

Changes in Corneal Endothelial Cell after Ahmed Glaucoma Valve Implantation and Trabeculectomy: 1-Year Follow-up

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Purpose: To compare changes in corneal endothelial cell density (CECD) after Ahmed glaucoma valve (AGV) implantation and trabeculectomy.

Methods: Changes in corneal endothelium in patients that underwent AGV implantation or trabeculectomy were prospectively evaluated. Corneal specular microscopy was performed at the central cornea using a non-contact specular microscope before surgery and 6 months and 12 months after surgery. The CECD, hexagonality of the endothelial cells, and the coefficient of variation of the cell areas were compared between the two groups.

Results: Forty eyes of 40 patients with AGV implantation and 28 eyes of 28 patients with trabeculectomy were studied. Intraocular pressure in the AGV implantation group was significantly higher than that in the trabeculectomy group ($p < 0.001$), but there was no significant difference in other clinical variables between the two groups. In the AGV implantation group, the mean CECD significantly decreased by 9.4% at 6 months and 12.3% at 12 months compared with baseline values (both, $p < 0.001$), while it decreased by 1.9% at 6 months and 3.2% at 12 months in the trabeculectomy group ($p = 0.027$ and $p = 0.015$, respectively). The changes at 6 months and 12 months in the AGV implantation group were significantly higher than those in the trabeculectomy group ($p = 0.030$ and $p = 0.027$, respectively). In the AGV implantation group, there was a significant decrease in the CECD between baseline and 6 months and between 6 months and 12 months ($p < 0.001$ and $p = 0.005$, respectively). However, in the trabeculectomy group, a significant decrease was observed only between baseline and 6 months ($p = 0.027$).

Conclusions: Both the AGV implantation group and the trabeculectomy group showed statistically significant decreases in the CECD 1 year after surgery. The decrease in CECD in the AVG implantation group was greater and persisted longer than that in the trabeculectomy group.

Key Words: Corneal endothelial cell loss, Glaucoma drainage implants, Trabeculectomy

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The corneal endothelium is the innermost layer of the cornea, where the hexagonal corneal endothelial cells are distributed in a single layer, and it is important for maintaining transparency. The corneal endothelial cell density (CECD) in healthy young adults is approximately 3,000 to 3,500 cells/mm² and its mean value is reduced by $0.5 \pm 0.6\%$ every year due to aging. Furthermore, variations in shape (pleomorphism) and size (polymegathism) of corneal endothelial cells increase with age [1-5].

The most common surgeries for glaucoma are trabeculectomy and glaucoma drainage device implantation. Previous studies have reported that trabeculectomy and glaucoma drainage device implantation, in addition to other intraocular surgeries or laser treatment, can damage corneal endothelial cells [6-14]. Various changes have been reported in CECD after glaucoma surgery. Storr-Paulsen et al. [7] reported that, after trabeculectomy, there were 9.5% and 10.0% decreases in the number of corneal endothelial cells after 3 months and 12 months, respectively, whereas Pastor et al. [13] reported 11.4% decrease in CECD 3 months after trabeculectomy. Shin et al. [14] reported that the post-trabeculectomy CECD was reduced by 7.7% after 3 months when viscoelastic substances were not used in the anterior chamber, whereas the CECD was reduced by 2.5% when viscoelastic substances were used in the anterior chamber. Of the studies, we could find by PubMed search on CECD change after glaucoma drainage device implantation, including three of our own [10-12,15-17], five studies were conducted with Ahmed glaucoma valve (AGV) implantation. Lee et al. [11] reported that the endothelial cell density of the central cornea was reduced by 8.6%, 12.6 %, and 15.4% at 6, 12, and 24 months after AGV implantation, respectively, and Kim et al. [12] reported that the endothelial cell density of the central cornea was reduced by 10.7% at 12 months after AGV implantation.

Postoperative CECD is reduced after AGV implantation and trabeculectomy. To our knowledge, however, there has been only one report that directly compared the effects of these two surgical procedures on CECD [18]. In addition, only short-term results at 3 months after AGV implantation and trabeculectomy were reported in that study. Therefore, in this study, we studied the long-term results of up to 1 year after surgery in order to compare continuous changes in CECD between AGV implantation and trabeculectomy.

