

# Long-term efficacy and safety of ExPress implantation for treatment of open angle glaucoma

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## Abstract

• **AIM:** To compare the long-term efficacy and safety of ExPress implantation and standard trabeculectomy in patients with primary open angle glaucoma (POAG).

• **METHODS:** In this retrospective study, we compared 17 eyes treated by ExPress implantation with 23 eyes treated by trabeculectomy. Efficacy was assessed according to the relevant intraocular pressure (IOP) values and success rates during the first year of follow-up. Postoperative corneal endothelial cell loss was also compared.

• **RESULTS:** The number of antiglaucoma medications and the IOP reduction were similar between the 2 groups during the follow-up period. Although the mean IOP was similar, the IOP-fluctuation rate during the early postoperative period was significantly lower in the ExPress group than in the trabeculectomy group ( $P=0.038$ ). A Kaplan-Meier survival curve analysis showed no significant success-rate difference between the groups ( $P=0.810$ ). The corneal endothelial cell loss rate, moreover, was significantly lower in the ExPress group ( $P=0.05$ ).

• **CONCLUSION:** ExPress implantation compared with trabeculectomy showed similar IOP-reduction and success rates along with lower IOP fluctuation and endothelial cell loss rates. For this reason, it can be considered to be the treatment of choice for patients with advanced glaucoma or low corneal endothelial cell density.

• **KEYWORDS:** primary open angle glaucoma; ExPress implant; trabeculectomy

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## INTRODUCTION

Trabeculectomy is the most commonly performed operation for intraocular pressure (IOP) reduction in glaucoma patients since 1968<sup>[1]</sup>. Potentially devastating complications including early hypotony, choroidal detachment and bleb-related problems, however, have prompted calls for a safer, better surgical option<sup>[2]</sup>. In recent years, several alternative procedures have been evaluated relative to trabeculectomy<sup>[3-4]</sup>. ExPress glaucoma filtration device (Alcon, Fort Worth, Texas, USA) implantation, for example, shows similar IOP-reduction efficacy with fewer complications<sup>[5-6]</sup>. The ExPress implant is a non-valved stainless steel tube that is inserted under a partial-thickness scleral flap to connect the anterior chamber to the subconjunctival space. The theoretical advantages of this device include increased reproducibility, simplicity, and reduced possibility of ocular tissue trauma.

Although glaucoma surgery has made significant progress in terms of safety, complications are still possible. One reportedly late postoperative complication of both trabeculectomy and implantation surgery is corneal decompensation<sup>[7]</sup>. Implantation surgery is considered to be a safer procedure overall, though it can cause more corneal complications than trabeculectomy<sup>[8-9]</sup>. Corneal decompensation for instance, based on a long-term follow-up study of Ahmed valve implantation, has been reported to occur in up to 30% of patients<sup>[10]</sup>. There are as yet no long-term follow-up reports on the safety of ExPress implantation in the corneal endothelium. In the present study, therefore, we compared the clinical outcomes of ExPress implantation and standard trabeculectomy in patients with medically uncontrolled glaucoma, in terms of not only the hypotensive effect, but also any complications related to corneal endothelial damage.

## SUBJECTS AND METHODS

**Subjects** We retrospectively reviewed the records of all patients treated consecutively by ExPress implantation or trabeculectomy between January 2014 and June 2014 at the Cheil Eye Hospital Glaucoma Clinic. Eyes treated by ExPress implantation were compared with eyes treated by trabeculectomy during an overlapping period. The main inclusion criterion was primary open angle glaucoma with unsatisfactory IOP control despite maximally tolerated topical and systemic medication. Additional inclusion criteria were noncompliance with antiglaucoma medication regimen, allergy

to medication, significant IOP fluctuation, and/or documented progression of visual field (VF) defect despite medication-controlled IOP. The exclusion criteria included previous ocular surgery except cataract surgery, closed or narrow angle, or ocular disease other than glaucoma. Cheil Eye Hospital Institutional Review Board approval was obtained prior to the review of the patients' medical records.

**Preoperative and Postoperative Examinations** All of the patients underwent a complete ophthalmic examination preoperatively, which included best-corrected visual acuity measurement, slit-lamp biomicroscopy, IOP using Goldmann applanation tonometry (Haag-Streit, Koeniz, Switzerland), gonioscopy, and optical coherence tomography (Cirrus HD-OCT; Carl Zeiss, Dublin, California, USA) of the optic disc and retinal nerve fiber layer. Additionally, standard automated perimetry using Swedish interactive threshold algorithm 30-2 (Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA, USA) was carried out. The corneal endothelial cell density (ECD), which is to say, the number of cells per square millimeter, was measured using the SP-3000P specular microscope (Topcon, Oakland, USA).

