Clinical Outcomes of Nanothin Descemet Stripping Automated Endothelial Keratoplasty in Korean patients with Corneal Endothelial Dysfunction

Ye Eun Han¹; Ho Seok Chung¹,²; Hun Lee¹; Jae Yong Kim¹; Hungwon Tchah¹*
¹Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
²Department of Ophthalmology, Dankook University Hospital, Dankook University College of Medicine, Cheonan, Republic of Korea

Corresponding author: Hungwon Tchah, MD, PhD
Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine
88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea
Tel: +82-2-3010-3680
Fax: +82-2-470-6440.
E-mail: hwtchah@amc.seoul.kr
INTRODUCTION

The recent evolution in corneal transplantation has provided a more selective replacement of the cornea. Particularly, the use of posterior lamellar keratoplasty (PLK) to replace only the dysfunctional endothelium and Descemet membrane has become a standard treatment for corneal endothelial dysfunction (CED). In previous studies, PLK was associated with faster recovery, improved visual outcome, and better globe stability compared to penetrating keratoplasty [1,2].

The two main techniques used in PLK are Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK). Although the overall visual outcomes and rejection rates of DSAEK are relatively inferior to those of DMEK [2,3], DSAEK remains the most commonly performed technique in PLK [4]. This may be because DMEK is technically challenging in graft manipulation [5] and is generally contraindicated in eyes with anatomical abnormalities [6,7].

The inferiority in the postoperative visual acuity and rejection rates of DSAEK is mainly because DSAEK grafts are thicker and contain variable degrees of donor stromal tissue in addition to the Descemet membrane and endothelium, compared with DMEK grafts [8]. Previous studies have suggested that a thinner DSAEK graft minimizes residual stroma and may provide faster visual recovery, better final visual acuity, and less immunologic rejection [6]. Moreover, one recent study reported that DSAEK using nanothin grafts (50 µm or thinner) provided visual outcomes comparable to those of DMEK [9]. In this context, using DSAEK grafts to a nanothin degree has become a current trend in performing endothelial keratoplasty in CED patients. However, to the best of our knowledge, no study has been reported regarding nanothin DSAEK in Korean patients. Therefore, this study aimed to evaluate the clinical outcomes of nanothin DSAEK in Korean patients.

MATERIALS AND METHODS

We conducted a retrospective medical chart review of patients who underwent DSAEK for CED using nanothin grafts (50 µm or thinner) by a single surgeon and followed up for more than one year from July 2019 to October 2021 at the Asan Medical Center. This study was approved by the institutional review boards of the Asan Medical Center and the University of Ulsan College of Medicine, Seoul, South Korea (Approval number: 2021-0774), and the need for informed consent was
waived due to the retrospective nature of the study. This study adhered to the tenets set forth in the Declaration of Helsinki.

**Donor Graft Preparation**

The DSAEK grafts were prepared by the Eversight Eye Bank (Chicago, IL, USA). The selection criteria for the donor tissues were as follows: (1) no previous ocular diseases, (2) a minimum corneal endothelial cell density (ECD) of 2000 cells/mm², and (3) a maximum time gap of 7 days between donor death and surgery. We ordered the prepared precut grafts to achieve a 40-μm thickness. The grafts were trephined from 8.0 to 8.5 mm in diameter during surgery.

