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**A New Graft Insertion Device for Descemet Stripping Automated Endothelial
Keratoplasty.**

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SHORT TITLE: A new graft insertion device for DSAEK

KEYWORDS: cornea, corneal endothelium, endothelial keratoplasty, DSAEK,

DISCLOSURES: Drs. Soma and Nishida, in conjunction with HOYA Japan, have filed for a worldwide a patent (code PCT/JP2011/067665, PCT/JP2015/055624) for the one-step corneal graft delivery system as described in this manuscript. Mr. Mitomo is an employee of HOYA Surgical Optics. The other authors have no commercial or proprietary interest in the products or companies mentioned in the current article.

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ABSTRACT

Purpose: Corneal endothelial dysfunction is a major indicator for corneal graft surgery worldwide, and whilst surgical intervention via a range of posterior lamellar surgeries has proven to be hugely beneficial, challenges remain. This is especially so where the anterior chamber is relatively shallow, as is often the case in the Asian population, though not exclusively so. Here, we introduce a new insertion device to deliver endothelial graft tissue for Descemet stripping automated endothelial keratoplasty (DSAEK).

Methods: A new surgical tool was designed and manufactured so as to enable a one-step insertion of corneal graft tissue into the anterior chamber based on a pressure-flow concept, rather than the a pull-through one. This was tested *ex vivo* to assess endothelial cell damage, then performed in 12 first-in-man surgeries.

Results: Pre-cut DSAEK lenticules implanted in donor corneas *ex vivo* via the new technique showed less endothelial cell damage occurs compared to a pull-through technique. Grafts were successful in all patients receiving the new surgery, with no cases of primary graft failure.

Conclusion: The newly developed DSAEK inserter is a simple and useful tool for endothelial graft delivery, lessening intraoperative mechanical stress on the graft tissue

INTRODUCTION

1
2 Although Descemet's membrane endothelial keratoplasty (DMEK)¹ has been
3 supplanting Descemet stripping automated keratoplasty (DSAEK) in recent years,
4 leading to faster visual rehabilitation and better visual outcome, graft detachments,
5 failures and difficulties manipulating the delicate tissue are associated risks, which
6 may in part account for the situation that established DSAEK surgery is often
7 preferred to DMEK. In DSAEK, however, folding and grasping the donor tissue with
8 forceps or pull-through technique using glides to enable graft insertion through a
9 small incision can represent a challenge,²⁻⁴ and this is particularly so in Asian eyes,
10 which tend to have shallower anterior chambers. One significant complication with
11 DSAEK is endothelial cell loss, especially in the early postoperative period.⁵⁻⁷
12 Consequently, there is a growing demand for a surgical graft delivery system for
13 DSAEK that allows for easy manipulation of graft tissue, whilst also minimizing
14 mechanical stress on the graft and helping prevent anterior chamber collapse during
15 surgery. Partially in response to this need, techniques such as the Sheets glide
16 insertion method and the Tan Endoglide were specifically developed for Asian eyes,
17 and their utility has been reported.^{8,9}

18 In cataract surgery, the shift away from intraocular lens (IOL) insertion using
19 forceps to graft insertion using injectors has undoubtedly contributed to improved

20 outcomes. In DSAEK, the superiority of graft insertion devices over forceps has not
21 been demonstrated unequivocally,¹⁰⁻¹² nevertheless, the use of insertion devices has
22 become increasingly popular in recent years. Essentially, DSAEK insertion devices
23 can be categorized into three groups based on their mechanism of action; the folding
24 technique (i.e. taco-folding), pull-through designs (glides) and push-in designs
25 (injectors).¹³ By applying the fundamental concept of an IOL injector to the DSAEK
26 insertion device, we have developed a new surgical tool in which the donor graft is
27 introduced into anterior chamber along with a steady flow of balanced salt solution
28 (BSS). Here, we describe the device's design, mode of action, and use in 12 first-in-
29 man surgeries.