Materials and Methods

This was a prospective study that was approved by the institutional review board of Chungnam National University Hospital. Informed consent was obtained from all patients. The study involved glaucoma patients who underwent AGV implantation or trabeculectomy at the Department of Ophthalmology, Chungnam National University Hospital from 2003 to 2005. We collected the specular microscopy data before and after surgery and compared the change in corneal endothelium between AGV implantation and trabeculectomy. If both eyes of a patient were treated, one was randomly selected and enrolled in the study. Age, sex, presence/absence of diabetes or hypertension, history of intraocular surgery or laser treatment, preoperative intraocular pressure (IOP), the number of IOP-lowering medications (a fixed combination agent was counted as two medications), and the diagnosis were recorded for all patients. We excluded patients with congenital glaucoma, preoperative corneal decompensation, corneal endothelial cell disease (including Fuchs' dystrophy, posterior polymorphous dystrophy, and iridocorneal endothelial syndrome), previous penetrating keratoplasty, and any other corneal epithelial or stromal disorders that could influence the quality of the specular microscopy. To study the natural course after uncomplicated surgery, patients with apparent tube-corneal contact were excluded. Cases that required additional surgery or laser treatment because the IOP increased after surgery or cases that required other intraocular surgery such as cataract surgery were included, and the data collected up to the second surgery were used in the analyses. Patients that were unable to complete the 1-year follow-up without specific reason were also excluded.

All surgeries were conducted by a single surgeon (CSK), after retrobulbar anesthesia. AGV implantation was performed on the superotemporal side of every eye. A traction suture through the clear cornea was used at the upper peripheral cornea to enhance exposure of the surgical field. A 10-mm incision was made in the conjunctiva and Tenon's capsule, circumferentially at 5 mm posterior from the corneal limbus, followed by a dissection between the Tenon's capsule and the sclera. The body of the AGV (model S2 with a surface area of 184 mm²; New World Medical, Rancho Cucamonga, CA, USA) was inserted under the Tenon's capsule between the superior rectus muscle and

lateral rectus muscle. The body of the AGV was fixed to the sclera by two 9/0 nylon anchoring sutures at the front edge of the plate on both sides, 8 to 9 mm from the corneal limbus. An anterior chamber puncture, parallel with the iris surface, was made 1 mm posterior to the corneal limbus, using a 23-gauge needle. A silicone tube was then cut, and a length of approximately 2 mm was inserted into the anterior chamber, in a bevel-up position. The silicone tube was fixed to the sclera by two anchoring sutures. The silicone tube near the corneal limbus was covered using a 4 × 3-mm full-thickness donor sclera. The surgery was completed with continuous running sutures of the Tenon's capsule and the conjunctiva.

Trabeculectomy was performed on the superotemporal or superonasal area, and a traction suture was performed on the upper peripheral cornea. A limbus-based conjunctival incision was performed in parallel to the corneal limbus at 8 mm posterior to the limbus, followed by a dissection between the Tenon's capsule and the sclera. Mitomycin C at a concentration of 0.3 mg/mL was applied to the subconjunctival space for 1 to 4 minutes and then thoroughly rinsed with balanced salt solution. Time was subjectively adjusted by the surgeon, based on the age of the patient and thickness and vascularity of the conjunctiva and Tenon's capsule. A 3.5 × 3-mm trapezoidal half-thickness scleral flap was made, and mitomycin C at the same concentration was applied again under the scleral flap for 1 to 2 minutes, and then washed out. The total mitomycin C application time did not exceed 5 minutes. The IOP was gradually lowered by an anterior chamber puncture and drainage of the aqueous humor, followed by injection of 0.05 mL of a viscoelastic substance (Healon; Pharmacia, Peapack, NJ, USA) into the anterior chamber. A 2.5 × 1-mm corneoscleral block was excised, and a peripheral iridectomy were performed. The viscoelastic substance was removed from the anterior chamber by injecting balanced salt solution through the premade paracentesis. The scleral flap was sutured to the scleral bed using 2 to 4 10/0 nylon sutures, the tightness was adjusted based on the degree of aqueous outflow filtration, and the conjunctiva and Tenon's capsule were closed with a continuous 10/0 nylon suture.

In all patients that underwent surgery, 1% Isopto atropine eye drops (Ocutropine; Samil, Seoul, Korea) were used for 2 days after the surgery, and 0.3% ofloxacin eye drops (Ocu-flox, Samil) and 0.12% prednisolone acetate eye drops (Ocu-Pred, Samil) were used four times a day for 2 weeks and ta-

pered over 6 months.

Specular microscopic examination of corneal endothelial cells was performed by an experienced examiner using a non-contact specular microscope (Robo SP-8000; Konan Medical, Nishinomiya, Japan) immediately before surgery and at 6 months and 12 months after surgery. This instrument automatically captures images of the endothelium once the subject fixates on a target. Then, the CECD (cells/mm²), the percentage of hexagonal cells (an index of pleomorphism), and the coefficient of variation in the cell area (%; standard deviation divided by mean cell area, an index of polymegathism) were determined semiautomatically; at least 50 contiguous endothelial cells centered on the screen were hand-marked, and a computer algorithm was used to calculate the values. We analyzed the results on the central area of the cornea.