**Surgical Procedure**

All the patients received topical anesthesia with 0.5% proparacaine hydrochloride eye drops (ALCAINE®; Alcon, USA). Cataract surgery (cataract extraction and intraocular lens insertion) was performed before DSAEK for patients with cataracts (n=3; 18.75). A peripheral side-port incision was made by MVR blade (Alcon, USA), through which an anterior chamber maintainer (ACM; Alcon, USA) was introduced. The continuous low flow of balanced salt solution (Alcon, USA) from ACM maintained the anterior chamber. The recipient’s Descemet membrane was stripped with a reversed Sinskey hook (Katena Products, Inc., USA) via a 4-mm sclero-corneal incision along with an 8.0-mm corneal surface marking. The prepared donor graft was folded over with the endothelial side facing inward and inserted into the anterior ocular chamber with an EndoSerter® (Ocular Systems Inc., USA) through a 4-mm sclero-corneal incision. After insertion, the graft was then dragged using a reversed Sinskey hook for centering. The ACM was removed and a 4-mm sclero-corneal incision was sutured and sealed. Sterile air was injected to unfold and attach the graft to the recipient's stroma or Descemet membrane. Partial air filling (75% to 80% of the anterior chamber volume) and intraocular pressure (IOP) measurement using a Tono-Pen AVIA® tonometer (Reichert, Inc., USA) were performed until a target pressure of 15–20 mmHg was achieved. After the patient was maintained in an absolute supine position for at least 3 h, the graft location and IOP were rechecked using a portable slit-lamp (Kowa American corporation, USA) and the Tono-Pen AVIA® tonometer. The surgeon performed partial air evacuation by anterior chamber paracentesis for increased IOP or rebubbling for graft dislocation. Postoperative medications included topical antibiotics (moxifloxacin
0.5%; VIGAMOX®; Norvatis, Japan) and steroid (prednisolone acetate 1%; Pred Forte®; Allergan, Ireland) eye drops four times a day for 1–2 months. Thereafter, the administration frequency was gradually reduced until it was discontinued 6 months postoperatively.

**Measurements**

The following variables were analyzed in each patient: (1) demographic variables (i.e., age, sex, and follow-up duration); (2) ocular characteristics (i.e., preoperative diagnosis and previous history of ocular disorders; (3) donor graft properties (i.e., graft thickness and endothelial cell count); (4) surgical procedures; (5) ophthalmologic examinations before surgery and 1, 3, 6, and 12 months after surgery (i.e., best corrected visual acuity [BCVA] measured by the logarithm of the minimum angle of resolution [logMAR], donor graft and central corneal thickness [CCT] by anterior segment optical coherence tomography [AS-OCT; Visante OCT, Carl Zeizz, Germany], and corneal ECD by specular microscopy [CellChek SL, Konan corp., Japan]); and (6) postoperative complications.

**Statistical Analysis**

Descriptive statistics are presented as percentages for categorical variables and as means ± standard deviations for continuous variables. Shapiro-Wilk normality test proved all continuous variables follow a normal distribution ($P > 0.05$). Repeated measures ANOVA was used to evaluate the differences between pre- and postoperative variables, including the BCVA, CCT, and ECD. A $P$-value of $< 0.05$ was used to determine statistical significance. All the statistical analyses were performed using SPSS software version 21.0 (IBM Corp., Armonk, NY, USA).

**RESULTS**

Sixteen eyes of 16 patients were included in this study. The demographics and clinical details of the patients are described in Table 1. The mean age of the patients was $61.18 ± 12.49$ years with a female-to-male ratio of 12:4. The mean follow-up period was $13.00 ± 0.96$ months (range: 12–15 months). The preoperative diagnoses included pseudophakic bullous keratopathy ($n=7; 43.75\%$), bullous keratopathy of unknown origin ($n=2; 12.50\%$), pseudoexfoliation syndrome ($n=1; 6.25\%$), posterior polymorphous corneal dystrophy ($n=1; 6.25\%$), Herpes endothelitis ($n=1; 6.25\%$), iridocorneal endothelial syndrome ($n=1; 6.25\%$), toxic anterior segment syndrome ($n=1; 6.25\%$), and
previous DSAEK graft failure (n=2; 12.50%). The mean donor graft thickness and graft ECD after precut processing were 47.71 ± 7.91 μm (range: 38.0–68.0 μm) and 2859.62 ± 228.34 cells/mm² (range: 2545–3390 cells/mm²), respectively. It should be noted that measuring graft thickness shortly after the cutting process or surgery may not precisely reflect its actual thickness because the graft is usually in an edematous state at that time. Therefore, we remeasured the graft thickness via AS-OCT at 3 months postoperatively. After deswelling, the average thickness was demonstrated to be 45.25 ± 4.59 μm (range: 38.0–50.0 μm) (Table 2).