Postoperative examinations with respect to IOP, antiglaucoma medication, and complications were carried out for 7 consecutive days as well as at the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, and 12<sup>th</sup> months postoperatively. The postoperative assessment was similar to that carried out preoperatively, but with particular attention paid to possible complications and the necessity of additional procedures or antiglaucoma medication change. In cases of elevated IOP, digital scleral massage or laser suturelysis was performed. For encapsulated or flat blebs, needling revision with or without subconjunctival injection of adjunctives (5-fluorouracyl) was performed.

During the 1<sup>st</sup> postoperative week, IOP measurements were taken twice at the same time each day, 9 a.m. and 5 p.m., regarding the diurnal variation. During the remainder of the follow-up period, measurements were taken also at the same time, but between 9 a.m. and 11 a.m. Long-term IOP fluctuation was defined in terms of the standard deviation (SD) in IOP values over a given period, with measurements occurring on different days. Large IOP fluctuation was defined as an IOP SD >3 mm Hg during a given time. Additionally, the ECD was measured at the postoperative 12<sup>th</sup> month, and the percentage loss of ECD relative to the baseline (ECD loss%) was calculated. Success was analyzed in two ways: complete and qualified. Complete surgical success was defined as IOP >5 mm Hg and IOP <21 mm Hg without use of antiglaucoma medications, without further glaucoma surgery, and the absence of complications. Qualified success was defined as IOP >5 mm Hg and IOP <21 mm Hg with a maximum of 2 antiglaucoma medications. Persistent hypotony, loss of light perception, and reoperation for IOP control were also defined as failure.

**Table 1 Basic demographics of patients** n (%)

| Parameters                      | ExPress (n=17) | Trabeculectomy (n=23) | P                  |
|---------------------------------|----------------|-----------------------|--------------------|
| Age (a)                         | 61.2±10.9      | 59.8±8.1              | 0.978 <sup>a</sup> |
| Female                          | 5 (29)         | 8 (35)                | 0.787 <sup>b</sup> |
| Laterality (right eye)          | 7 (41)         | 9 (39)                | 0.914 <sup>b</sup> |
| IOP (mm Hg)                     | 27.1±10.1      | 25.8±6.4              | 0.607 <sup>a</sup> |
| BCVA (logMAR)                   | 0.7±0.5        | 0.5±0.4               | 0.302 <sup>a</sup> |
| No. of antiglaucoma medications | 2.8±0.5        | 2.6±0.7               | 0.609 <sup>a</sup> |
| Central corneal thickness (µm)  | 497.7±60.4     | 551.4±60.0            | 0.368 <sup>a</sup> |
| Mean visual field deviation     | -23.6±8.6      | -18.5±10.1            | 0.166 <sup>a</sup> |

IOP: Intraocular pressure; BCVA: Best-corrected visual acuity. <sup>a</sup>Mann-Whitney U test; <sup>b</sup>Chi-square test.

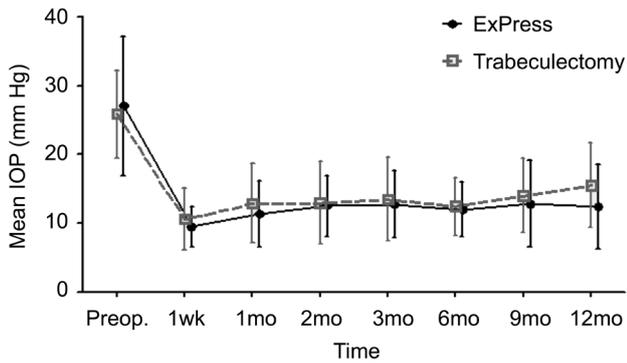
**Surgical Procedures** All of the surgical procedures were performed, for consistency, by one experienced surgeon (Lee KW) using a standardized technique for each surgery type. In both procedures, a fornix-based conjunctiva flap was created with a relaxing incision on one side. Next, a 50% thickness limbus-based trapezoidal (3 mm×3 mm) scleral flap was constructed. In the ExPress group, after creation of the pilot hole using a 26 gauge needle, the filtration device (Ex-PRESS P 50) was implanted under the scleral flap; in the trabeculectomy group, sclerectomy was performed under the scleral flap, in the grey limbal zone, and a peripheral iridectomy was created. During both surgeries, the scleral wound bed was treated for 2min with 0.02% mitomycin C-soaked sponges. The scleral flap and conjunctiva were closed with 10/0 nylon sutures. Postoperatively, topical antibiotics and steroid treatment were administered.