Statistics

PASW ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of all data. The Mann-Whitney *U*-test was used to compare age, history of intraocular surgery or laser treatment, preoperative and postoperative IOP at 6 months and 12 months after surgery, the number of glaucoma medications, the CECD, the percentage of hexagonal cells, and the coefficients of variation of cell areas between the AGV implantation and trabeculectomy groups. The chi-square test was used to evaluate differences in sex, diabetes, and hypertension between the two groups. The Wilcoxon's signed-rank test was used to compare changes in the CECD, percentage of hexagonal cells, and the coefficient of variation of cell areas before and after surgery. The Kaplan-Meier survival curve and the log-rank tests were used for survival analyses to assess patients whose postoperative corneal endothelial cells were reduced by 10% or less compared to preoperative levels. A univariate linear regression analysis was performed to identify variables associated with large amounts of CECD reduction. The Pearson's correlation coefficient was calculated to compare preoperative and postoperative CECD at 12 months in each group. A *p*-value less than 0.05 was considered statistically significant.

Results

Forty eyes of 40 patients, with a mean age of 55.3 ± 11.6 years, underwent AGV implantation. There were 29 males and 11 females in the group. The preoperative IOP was 38.1 ± 12.9 mmHg, and the preoperative number of glaucoma medications was 3.6 ± 0.7 . Among the 40 eyes that received AGV implantation, 22 (55.0%) were diagnosed with neovascular glaucoma, 14 (35.0%) were diagnosed with secondary glaucoma, 3 (7.5%) were diagnosed with primary open-angle glaucoma, and 1 (2.5%) was diagnosed with

primary angle-closure glaucoma.

Twenty-eight eyes of 28 patients, with a mean age of 58.7 ± 11.0 years, underwent trabeculectomy. There were 22 males and six females in the group. The preoperative IOP was 24.7 ± 7.3 mmHg, and the preoperative number of glaucoma medications was 3.9 ± 0.3 . Among the 28 eyes, 20 (71.4%) were diagnosed with primary open-angle glaucoma, 6 (21.4%) were diagnosed with primary angle-closure glaucoma, 1 (3.6%) was diagnosed with neovascular glaucoma, and 1 (3.6%) was diagnosed with secondary glaucoma. IOP before surgery was greater in the AGV im-

Table 1. Demographics of patients with Ahmed glaucoma valve implantation or trabeculectomy

	Ahmed glaucoma valve implantation	Trabeculectomy	<i>p</i> -value
No. of patients (no. of eyes)	40 (40)	28 (28)	
Age at surgery (yr)	55.3 ± 11.6	58.7 ± 11.0	0.161*
Sex (male / female)	29 / 11	22 / 6	0.569†
Diabetes mellitus	14	14	0.216†
Hypertension	14	15	0.247†
No. of previous ocular interventions	0.7 ± 0.8	0.6 ± 0.7	0.122*
Cataract surgery	16	9	
Trabeculectomy	2	1	
Pars plana vitrectomy	5	0	
Others‡	2	6	
Intraocular pressure (mmHg)			
Baseline	38.1 ± 12.9	24.7 ± 7.3	<0.001*
Postoperative 6 mon	19.5 ± 6.3	17.0 ± 2.9	0.108*
Postoperative 12 mon	19.0 ± 7.8	16.3 ± 4.8	0.117*
No. of glaucoma medications			
Baseline	3.6 ± 0.7	3.9 ± 0.3	0.085*
Postoperative 6 mon	1.6 ± 1.0	0.8 ± 1.1	<0.001*
Postoperative 12 mon	1.9 ± 1.1	1.1 ± 1.2	0.004*
Diagnosis, no. of eyes			
Neovascular glaucoma	22 (55)	1 (3.6)	<0.001§
Secondary glaucoma	14 (35)	1 (3.6)	0.002§
Primary open-angle glaucoma	3 (7.5)	20 (71.4)	<0.001§
Primary angle-closure glaucoma	1 (2.5)	6 (21.4)	0.011§
Corneal specular microscopy			
Endothelial cell density (cells/mm ²)	$2,502.2 \pm 436.3$	$2,381.0 \pm 450.0$	0.217*
Hexagonality (%)	55.6 ± 9.3	56.2 ± 11.6	0.349*
Coefficient of variation of cell area (%)	41.8 ± 54.1	33.4 ± 6.2	0.827*

Values are presented as mean \pm standard deviation or number (%).

