico (Westmont, IL, USA)	Kobayashi and Busin	Yes	5.0	Reusable	Pull in and pull out	Yes	20-47.5
Macaluso inserter	E. Janach (Como, Italy)	Claudio Macaluso	No	4.2	Reusable	Pull in and pull out	Yes	Not reported
Endoglide	Angiotech (Vancouver, BC, Canada)	Donald Tan	Yes	4.0-4.5	Disposable	Pull in and pull out	Yes	13-26
Neusidl corneal inserter	Fischer Surgical (Arnold, MO, USA)	William B. Neusidl	Yes	5.0-5.5	Disposable	Pull in and push out (two-way)	No	13-33
Endoinjector	Keramed (San Jose, CA, USA)	Yichieh Shuey	No	3.2	Disposable	Place in and push out (one-way)	Yes	13
Endoserter	Ocular Systems (Winston-Salem, NC, USA)	Keith A. Walter	Yes	4.0	Disposable	Pull in and push out (two-way)	No	26-31

FDA, food and drug administration; AC, anterior chamber; ECD, endothelial cells density

pressure may lead to AC collapse, complicating graft handling since glides require the use of both hands by the surgeon. Endothelial glides come in different shapes and designs depending on the manufacturer and some of these glides have already received Food and Drug Administration (FDA) clearance.

BUSIN GLIDE

The Busin glide is a 126 mm long all metallic, FDA approved, reusable corneal allograft insertion device which was invented by Kobayashi and Busin. It consists of a handle with a pan at the end. The allograft is placed endothelial side up inside the marked space of the pan. This marked space is 8 mm in diameter, and it aids in proper centering of the allograft. Once the allograft is in correct position, grasping forceps are used to bring the allograft towards the peripheral opening of the device. While proceeding towards the opening, the allograft rolls and takes the shape of the peripheral tip of the device. Having the allograft at the tip, aids in grasping it once the tip of the Busin glide is inside the AC. The nontapered/elliptical peripheral opening of the Busin glide is inserted into the AC through a 5.0 mm incision in the eye [Figure 1].^[40] It has a semicircular cutout, which aids in grasping the allograft once inside the AC. Note that during this procedure AC pressure is maintained via an AC maintainer. The elliptical tip of the Busin glide protects the allograft from ICP and prevents folding of the allograft as well. The maximum diameter of the allograft that Busin glide can hold without overlap is 8 mm. The majority of surgeons place the Busin glide slightly outside the incision, to avoid AC collapse; however, this exposes the allograft to ICP and leads to endothelial trauma. Other surgeons insert the glide inside the incision to save the allograft from ICP; nevertheless, this increases the possibility of AC collapse, which in turn may lead to other complications.^[41] The



Figure 1. Busin glide inserter.

performance of this device is well documented along with ECD loss ranging from 20 to 47.5% six months after the operation.^[33,34,42,43]

MACALUSO INSERTER

The Macaluso inserter is an all metallic reusable glide which is named after its inventor Claudio Macaluso [Figure 2].^[44-46] This device is being used in Europe and has not yet been approved by the FDA for use in the USA. The Macaluso inserter employs a close chamber technique, which aids in maintaining a well formed AC.^[45] The allograft is placed endothelial side up on the concave winglet, and some viscoelastic is applied, the winglet has a circular region marked for assisting in centration of the allograft. The allograft is then grasped with forceps and pulled towards the opening of the insertion device. While proceeding towards the tip, the allograft rolls and conforms to the shape of the device tip. Once the allograft is in a position at the tip, a plunger is used to seal the allograft inside the tip and consequently the allograft and cornea medium are confined in a closed space. The peripheral opening of the device has a tapered elliptical shape with a 'V' shaped cutout to provide easier access for 23 gauge coaxial grasping forceps. A 4.2 mm incision is usually recommended when using this device in DSAEK procedures. Furthermore, at all times during insertion, an AC maintainer is employed to maintain the AC depth. The maximum diameter of the donor allograft that can be held inside the Macaluso inserter is 8-8.5 mm according to the manufacturer. However, what sets this inserter apart from other glides is the provision of a push plunger which seals the system from the environment. Hence, when the device is inserted inside the AC for allograft injection, the AC and inserter act as one sealed system, allowing the AC to remain stable. The metallic body of the Macaluso inserter makes it non-transparent. However, it can be sterilized and reused. There is not a lot of information available in the published literature