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METHODS

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Device Design and Surgical Technique

33 The new DSAEK graft inserter consists of the main body of the device, which is
34 made of polypropylene, with a hydrophilically coated and flexible polyethylene
35 platform at its front end on which the pre-cut graft lenticule is placed just prior to
36 surgery, endothelial cells facing upwards. A movable polypropylene cartridge is fitted
37 to the main body, along with a valved conduit made of silicone rubber. A 2.5ml
38 syringe, to be filled with BSS prior to surgery, is continuous with the main body of the

39 inserter. Overall, the device measures 8.5 mm in width, is 63 mm long, and weighs
40 1.85 g. The major and minor axes of the lumen of the new inserter's nozzle are 3.57
41 mm and 2.02 mm, respectively. It is intended for single use (Figure 1).

42 To operate, the syringe is first filled with BSS after which the plunger is
43 partially depressed to lubricate the surface of the hydrophilic platform with BSS. The
44 DSAEK graft is then carefully placed onto the platform (Figure 2A), endothelial cells
45 facing upwards, using forceps. Importantly, the surface of the graft insertion platform
46 remains lubricated owing to the hydrophilic nature of the platform's coating, which is
47 a key design feature to prevent the graft from adhering to the platform. After the graft
48 coated with viscoelastic gel is in place on the platform, the flexible platform and graft
49 are partially rolled up and drawn within the main body of the inserter by steadily
50 moving the cartridge forward (Figure 2B). This is achieved via another important
51 design feature, i.e. a valved conduit located on the inner tube of the movable
52 cartridge. Thus, when the cartridge is moved forward over the platform holding the
53 graft, a negative pressure is generated which keeps the graft in position as the
54 flexible platform is partially rolled up and enclosed in the inner cylinder of main body
55 of the device. This closed system for fluid flow has an additional benefit in that it
56 prevents anterior chamber collapse when delivering the corneal graft into the
57 recipient's eye. Prior to inserting the graft into the recipient's eye the insertion device

58 is rotated 180 degrees around its axis, so that the corneal endothelial cells on the
59 inner aspect of the partially rolled-up lenticel face away from the posterior corneal
60 surface once injected into the anterior chamber. During graft insertion through a pre-
61 made, 4.6 mm incision in the peripheral cornea, the leading edge of the cartridge tip
62 of the inserter enters the anterior chamber, but is not projected deeply into the
63 chamber. The graft can then be delivered into anterior chamber, along with BSS, by
64 gently depressing the syringe's plunger (Figure 2C). The graft moves readily into the
65 anterior chamber because water molecules retained on the hydrophilic polymers of
66 the platform on which it sits work as carrier to allow the graft to slip smoothly across
67 and off the platform once the flow of BSS is started.

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69

Ex Vivo Testing

70 A single donor cornea, obtained from the SightLife Eye Bank (Seattle, WA, USA) was
71 used as an *ex vivo* proxy to represent the recipient tissue. This was secured on an
72 artificial anterior chamber (K20-2125 Barron Artificial Anterior Chamber, Katena,
73 Denville, NJ, USA). A 20 gauge chamber maintainer (#19092, Moria) was used to
74 maintain the tissue's shape, after which a 5.0 mm corneal incision was created in the
75 corneal periphery to allow graft insertion. Ten research pre-cut corneal lenticules
76 from the same Eye Bank were obtained, and DSAEK was carried out in 10 test

77 surgeries; five using the new DSAEK insertion system and five using a 5.0 mm Busin
78 spatula (#19098, Moria, Doylestown, PA) and the pull-through technique. The mean
79 thickness of pre-cut donor grafts used for the pull-through Busin glide surgery was
80 113 ± 11 µm (average ± SD, range; 96-124 µm); for the inserter test-surgeries it was
81 126 ± 22 µm (range; 98-149 µm). Donor lenticules were 8 mm in diameter. After
82 each procedure the graft tissue was removed from the anterior chamber and stained
83 with 0.25% alizarin Red S and 4 % trypan blue for 90 s to assess the general level of
84 endothelial cell damage¹⁴ using Image J in accordance with method of Saad and
85 associates.¹⁵