*Mann-Whitney *U*-test; †Chi-square test; ‡Peripheral laser iridotomy; §Fisher's exact test.

plantation group than in the trabeculectomy group ($p < 0.001$, Mann-Whitney U -test), but the number of glaucoma medications was not different in the two groups ($p = 0.085$). The preoperative mean CECD in the AGV group and the trabeculectomy group was $2,502.2 \pm 436.3$ and $2,381.0 \pm 450.0$ cells/mm², respectively, with no significant difference ($p = 0.217$). No significant differences were

found in either hexagonality or the coefficient of variation of the cells ($p = 0.349$ and $p = 0.827$). Other parameters of age, sex, accompanied systemic diseases, and number of previous ocular surgeries were not significantly different between the two groups. The IOPs at 6 months and 12 months after the surgery were not significantly different between the groups (all, $p > 0.1$), but the number of glauco-

Table 2. Change in corneal endothelial cell density in the Ahmed glaucoma valve implantation and trabeculectomy groups

Follow-up period	Ahmed glaucoma valve implantation	p -value*	Trabeculectomy	p -value*
Baseline	$2,502.2 \pm 436.3$	-	$2,381.0 \pm 450.0$	-
Postoperative 6 mon	$2,284.7 \pm 549.2$	<0.001	$2,332.5 \pm 427.8$	0.027
Postoperative 12 mon	$2,212.0 \pm 575.9$	<0.001	$2,311.6 \pm 483.0$	0.015

Values are presented as mean \pm standard deviation.

*Compared to baseline (Wilcoxon signed-rank test).

Table 3. Univariate linear regression analyses of clinical variables associated with corneal endothelial cell loss

	Regression coefficient	95% confidence interval	p -value
Age at surgery (yr)	-0.025	-0.248 to 0.197	0.821
Sex (male)	0.767	-4.956 to 6.491	0.790
Diabetes mellitus	3.796	-1.063 to 8.654	0.123
Hypertension	4.187	-0.845 to 9.219	0.101
No. of previous ocular interventions	-2.141	-6.033 to 1.752	0.276
Presence of an Ahmed glaucoma valve implant	-6.056	-10.867 to -1.246	0.014
Intraocular pressure (mmHg)			
Baseline	-0.154	-0.342 to 0.034	0.107
Postoperative 6 mon	-0.046	-0.461 to 0.369	0.823
Postoperative 12 mon	-0.455	-1.402 to 0.492	0.332
No. of glaucoma medications			
Baseline	1.376	-3.462 to 6.213	0.572
Postoperative 6 mon	-0.814	-3.788 to 2.160	0.586
Postoperative 12 mon	-0.661	-3.334 to 2.013	0.623
Diagnosis, no. of eyes			
Neovascular glaucoma	-1.725	-6.772 to 3.322	0.497
Secondary glaucoma	-5.396	-11.927 to 1.134	0.104
Primary open-angle glaucoma	2.721	-2.297 to 7.739	0.283
Primary angle-closure glaucoma	4.959	-2.698 to 12.616	0.200
Corneal specular microscopy			
Cell density (cells/mm ²)	0.002	-0.004 to 0.007	0.592
Hexagonality (%)	-0.023	-0.284 to 0.237	0.858
Coefficient of variation of cell area	0.026	-0.032 to 0.084	0.369

ma medications after surgery was smaller in the trabeculectomy group than in the AGV group at 6 and 12 months after surgery ($p < 0.001$ and $p = 0.004$, respectively) (Table 1).

In the AGV implantation group, the CECD was $2,502.2 \pm 436.3$ cells/mm² before surgery and decreased significantly to $2,284.7 \pm 549.2$ cells/mm² at 6 months after surgery ($p < 0.001$) and $2,212.0 \pm 575.9$ cells/mm² at 12 months after surgery, ($p < 0.001$) compared to baseline; the amount of change between 6 and 12 months after surgery was significantly different ($p = 0.005$). In the trabeculectomy group, the CECD was $2,381.0 \pm 450.0$ cells/mm² before surgery and decreased significantly to $2,332.5 \pm 427.8$ cells/mm² at 6 months after surgery ($p < 0.027$) and $2,311.6 \pm 483.0$ cells/mm² at 12 months after surgery ($p = 0.015$) compared to the baseline; there was no significant difference in the CECD between 6 months and 12 months after surgery ($p = 0.322$) (Table 2). When the percentage of change in CECD from the baseline value was compared, the AGV implantation group showed 9.4% and 12.3% decreases in CECD at 6 months and 12 months after surgery; these changes were significantly greater than 1.9% and 3.2% in the trabeculectomy group ($p = 0.030$ and $p = 0.027$, respectively, Mann-Whitney *U*-test) (Fig. 1).