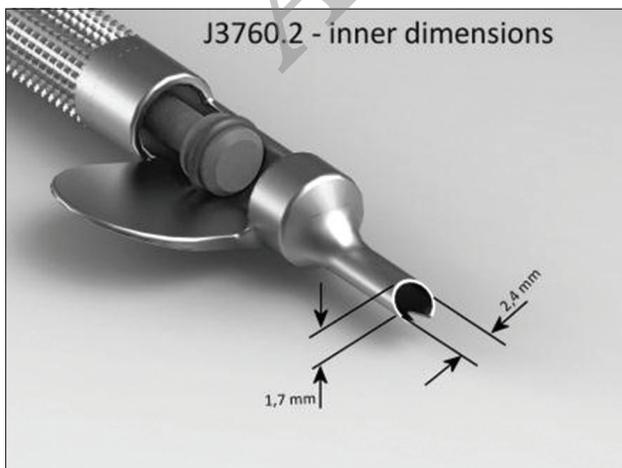


Figure 2. Macaluso endothelial inserter.^[46]

discussing the clinical performance of this device. More research is recommended to assess the postoperative outcomes of this device.

TAN ENDOGLIDE

The Tan Endoglide is an FDA approved, transparent, disposable endothelial allograft inserter invented by Donald Tan. It consists of a preparation base, glide cartridge and glide introducer [Figure 3a].^[37] The allograft is placed endothelial side up on the Endoglide cartridge, which is first slotted into the preparation base, and some lubricating liquid is applied. Grasping forceps are introduced from the tip of cartridge, and the endothelial allograft is pulled inside the cartridge. As the allograft is pulled towards the tip of cartridge, it takes the shape of the tip which induces a "double coil" configuration shape to the endothelial allograft [Figure 3b]. Once the allograft is at the tip, the Endoglide introducer is connected to the back of cartridge, sealing the back end in the process. The Endoglide is then flipped and inserted inside the AC through a 4.0-4.5 mm scleral or corneal incision,^[47] with the AC maintainer already inside the AC. Once the Endoglide is inside the AC, it seals it and creates a closed system. It prevents fluid from flowing out through the incision or the glide itself, and once the glide is in place, grasping forceps are introduced inside the AC from the opposite side and the allograft is gently pulled inside the AC. The tip of the Endoglide is oval in shape and can hold an allograft up to 250 μ m in thickness. However, what sets Endoglide apart is its "double coil" tip shape, which enables this device to use the space more efficiently hence it enables the insertion of a larger diameter allograft through a relatively smaller incision. Various DSAEK clinical studies have been conducted using the Endoglide for allograft insertion, and most of them show less ECD loss as compared to forceps insertion. ECD loss has been reported to range from 13 to 26% six months postoperatively.^[35,37,41]

ENDOTHELIAL ALLOGRAFT INJECTORS

To operate endothelial injectors, a corneal allograft is inserted into the AC using a pushing mechanism.

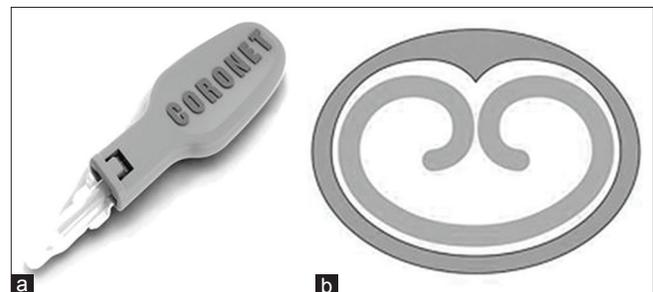


Figure 3. (a) Tan endoglide (b) Double coil.

These are usually single hand operated devices in which the allograft endures considerably less trauma during insertion as compared to forceps insertion.^[34] Some injectors have the added advantage of an inbuilt capability to maintain AC pressure hence an external AC maintainer is not required. The injector body is usually filled or coated with lubricating liquid before the allograft is inserted into the device. The inserted allograft takes the shape of the injector tip as it slides toward the opening. The lubricating liquid helps reduce friction and protects the allograft from damage. Injectors come in different shapes and designs depending on the manufacturer; some of these injectors have already received FDA clearance while others are still waiting.