86

87

Clinical Applicability

88 Twelve patients underwent DSAEK with the new insertion device between July 2016
89 and Jan 2017, after which intra- and early postoperative outcomes were examined.
90 Underlying diseases were cytomegalovirus endotheliitis (3 eyes), pseudophakic
91 bullous keratopathy (2 eyes), post intraocular surgery (2 eyes), exfoliation syndrome
92 (2 eyes), Fuchs' endothelial corneal dystrophy (2 eyes), and argon laser iridotomy-
93 induced bullous keratopathy (1 eye) and the average observation period was 172
94 days ± 62 days (range, 89-265 days). In particular, we sought signs of a failure of the
95 graft tissue to be smoothly and successfully inserted into the eye, of anterior

96 chamber collapse during surgery, and of graft dislocation or detachment afterwards.

97 The work adhered to the tenets of the Declaration of Helsinki and was approved by

98 the institutional review board of Osaka University Hospital.

99 All surgeries were performed by one of two surgeons (T.S., K.N.), both of

100 whom had previously used a Busin glide to conduct DSAEK, either under local

101 retrobulbar anasthesia and facial nerve block or under general anaesthesia. Pre-cut

102 donor corneas (target thickness, 100 μ m) from SightLife Eye Bank were used in all

103 cases. After the anterior chamber maintainer was set-up, Descemet membrane and

104 the endothelium were stripped from the recipient's central cornea (this step was

105 omitted in the case of non-Descemet stripping automated endothelial keratoplasty

106 (nDSAEK)).¹⁶ An inferior peripheral iridectomy was then created with 25-gauge

107 vitreous cutter, and two nasal and temporal vent incisions were fashioned at the

108 inner side of the recipient corneal marking. Following its trephination, the donor graft

109 was placed on the flexible, hydrophilic graft insertion platform of the new inserter.

110 After applying dispersive ophthalmic viscoelastic material (Viscoat; Alcon

111 laboratories, Fort Worth, TX) over the entire endothelial graft, the platform and graft

112 were rolled up and enclosed into the main body of the device by sliding the movable

113 cartridge forward. (Figure 2 and Supplementary Information 1). As mentioned earlier,

114 as a result of the negative pressure exerted by the inserter, the lenticule is rolled up

115 and engulfed into the main body of the device (while still on the flexible hydrophilic
116 platform) without being touched with forceps or any other surgical tool. Also, we note
117 here that after the placement of the graft on the platform (the last time it is contacted
118 physically) it should be coated with a dispersive ophthalmic viscosurgical formulation
119 rather than a cohesive form to lessen the risk of clumps of material being flushed into
120 the anterior chamber when BSS flow is initiated. Once the graft had been loaded into
121 the inserter, the nozzle was placed into anterior chamber through the 4.6 mm
122 temporal corneoscleral tunnel and the graft delivered into the anterior chamber along
123 with a flow of BSS by simply depressing the plunger of the syringe. The anterior
124 chamber maintainer was turned off during graft insertion (Figure 2 and
125 Supplementary Information 1), its use only being needed during the peripheral
126 iridectomy using vitreous cutters and Descemetorhexis. After removal of the insertion
127 device an air tamponade was performed to ensure good graft-host apposition. All
128 patients held their posture facing upward on their beds for three hours following the
129 operation.

130

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RESULTS

132

Preliminary *ex vivo* test surgeries established the successful working of the

133

procedure and the new insertion device. Figure 3 shows the post-operative corneal

134 staining patterns for all 10 test surgeries, five conducted using the Busin glide and
135 five with the new inserter. No unusual staining characteristics of note were detected
136 in the corneas following surgery with the new inserter. Average endothelial cell loss,
137 calculated as pixels in the endothelial damage area divided by pixels in the whole
138 area x 100%, was 10.8 ± 2.7 % in the new inserter group and 23.9 ± 2.0 % in the
139 Busin glide group, pointing to the clinical promise of the new DSAEK inserter.

140 All twelve surgeries in patients using the new DSAEK inserter were
141 successful and uneventful. Donor grafts were smoothly inserted into anterior
142 chamber in all cases, and in no cases did an anterior chamber collapse occur. All
143 grafts became successfully attached with no incidences of graft dislocation or
144 detachment, postoperatively. No primary graft failures occurred in the immediate
145 postoperative period.