The cumulative Kaplan-Meier survival analysis of the 10% loss of CECD from baseline was 66.9% in the AGV implantation group and 96.4% in the trabeculectomy group at 6 months after surgery. At 12 months after surgery, the

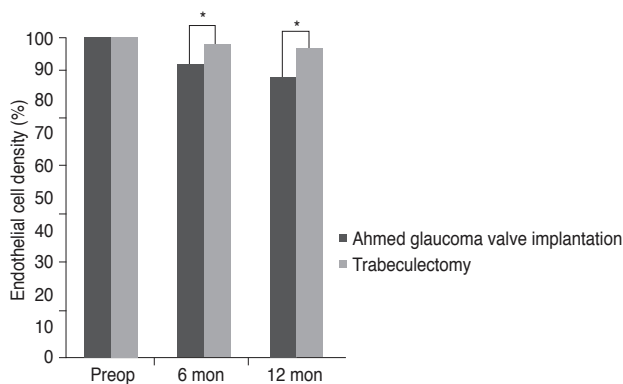


Fig. 1. Postoperative percentage change following Ahmed glaucoma valve implantation or trabeculectomy. At 6 months, this change was 90.6% in the Ahmed glaucoma valve implantation group and 98.1% in the trabeculectomy group ($p = 0.030$, Mann-Whitney *U*-test). At 12 months, this change was 87.7% in the Ahmed glaucoma valve implantation group and 96.8% in the trabeculectomy group ($p = 0.027$). Preop = preoperative. * $p < 0.05$, Mann-Whitney *U*-test.

survival rate in the AGV implantation group was 54.0%, while that in the trabeculectomy group was 85.6% ($p = 0.005$, log-rank test) (Fig. 2). A scatter plot showing the differences between preoperative and postoperative CECD at 12 months in each group indicates that the AGV implantation group (Fig. 3A) showed wider variation in postoperative CECD compared to the trabeculectomy group (Fig. 3B) (Pearson's correlation coefficient, $r = 0.777$ and 0.948 , respectively; $p = 0.002$, Fisher's *Z* transformation).

We aimed to identify factors that were associated with large amounts of reduction in CECD. Based on the regression analysis, the presence of AGV implant was the only variable relevant to the rate of the CECD loss (regression coefficient = -6.056 , $p = 0.014$). Age, sex, diabetes, hypertension, previous intraocular surgery or laser treatment time, preoperative IOP, the number of glaucoma medications for IOP, clinical diagnosis, CECD, percentage of hexagonal cells, and the coefficient of variation of the cell areas were not significantly associated (all $p > 0.05$) (Table 3).

Discussion

The corneal endothelium is an essential structure for maintaining the transparency of the cornea [4,5]. Reports have indicated that the CECD can be reduced due to surgery, trauma, and aging. When the CECD is reduced below a

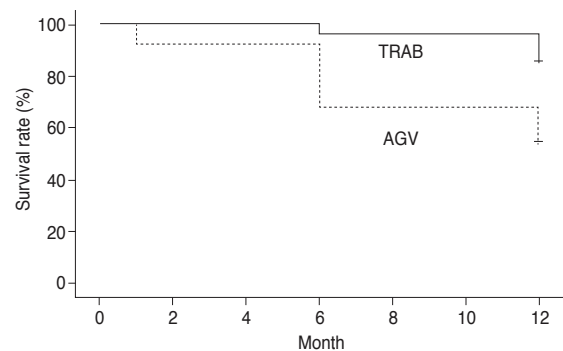


Fig. 2. A Kaplan-Meier survival curve showing survival of patients with a decrease in corneal endothelial cell density less than 10% from baseline. The survival was 66.9% in the Ahmed glaucoma valve (AGV) implantation group and 96.4% in the trabeculectomy (TRAB) group at 6 months and 54.0% in the AGV group and 85.7% in the TRAB group at 12 months ($p = 0.005$, log-rank test).