NEUSIDL CORNEAL INSERTER

This device is named after its inventor William B Neusidl. It is an irrigation incorporated, nontransparent, disposable corneal inserter which is FDA approved [Figure 4].^[48] It consists of a body with a flexible platform upfront where the allograft is placed endothelial side up, once the surface has been lubricated.^[49] The flexible platform is able to hold 8-8.5 mm allografts and ensures that the delivery of the allograft is in the correct orientation; therefore the need for marking the stromal side of the allograft is eliminated. A lever is used to extend the flexible surface, the allograft is placed on this surface and subsequently the lever is used to retract the flexible surface along with the allograft inside the injector. While moving inside the tapered elliptical opening of the device, the allograft conforms to the shape of the inner wall of the elliptical tip and at all times it avoids touching or folding the endothelium. Once the allograft is securely retracted inside, the irrigation is attached and tested. The injector is then rotated such that it is oriented bevel down. In this orientation, the injector is inserted inside the AC through a 5.0-5.50 mm incision.^[36] In fact, the bevel down orientation aids in unfolding of the allograft inside the AC.

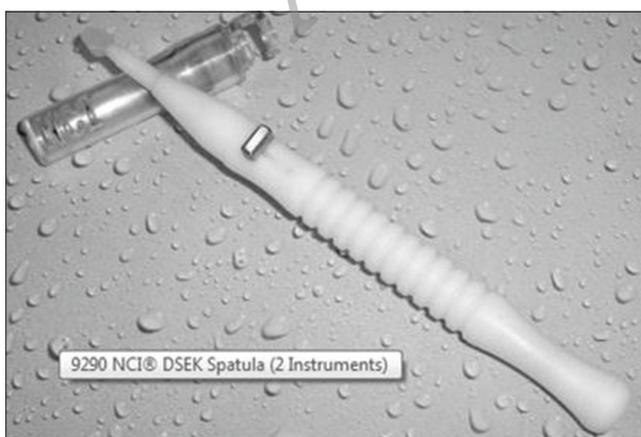


Figure 4. Neusidl injector.

A surgical stop is provided in the device, which results in better sealing of the wound and acts as an indicator for the surgeon confirming that the recommended insertion has been achieved inside the AC. This, however, is a slight generalization since AC dimensions of patients vary slightly. During the insertion of the allograft, the elliptical tip of the device protects the allograft from ICP, and the irrigation pressure ensures a deep chamber. Having a deep chamber is essential since it provides more space for the allograft to unfold which in turn means that the allograft will experience less trauma.^[50] The irrigation provision in the Neusidl inserter is compatible with standard cataract surgery irrigation equipment, hence an AC maintainer is not required. Various DSAEK clinical studies have been conducted using the Neusidl inserter for allograft insertion and most of them show comparable or reduced ECD loss as compared to insertion forceps. ECD loss six 6 months postoperatively ranges from 13 to 33%.^[51] However, some surgeons have highlighted that the allograft occasionally sticks to the platform and requires shaking of the device to get it off.^[36] A lubricant to alleviate this problem would be beneficial.

ENDOINJECTOR

Previously known as the Endoshield, the Endoinjector was invented by Yichieh Shuey. It is a nontransparent, single use corneal allograft inserter, which has the European CE mark approval and is awaiting FDA approval.^[52] It consists of an injector body, injector cartridge, and a foam tip plunger [Figure 5]. The injector cartridge comprises of a central ridge in the cartridge lumen, which guides the allograft to form a double coil as the allograft is advanced, therefore preventing allograft rotation in the process. The balanced salt solution (BSS) soaked allograft is placed endothelial side up inside the loading area, and fluid propulsion is used to guide the allograft forward to the beveled cartridge tip. The Endoinjector has been designed to