The mean logMAR BCVA improved from 1.37 ± 0.53 preoperatively to 0.68 ± 0.46, 0.55 ± 0.35, 0.40 ± 0.25, and 0.39 ± 0.25 at 1, 3, 6, and 12 months postoperatively (P=0.005, P<0.001, P<0.001, and P<0.001), respectively (Table 3) (Figure 1). The mean CCT improved from 752.00 ± 129.11 μm to 592.57 ± 66.95 μm, 558.38 ± 64.12 μm, 549.67 ± 55.44 μm, and 555.75 ± 54.66 μm at 1, 3, 6, and 12 months postoperatively (P=0.007, P=0.004, P=0.002, and P=0.006, respectively) (Table 4) (Figure 2). The mean donor ECD decreased from 2859.62 ± 228.34 cells/mm² preoperatively to 2069.90 ± 613.75, 1872.00 ± 644.39, 1554.16 ± 577.23, and 1542.25 ± 627.34 cells/mm² at 1, 3, 6, and 12 months postoperatively (P=0.294, P=0.106, P=0.015, and P=0.012), respectively (Table 5) (Figure 3). Figure 4 shows an example of the ophthalmologic examination of an eye before and 12 months post-nanothin DSAEK.

The most common adverse event was increased IOP (n=3; 18.75%), followed by graft dislocation (n=1; 6.25%). No other adverse events were encountered. All of the increased IOP events were caused by intraoperative air over-filling, resulting in a pupillary block, and successfully controlled with partial air removal by anterior chamber paracentesis. Graft dislocation was also successfully reattached via rebubbling.

DISCUSSION

In this one-year follow-up study, we demonstrated that nanothin DSAEK provided significant visual acuity improvements without inducing serious adverse events. With respect to visual outcomes, our study showed that nanothin DSAEK provided a mean logMAR BCVA improvement from 1.37 ± 0.53 preoperatively to 0.39 ± 0.25 at 12 months postoperatively. Tourabaly et al. [10] reported visual outcomes of PLK according to the graft thickness: the mean logMAR BCVA improved from 0.97 to 0.14 after conventional DSAEK (150–250 μm), from 0.84 to 0.14 after thin DSAEK (100–149 μm),
from 0.84 to 0.16 after ultra-thin DSAEK (50–99 µm), from 0.85 to 0.11 after nanothin DSAEK (15–49 µm), and from 0.48 to 0.09 after DMEK at more than 6 months postoperatively. Kurji et al. [9] also concluded that the mean logMAR BCVA improved from 0.32 ± 0.16 to 0.07 ± 0.09 after DSAEK and from 0.33 ± 0.19 to 0.07 ± 0.11 after DMEK at 12 months postoperatively. A recent meta-analysis [11] found that the 12-month postoperative mean logMAR BCVA of DSAEK was 0.35 (range: 0.2 to 0.45), whereas that of DMEK was 0.14 logMAR better (95% CI: -0.18 to -0.10). Compared with those previous reports, our nanothin DSAEK resulted in a greater mean BCVA improvement (-0.98 logMAR better than baseline BCVA at 12 months postoperatively) than any other types of DSAEK techniques or even DMEK. However, the absolute value of the final BCVA in our patients was not superior to that of other study populations. We assumed that this was because our patients had poorer baseline BCVAs than other study populations.

Previous studies reported endothelial cell loss from 32% to 39% at 12 months after conventional DSAEK [12,13]. Excessive graft manipulation causing graft trauma has been considered the main cause of lower endothelial cell count, although not significant, in DSAEK- versus PKP-treated eyes [14]. In this study, nanothin DSAEK showed a continuous decrease of endothelial cell density during the postoperative follow-up period. The endothelial cell loss became significant at 6 months postoperatively and reached about 50% at 12 months postoperatively, which was greater than that of conventional DSAEK in previous reports. We assumed that it was because the nanothin DSAEK graft is thinner and therefore more difficult to handle than conventional DSAEK graft. This result also suggests that a longer observation period, longer than one year, is needed to evaluate possible additional endothelial cell loss. However, despite the significant postoperative endothelial cell loss, most grafts remained clear without increasing the CCT.