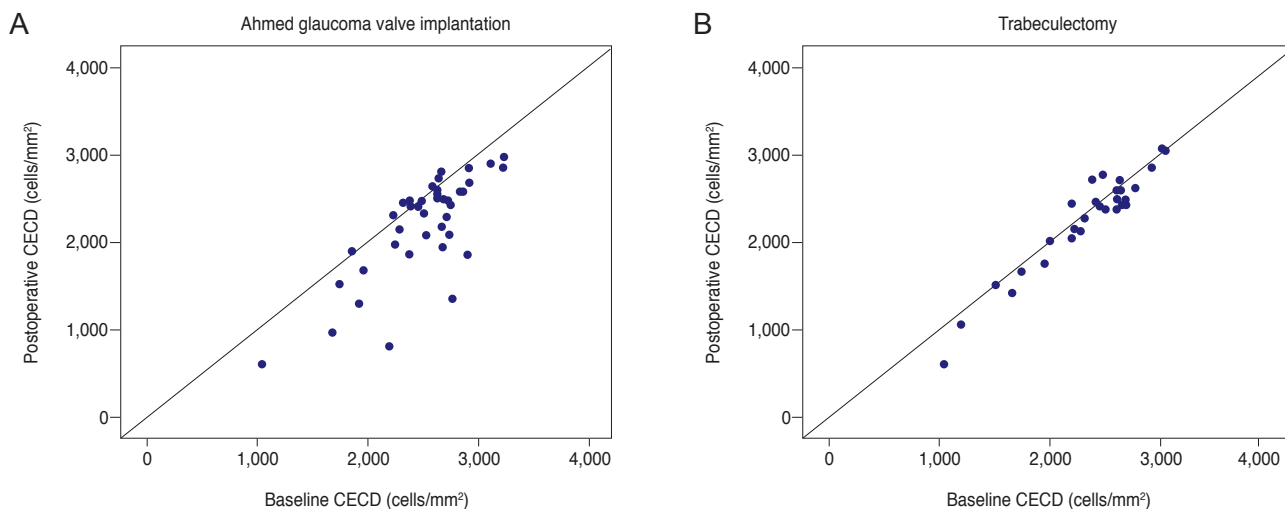


Fig. 3. Scatter plot of corneal endothelial cell density (CECD) at 12 months postoperative, according to preoperative baseline CECD. In the Ahmed glaucoma implantation group (A), the scatter plot indicates a weaker correlation between preoperative and postoperative CECD (Pearson's correlation coefficient, $r = 0.770$) than in the trabeculectomy group (B) ($r = 0.948$) ($p = 0.002$, Fisher's Z transformation).

minimum level, decompensation results in decreased corneal transparency, and corneal transplantation is needed [19].

Trabeculectomy, introduced by Sugar [20] in 1961, has been the procedure of choice for surgically treating glaucoma. Following introduction of mitomycin C by Chen et al. [21] and Palmer [22], surgical outcomes have improved, and this procedure is now a front line surgical treatment for glaucoma patients whose IOP cannot be controlled by medication [23]. However, recent studies have reported that the postoperative CECD is reduced by 2.5% to 16.6% after trabeculectomy [7,13,14,24,25]. Various factors have been discussed as possible mechanisms of CECD reduction after trabeculectomy in patients with glaucoma. Gagnon et al. [26] reported that the CECD significantly decreased in eyes with glaucoma compared with normal eyes, suggesting that CECD decrease could be caused by direct damage of corneal endothelial cells due to high IOP. In addition, ischemic changes induced by impaired flow of the aqueous humor, the cytotoxicity of glaucoma medications, and/or congenital corneal endothelial cell abnormalities have been proposed as possible mechanisms. Mechanical damage, such as intraoperative or postoperative iris-cornea contact or lens-cornea contact, and postoperative ocular hypertension caused by uveitis are also possible causes of corneal damage [24]. Mitomycin C can decrease the density of corneal endothelial cells after trabeculectomy. McDermott et al. [27] reported that corneal edema and

disruption of cellular organelles increased when human corneas were exposed to 0.2 mg/mL mitomycin C. Use of viscoelastic substances in trabeculectomy is reported to have a protective effect on the corneal endothelium. Shin et al. [14] reported that use of a viscoelastic substance resulted in a 2.5% decrease in CECD density at 3 months after surgery, compared to a 7.7% decrease in the CECD when a viscoelastic substance was not used in the same procedure. In this study, trabeculectomy was performed with adjunctive mitomycin C, and a viscoelastic substance was used. As a result, the CECD was reduced by 1.9% at 6 months and by 3.2% at 12 months after the surgery, comparable to a trabeculectomy study that applied adjunctive mitomycin C and viscoelastic substance.

Glaucoma drainage device implantation for aqueous humor was introduced by Zorab [28] in 1912. The procedure can be performed in patients with refractory glaucoma and patients with a high risk of trabeculectomy failure [29]. Glaucoma drainage device implantation is currently comparable to trabeculectomy in terms of success rate and the possibility of complications [30]. However, glaucoma drainage device implantation is associated with persistent damage to the corneal endothelium [10-12,16,31], contrary to other intraocular procedures including trabeculectomy, in which corneal damage is thought to occur only during the treatment [6-9,13,14,32]. Lee et al. [11] reported that the endothelial cell density of the central cornea was reduced by

12.6% at 12 months and by 15.4% at 24 months after AGV implantation. In addition, Kim et al. [12] reported that the reduction of CECD in eyes with AGV implantation was significantly higher than that in fellow control eyes that received glaucoma medications without AGV implantation, up to 2 years after surgery.