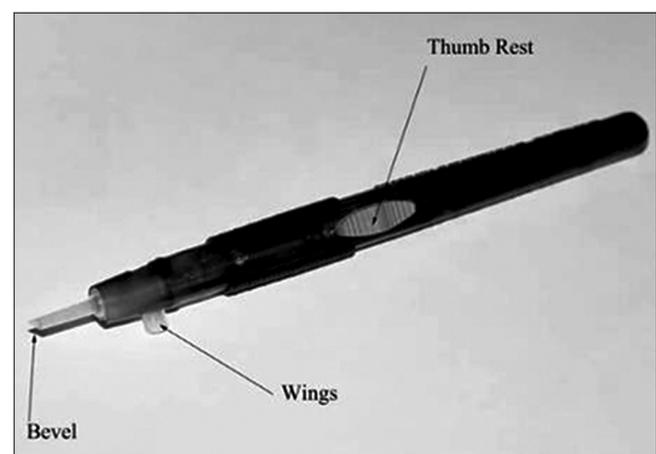


Figure 5. Endoinjector.

atraumatically deliver 8-9 mm allografts inside the AC in the correct orientation.^[52] Once the allograft is placed in the loading area and the wings of the cartridge are closed, the cartridge is loaded in the injector body and the wings are rotated clockwise for a right handed surgeon and vice versa. However, before the cartridge is loaded onto the injector body, Healon and BSS are used to plug and fill the cartridge in order to make the device act similar to a fluid chamber, thus making it a multi-step process. Once the cartridge is ready and loaded onto the injector body, pressure is applied to the thumb rest to move the allograft forward towards the end of the cartridge. Once the allograft is at the tip of the cartridge, an AC maintainer is inserted inside the AC. The Endoinjector is then rotated bevel down and inserted inside the AC through a 3.2 mm corneal incision, this bevel orientation aids in unfolding the allograft inside the AC. During insertion of the allograft, the Endoinjector protects the allograft from ICP, and the AC maintainer ensures a deep chamber. There are few clinical studies utilizing the Endoinjector for corneal allograft insertion in DSAEK. However, one study found the ECD loss to be 13%.^[52] More results of clinical trials seem necessary to be published in the literature using this device for accurate assessment of postoperative outcomes of this device.

ENDOSERTER

The Endoserter is an endothelial allograft insertion device invented by Keith Walter. It is an irrigation incorporated, nontransparent, disposable corneal inserter which is FDA approved [Figure 6].^[53] It consists of a flexible platform where the allograft is placed endothelial side up, once the device has been flushed with BSS by connecting the irrigation tubing to the lower end connector of the Endoserter.^[54] This flexible platform can accommodate allografts 8.5 mm or less in diameter and 175 μ m in central thickness. Besides, it ensures the delivery of the allograft in the correct orientation. A rotating wheel is used to retract the allograft carrier inside the injector. While moving inside the tip of the injector, the allograft conforms to the shape of the inner wall of the beveled tip and at all times touching or folding the endothelium is avoided. The

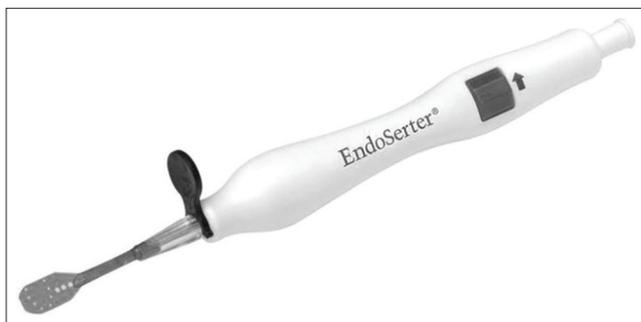


Figure 6. Endoserter.

injector is then rotated bevel down and in this orientation the Endoserter is inserted into the AC through a 4.0 mm incision. This bevel down orientation aids in unfolding the allograft inside the AC. During insertion of the allograft, the Endoserter protects the allograft from ICP, and the irrigation pressure ensures a deep chamber. The irrigation provision in the Endoserter is compatible with standard cataract irrigation equipment. A recent DSAEK clinical study conducted using the Endoserter reported a mean ECD loss of 29% six months postoperatively.^[36] More results of clinical studies/trials need to be published in the open literature using this device so that its postoperative outcomes can be assessed.