According to a large multicenter retrospective study, the common postoperative complications of conventional DSAEK were graft dislocation (23%), graft failure (18%), graft rejection (6%), and increased IOP (2%) [15]. Compared with the previous reports, our nanothin DSAEK showed higher prevalence in increased IOP (n=3; 18.75%) and lower prevalence in graft dislocation (n=1, 6.25%), all of which were successfully resolved by anterior paracentesis or rebubbling. In addition, there were no other serious complications until 12 months postoperatively. Based upon these results, we assumed that complications of nanothin DSAEK may occur but can be managed by relatively simple procedures. Moreover, in accordance with a previous study [9], our nanothin DSAEK
also did not experience immunologic rejection. We believe immunologic rejection in nanothin DSAEK is less likely to occur because the endothelial graft rejection rate is related to the amount of residual stromal tissue. The reported mean endothelial graft rejection rates are approximately 10% in conventional DSAEK [16], 2.8% in ultra-thin DSAEK [17], and 0% for both nanothin DSAEK and DMEK [9].

In this study, the nanothin DSAEK technique itself was not very different from conventional DSAEK, except for the following step: For graft positioning during conventional DSAEK, it is generally recommended to perform complete air filling for 10 mins with the IOP ranging from 40 mmHg to 50 mmHg, followed by removing 20% to 25% of the air [18]. However, during our nanothin DSAEK, the surgeon performed a partial air-fill only, resulting in successful graft adherence. We assumed that the nanothin DSAEK graft is thinner and therefore lighter than a conventional DSAEK graft, requiring a relatively small amount of buoyance for its adhesion to the recipient cornea.

There are several limitations in this study. First, this study included a small number of patients, resulting in limited statistical power. Second, this study only included patients who underwent nanothin DSAEK; therefore, direct comparisons between nanothin DSAEK and other PLK techniques were not feasible. Third, not all patients underwent the same surgical procedures: some underwent cataract surgery with DSAEK, but others only received DSAEK. Ultimately, large-scale comparative studies investigating the clinical outcomes of nanothin DSAEK and thicker DSAEKs and DMEK over a long-term follow-up period are necessary to corroborate the effectiveness of nanothin DSAEK. Nevertheless, this study is significant because it is the first to investigate the surgical outcomes of nanothin DSAEK in Korea.

In conclusion, this one-year follow-up study showed that nanothin DSAEK produced significant and stable visual improvements without serious postoperative complications. We expect that nanothin DSAEK could be a helpful treatment option for Korean patients with CED.

DECLARATIONS

Source of funding

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Financial Disclosures: none

Acknowledgments: none
References


Table 1. Demographic and clinical characteristics of study subjects

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<tr>
<th>Demographics</th>
<th>Range</th>
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<tr>
<td>Age* (years), Mean ± SD</td>
<td>61.18 ± 12.49</td>
</tr>
<tr>
<td>Male:Female ratio (N:N)</td>
<td>12:4</td>
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<tr>
<td>Pseudophakia (N, %)</td>
<td>13 (81.25)</td>
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<table>
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<tr>
<th>Diagnosis</th>
<th>No. of Eyes (%)</th>
</tr>
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<tr>
<td>PBK</td>
<td>7 (43.75)</td>
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<tr>
<td>BK of unknown origin</td>
<td>2 (12.50)</td>
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<tr>
<td>PXS</td>
<td>1 (6.25)</td>
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<tr>
<td>PPMD</td>
<td>1 (6.25)</td>
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<tr>
<td>Herpes endothelitis</td>
<td>1 (6.25)</td>
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<tr>
<td>ICE syndrome</td>
<td>1 (6.25)</td>
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<tr>
<td>TASS</td>
<td>1 (6.25)</td>
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<tr>
<td>Previous DSAEK graft failure</td>
<td>2 (12.50)</td>
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*Age at time of surgery

(P)BK = (Pseudophakic) bullous keratopathy, PXS = Pseudoexfoliation syndrome, PPMD = Posterior polymorphous corneal dystrophy, ICE = Iridocorneal endothelial, TASS = Toxic anterior segment syndrome, DSAEK = Descemet stripping automated endothelial keratoplasty, SD = Standard deviation
Table 2. Donor graft properties