Although the mechanism of corneal endothelial cell damage after glaucoma drainage device implantation is not known, many theories have been proposed. In addition to the damage caused by glaucoma itself, the silicon tube of the implant located in the anterior chamber might cause long-term damage to corneal endothelial cells and can even cause corneal decompensation [33]. McDermott et al. [15] suggested that corneal injury could be caused by the jet stream of aqueous humor through the silicon tube during heart beating. In addition, if patients severely squeeze or rub their eyes, this can damage the corneal endothelial cells through intermittent contact between the silicone tube and the cornea [34]. Since the anterior chamber is exposed to the extraocular space, the composition of the aqueous humor can be altered, which might affect the corneal endothelium. Because of the presence of the silicon tube in the anterior chamber after glaucoma drainage device implantation, there is always some possibility of damage to corneal endothelial cells [11,12].

In this study, both surgeries showed a significant decrease in CECD at 6 and 12 months after surgery, compared to preoperative values, and the decrease was greater in the AGV implantation group. While the change between 6 and 12 months after trabeculectomy was not statistically significant, there was a significant change in CECD between 6 and 12 months after surgery in the AGV implantation group. In addition, the CECD at 12 months after surgery varied in the patients (Fig. 3). With the exception of AGV implantation, we did not identify factors that were associated with greater damage to the CECD. These results indicate that the damage to the corneal endothelium in AGV surgery is greater, more persistent, and more unpredictable compared with that in trabeculectomy.

There were some limitations to this study. First, the number of patients was small. Of the patients who underwent AGV implantation or trabeculectomy in the study period, a considerable number of patients were excluded due to our strict inclusion and exclusion criteria. Second, there were some differences in patient demographics between the two surgery groups. The IOP before surgery was higher in the

AGV implantation group, and the composition of the glaucoma types was different. This might be inevitable because the surgical indications of each surgery are different. However, there was no difference in the CECD before surgery in the two groups, which was consistent with the other demographics. The IOPs after surgery did not differ during the study period. Additionally, it is possible that the differences in the number of glaucoma medications between the two groups could have differently affected the corneal endothelium [26,35]. However, univariate regression showed no variables, except presence of an AGV implant, that affected the amount of CECD reduction. Third, it is possible that, despite our best efforts, we might not have examined the exact same area of the cornea at every visit, despite using the same fixation target at each examination. There might have been errors in the calculation of cell density, although all examinations were performed by a single skilled examiner in order to minimize the occurrence of such errors.