146

147

DISCUSSION

148 Although endothelial cell loss after DSAEK is reported to be influenced by both donor
149 and recipient factors,¹⁷ it is widely accepted that donor tissue manipulation during
150 surgery can directly contribute to cell loss and damage. Currently, the pull-through
151 technique is a standard procedure for DSAEK and one of the most widely used
152 devices is the Busin Glide. In this approach, a rolled-up donor graft is delivered into

153 anterior chamber and spontaneously opens, causing less endothelial cell damage
154 compared to the taco-folding method.¹⁸⁻²⁰ However, pull-through techniques are
155 accompanied by the risk of anterior chamber collapse during graft insertion, and this
156 can occur too often in the eyes of Asian patients, in which the angle tends to be
157 narrow and the anterior chamber depth shallow. In the new surgery, described here,
158 a combination of the negative pressure, which allows the graft lenticule to become
159 incorporated within the new surgical device without the need for mechanical
160 manipulation, aligned to the hydrophilic nature of the flexible platform's surface,
161 ensuring that the graft moves smoothly off the platform in the absence of any need to
162 pull-through, means that mechanical contact with the graft tissue during the
163 procedure introduced here is minimised, thus reducing the likelihood of graft trauma.

164 Commercially available surgical insertion tools for DSAEK, which are based
165 on push-in designs include the Neusidl corneal injector (Fischer Surgical, Arnold,
166 MO, USA) and the Endoserter (Ocular Systems, Winston-Salem, NC, USA).¹⁴ Both
167 are single use devices, and several studies have reported the clinical outcomes of
168 their use.^{10,11,21} These devices have a platform which holds the donor graft tissue, as
169 does ours. However, neither of the aforementioned designs incorporates a negative
170 pressure system to help hold the graft on the platform, so there is a risk that the graft
171 can become inadvertently dislodged from its proper position on the platform during

172 surgical manipulation. DSAEK with all injector devices requires the platform to be
173 introduced into the anterior chamber to deliver the graft, however, the negative
174 pressure feature of our new inserter means that, unlike with the Neusidl and
175 Endoserter devices, we do not need to perform continuous anterior chamber
176 irrigation. This is a significant advantage because continuous irrigation increases the
177 intraoperative pressure within the anterior chamber, which can lead to the unwanted
178 situation whereby the graft accidentally flows out of the anterior chamber through the
179 incision as the insertion device is being removed. The new DSAEK device described
180 here utilizes the flow of BSS for graft injection into the anterior chamber. Only a small
181 volume of BSS (approximately 0.1 ml) is required, and this carries along with the
182 unfolding graft lenticule to achieve graft insertion in a quick and simple one-step
183 action.

184 A clinical trial of this approach in a larger number of the patients has been
185 initiated to extend the results presented here. The aim is to enhance the application
186 of DSAEK to eyes, especially those at risk of endothelial cell damage because of a
187 shallow anterior chamber. In summary, initial first-in-man studies indicate that the
188 new graft inserter can provide for endothelial graft delivery for DSAEK without
189 anterior chamber collapse and can results in successful graft attachment.

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FIGURE LEGENDS

FIGURE 1.

Photographic and schematic images of the new DSAEK insertion device. **(A)** Without and **(B)** with the syringe attached. **(C)** A valved conduit made of silicone rubber located on the inner tube of the movable cartridge.

FIGURE 2.

(A) DSAEK graft is placed onto the platform. **(B)** By sliding the movable cartridge forward the flexible platform and graft are rolled-up and drawn into the inserter via the effect of negative pressure. **(C)** The graft can be easily delivered into the anterior chamber, carried along by the flow of BSS flow simply by depressing the syringe plunger.

FIGURE 3.

Corneal staining patterns after use of **(A)** the new inserter and **(B)** a Busin glide in 10 *ex vivo* test DSAEK surgeries. No unusual staining patterns are seen after a test-surgery with the new inserter, and the area of endothelial cell damage compares favorably to that which resulted from Busin glide surgery.