<table>
<thead>
<tr>
<th>Donor characteristics</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tr>
<td>Graft thickness after precut processing (µm)</td>
<td>47.71 ± 7.91</td>
<td>38.0–68.0</td>
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<tr>
<td>Graft thickness after deswelling (µm)</td>
<td>45.25 ± 4.59</td>
<td>38.0–50.0</td>
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<td>Graft endothelial density (cells/mm²)</td>
<td>2859.62 ± 228.34</td>
<td>2545–3390</td>
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*SD = standard deviation*
<table>
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<tr>
<th>BCVA (LogMAR, Mean ± SD)</th>
<th>Preoperative BCVA</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
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<tbody>
<tr>
<td>1.37 ± 0.53</td>
<td>0.68 ± 0.46</td>
<td>0.55 ± 0.35</td>
<td>0.40 ± 0.25</td>
<td>0.39 ± 0.25</td>
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<tr>
<td>BCVA (LogMAR, Range)</td>
<td>0.10–2.00</td>
<td>0–1.80</td>
<td>0–1.30</td>
<td>0–0.82</td>
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<tr>
<td>P-value†</td>
<td>0.005*</td>
<td>&lt;0.001*</td>
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*Shows statistically significant difference compared to the preoperative value (p < 0.05, Repeated measures ANOVA)

BCVA = best corrected visual acuity, SD = standard deviation
Table 4. Pre- and post-operative central corneal thickness

<table>
<thead>
<tr>
<th></th>
<th>Preoperative values</th>
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<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
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<tr>
<td><strong>CCT (µm, Mean ± SD)</strong></td>
<td>752.00 ± 129.11</td>
<td>592.57 ± 66.95</td>
<td>558.38 ± 64.12</td>
<td>549.67 ± 55.44</td>
<td>555.75 ± 54.66</td>
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<tr>
<td><strong>CCT (µm, Range)</strong></td>
<td>572-946</td>
<td>489-705</td>
<td>442-693</td>
<td>453-650</td>
<td>452-650</td>
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<tr>
<td><strong>P-value(^{†})</strong></td>
<td>0.007 *</td>
<td>0.004*</td>
<td>0.002*</td>
<td>0.006*</td>
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*Shows statistically significant difference compared to the preoperative value (p < 0.05, Repeated measures ANOVA)*

CCT = central corneal thickness, SD = standard deviation
<table>
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<th>Postoperative Values</th>
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<tr>
<td></td>
<td>1 Month</td>
<td>3 Months</td>
</tr>
<tr>
<td>ECD (cells/mm², Mean ± SD)</td>
<td>2859.62 ± 228.34</td>
<td>2069.90 ± 613.75</td>
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<tr>
<td>ECD (cells/mm², Range)</td>
<td>2545.00-3390.00</td>
<td>1149-3125</td>
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<tr>
<td>P-value</td>
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<td>0.106</td>
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* Shows statistically significant difference compared to the preoperative value (p < 0.05, Wilcoxon signed ranks test)

ECD = endothelial cell density, SD = standard deviation
Figure legends

Figure 1. Changes in best corrected visual acuity at four different follow-up visits after nanothin DSAEK compared to preoperatively

*Significant difference compared to the preoperative value (p <0.05, Repeated measure ANOVA)

BCVA = best corrected visual acuity

Figure 2. Changes in central corneal thickness at four different follow-up visits after nanothin DSAEK compared to preoperatively

*Significant difference compared to the preoperative value (p <0.05, Repeated measure ANOVA)

CCT = central corneal thickness

Figure 3. Donor endothelial cell density at four different follow-up visits after nanothin DSAEK compared to preoperatively

*Significant difference compared to the preoperative value (p <0.05, Repeated measure ANOVA)

ECD = endothelial cell density

Figure 4. Images of the eye before and 12 months after nanothin DSAEK

This eye was diagnosed with pseudophakic bullous keratopathy and underwent nanothin DSAEK

DSAEK = Descemet stripping automated endothelial keratoplasty, AS-OCT = Anterior segment optical coherence tomography