In conclusion, there were significant decreases in CECD at 6 months and 12 month after AGV implantation surgery and trabeculectomy. However, reduction in CECD in the AGV implantation group was greater than that in the trabeculectomy group at 6 and 12 months after surgery. While the CECD results were not significantly different between 6 and 12 months after trabeculectomy, the loss of CECD after AGV implantation surgery progressed at 12 months compared to 6 months after surgery. The amount of CECD loss was more unpredictable in AGV surgery compared to the trabeculectomy. These results suggest that AGV implantation might cause greater damage to the corneal endothelium than trabeculectomy, so it is important to advise patients when discussing surgical options. If AGV surgery is needed to control IOP, surgeons must be careful not to damage the cornea during surgery, and patients should be warned about and monitored for possible corneal problems.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Laule A, Cable MK, Hoffman CE, Hanna C. Endothelial cell population changes of human cornea during life. *Arch Ophthalmol* 1978;96:2031-5.
2. Freeguard TJ. The physical basis of transparency of the normal cornea. *Eye (Lond)* 1997;11 (Pt 4):465-71.
3. Bourne WM, Nelson LR, Hodge DO. Central corneal endothelial cell changes over a ten-year period. *Invest Ophthalmol Vis Sci* 1997;38:779-82.
4. Tuft SJ, Coster DJ. The corneal endothelium. *Eye (Lond)* 1990;4 (Pt 3):389-424.
5. Mishima S. Clinical investigations on the corneal endothelium-XXXVIII Edward Jackson memorial lecture. *Am J Ophthalmol* 1982;93:1-29.
6. Bourne RR, Minassian DC, Dart JK, et al. Effect of cataract surgery on the corneal endothelium: modern phacoemulsification compared with extracapsular cataract surgery. *Ophthalmology* 2004;111:679-85.
7. Storr-Paulsen T, Norregaard JC, Ahmed S, Storr-Paulsen A. Corneal endothelial cell loss after mitomycin C-augmented trabeculectomy. *J Glaucoma* 2008;17:654-7.
8. Shah P, Lee GA, Kirwan JK, et al. Cyclodiode photocoagulation for refractory glaucoma after penetrating keratoplasty. *Ophthalmology* 2001;108:1986-91.
9. Friberg TR, Doran DL, Lazenby FL. The effect of vitreous and retinal surgery on corneal endothelial cell density. *Ophthalmology* 1984;91:1166-9.
10. Kim CS, Yim JH, Lee EK, Lee NH. Changes in corneal endothelial cell density and morphology after Ahmed glaucoma valve implantation during the first year of follow up. *Clin Experiment Ophthalmol* 2008;36:142-7.
11. Lee EK, Yun YJ, Lee JE, et al. Changes in corneal endothelial cells after Ahmed glaucoma valve implantation: 2-year follow-up. *Am J Ophthalmol* 2009;148:361-7.
12. Kim KN, Lee SB, Lee YH, et al. Changes in corneal endothelial cell density and the cumulative risk of corneal decompensation after Ahmed glaucoma valve implantation. *Br J Ophthalmol* 2016;100:933-38.
13. Pastor SA, Williams R, Hetherington J, et al. Corneal endothelial cell loss following trabeculectomy with mitomycin C. *J Glaucoma* 1993;2:112-3.
14. Shin DB, Lee SB, Kim CS. Effects of viscoelastic material on the corneal endothelial cells in trabeculectomy with adjunctive mitomycin-C. *Korean J Ophthalmol* 2003;17:83-90.
15. McDermott ML, Swendris RP, Shin DH, et al. Corneal endothelial cell counts after Molteno implantation. *Am J Ophthalmol* 1993;115:93-6.
16. Nassiri N, Nassiri N, Majidi-N M, et al. Corneal endothelial cell changes after Ahmed valve and Molteno glaucoma implants. *Ophthalmic Surg Lasers Imaging* 2011;42:394-9.
17. Kalinina Ayuso V, Scheerlinck LM, de Boer JH. The effect of an Ahmed glaucoma valve implant on corneal endothelial cell density in children with glaucoma secondary to uveitis. *Am J Ophthalmol* 2013;155:530-5.
18. Casini G, Loiodice P, Pellegrini M, et al. Trabeculectomy versus Ex-PRESS shunt versus Ahmed valve implant: short-term effects on corneal endothelial cells. *Am J Ophthalmol* 2015;160:1185-90.e1.
19. Gedde SJ, Herndon LW, Brandt JD, et al. Postoperative complications in the Tube Versus Trabeculectomy (TVT) study during five years of follow-up. *Am J Ophthalmol* 2012;153:804-14.e1.
20. Sugar HS. Experimental trabeculectomy in glaucoma. *Am J Ophthalmol* 1961;51:623-7.
21. Chen CW, Huang HT, Bair JS, Lee CC. Trabeculectomy with simultaneous topical application of mitomycin-C in refractory glaucoma. *J Ocul Pharmacol* 1990;6:175-82.
22. Palmer SS. Mitomycin as adjunct chemotherapy with trabeculectomy. *Ophthalmology* 1991;98:317-21.
23. Korey M, Gieser D, Kass MA, et al. Central corneal endothelial cell density and central corneal thickness in ocular hypertension and primary open-angle glaucoma. *Am J Ophthalmol* 1982;94:610-6.
24. Barak A, Alhalel A, Kotas R, Melamed S. The protective effect of early intraoperative injection of viscoelastic material in trabeculectomy. *Ophthalmic Surg* 1992;23:206-9.
25. Arnavielle S, Lafontaine PO, Bidot S, et al. Corneal endothelial cell changes after trabeculectomy and deep sclerectomy. *J Glaucoma* 2007;16:324-8.
26. Gagnon MM, Boisjoly HM, Brunette I, et al. Corneal endothelial cell density in glaucoma. *Cornea* 1997;16:314-8.
27. McDermott ML, Wang J, Shin DH. Mitomycin and the human corneal endothelium. *Arch Ophthalmol* 1994;112:533-7.
28. Zorab A. The reduction of tension in chronic glaucoma. *Ophthalmoscope* 1912;10:258-61.
29. Lim KS, Allan BD, Lloyd AW, et al. Glaucoma drainage devices; past, present, and future. *Br J Ophthalmol* 1998;82:1083-9.
30. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. *Am J Ophthalmol* 2012;153:789-

803.e2.

31. Bailey AK, Sarkisian SR Jr. Complications of tube implants and their management. *Curr Opin Ophthalmol* 2014;25:148-53.
32. Wang PX, Koh VT, Loon SC. Laser iridotomy and the corneal endothelium: a systemic review. *Acta Ophthalmol* 2014;92:604-16.
33. Allingham RR, Damji KF, Freedman S, et al., editors. *Shields textbook of glaucoma*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 534.
34. Topouzis F, Coleman AL, Choplin N, et al. Follow-up of the original cohort with the Ahmed glaucoma valve implant. *Am J Ophthalmol* 1999;128:198-204.
35. Konowal A, Morrison JC, Brown SV, et al. Irreversible corneal decompensation in patients treated with topical dorzolamide. *Am J Ophthalmol* 1999;127:403-6.