DISCUSSION

DSAEK is an evolving procedure which has already demonstrated many advantages over traditional PK and is gradually becoming the procedure of choice among surgeons. Some challenges regarding its implementation still exist, which are being addressed to some extent with the use of endothelial inserters, since forceps have inherent limitations. Using forceps is a simple technique; however, forceps apply excessive pressure at the points of contact and do not protect the allograft from ICP, leading to higher postoperative ECD loss. Through the present review, it can be safely concluded that each of the six reviewed inserters has its own advantages and limitations regarding ECD loss, the probability of AC collapse, ease of use, number of hands required by the surgeon for usage, required incision size, reusability and cost [Table 1]. However, the primary objective of every inserter is to reduce the amount of trauma experienced by the allograft in order to reduce ECD loss sustained during the surgical procedure. All corneal inserters discussed in this review showed better postoperative ECD results as compared to traditional forceps. Endoglide, Endoinjector and Neusidl corneal inserters seemed to show better ECD results than all three injectors registering a minimum of 13% ECD loss according to published data.

Apart from ECD loss, another important issue faced by surgeons is flipping of the donor allograft inside the AC. Since visibility is low inside the AC, flipping of donor allograft poses a significant complication which may result in failure of the DSAEK procedure. All the six inserters discussed herein address this issue properly; however, since grasping forceps are used to insert donor allografts in glides, therefore glides have an almost perfect chance of donor allograft unfolding in the correct orientation. Some surgeons write, "S" or "Z" on the stromal side of the donor allograft so that they can unfold the allograft in the correct orientation in the AC. Nevertheless, the writing ink contains alcohol, which may seep through the stroma and damage ECs.^[55] Thus, it would be best to avoid it altogether or the surgeon should write the letter on his glove or use a stamp, wait

till the alcohol evaporates and then use it as a branding stamp to mark the donor allograft.^[56] The postoperative ECD comparison results presented in this review provide a valuable overview of commercially available DSAEK inserters and present a much required perspective regarding DSAEK allograft inserters. However, current ECD results were acquired from clinical studies which involved patients from different demographics and utilized different mechanisms to measure postoperative ECD such as specular microscopy and vital dye staining with use of graphic software. Consequently, the comparisons made between the inserters lack a common denominator. To accurately compare ECD loss efficiency with these inserters, all six of them should be used in a single study in the future. At present, most clinical studies have not yet involved more than two DSAEK allograft inserters therefore a study employing and comparing all commercially available inserters seems necessary. Such a study will be able to act as a benchmark regarding inserter comparison and will aid in identification of the inserter that imparts the least trauma to the allograft. Furthermore, trauma patterns can be studied and correlated with allograft insertion parameters such as orientation angle and insertion speed, and hence techniques can be refined and standardized.

Apart from prevention of ECD loss and correct allograft unfolding, other factors of note in DSAEK are AC maintainer requirement and incision size. Both of these factors are of significance and to some extent correlated since a bigger incision leads to hypotony, invariably leading to AC collapse and allograft failure. A smaller incision reduces the probability of AC collapse and requires less sutures thereby reducing surgery time. Among the inserters reviewed herein, the Endoinjector requires the smallest incision size of 3.2 mm. All of the inserters in the present paper require an AC maintainer, except the Neusidl inserter and Endosserter. An inserter which does not require an AC maintainer is a definite advantage; however, a smaller incision size may be considered as a two-edged sword since on one hand it means less or no sutures and less chance of AC collapse, while on the other hand it entails more ECD loss.^[30,43] An optimum inserter head size/incision size needs to be investigated and studied. This knowledge will improve DSAEK outcomes, make it more streamlined and hence easier for inexperienced surgeons to adopt.

In summary, DSAEK is a relatively new and evolving surgical procedure with a respectable success rate. However, there is still room for improvement to achieve more ideal postoperative visual outcomes. Hence, corneal inserters, as compared to forceps, should be adopted since they seem to be promising for preventing complications, improving surgical outcomes and reducing the learning curve associated with the surgery. The inserters reviewed in this paper have their own advantages and limitations, therefore further studies/research on their efficacy should

be performed. The results or feedback from these studies may assist to improve the designs of existing inserters and develop new inserters with the capability to address all prevailing issues.

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