**Statistical Analysis** IBM SPSS Statistics ver. 21.0 software (SPSS, Chicago, IL, USA) was used for the statistical analysis. Data were obtained in the forms of mean±SD and frequency percentage. The inter-group analysis was performed by Mann-Whitney U test. For categorical data, the Chi-square and Fisher exact tests were used. Intra-group differences, obtained from data taken at different time points, were evaluated using the Wilcoxon signed-rank test. The success rates between the groups were compared by Kaplan-Meier life table analysis and log rank test. P values <0.05 were considered to be significant.

**RESULTS**

In total, 40 eyes of 40 participants were enrolled, 17 of which were subject to ExPress glaucoma filtration device implantation (ExPress) and 23 standard trabeculectomy (Trab). The demographic data are summarized in Table 1. There were no significant differences in sex, mean age, visual acuity, glaucoma severity, IOP or number of antiglaucoma medications between the 2 groups.

**Intraocular Pressure** Figure 1 shows the mean postoperative IOP in both groups. The mean preoperative IOP in the ExPress group was 27.1±10.1 mm Hg. After 12mo of follow up, it had decreased by 55.1%, to 12.1±4.2 mm Hg (P=0.01).



**Figure 1 Mean values and standard deviations of IOP during each follow-up period after ExPress implantation and trabeculectomy.**

Over the same time period, the mean IOP in the Trab group had decreased by 39.9%, from 25.8±6.4 to 15.5±6.2 mm Hg ( $P<0.01$ ). Throughout the duration of the study, there were no statistically significant inter-group differences ( $P>0.05$ ) (Table 2).

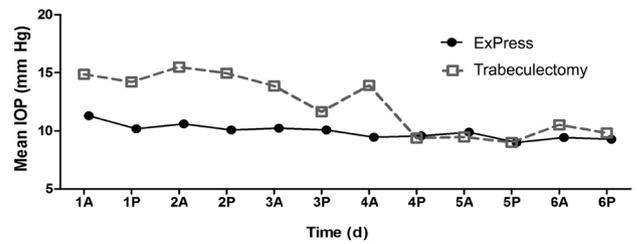
**Antiglaucoma Medication** Preoperatively, the average number of antiglaucoma medications was 2.75±0.45 in the ExPress group and 2.55±0.74 in the Trab group. Over the 12-month evaluation period, the number of medications in the ExPress group decreased to 0.53±0.80 ( $P<0.01$ ), and in the Trab group, to 0.78±1.13 ( $P<0.01$ ). There were no statistically significant inter-group differences in the number of medications at any time pre- or postoperatively (Table 3).

**Long-term Intraocular Pressure Fluctuation** The IOP fluctuation during the 1<sup>st</sup> week postoperatively was 2.4 mm Hg (SD) in the ExPress group and 4.2 mm Hg (SD) in the Trab group ( $P=0.027$ ). The IOP of the ExPress group was maintained more stably during this 1<sup>st</sup> week (Figure 2).

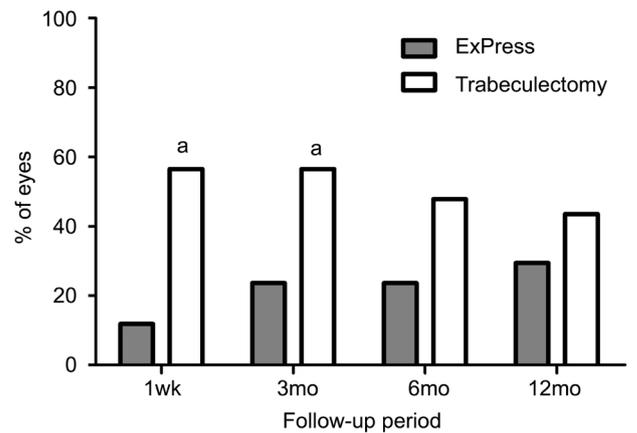
The long-term fluctuations of IOP in the ExPress and Trab groups are summarized in Table 4. During that 1<sup>st</sup> week, 2 eyes from the ExPress group (11.8%) and 13 from the Trab group (56.5%) showed large fluctuation ( $P=0.009$ ). At 3mo postoperatively, the number of eyes with large fluctuation in the ExPress group (23.6%) was still lower than that (56.5%) in the Trab group ( $P=0.038$ ) (Figure 3).

**Endothelial Cell Count** The preoperative corneal endothelial cell count was 1906.6±605.8 in the ExPress group and 2186.7±367.9 in the Trab group ( $P=0.241$ ). After 12mo of follow up, the number of endothelial cells decreased by 10.0%±7.0% ( $P=0.139$ ) in the ExPress group and by 18.2%±13.3% ( $P=0.021$ ) in the Trab group. That is, more significant endothelial cell loss was observed in the Trab group ( $P=0.05$ , Table 5).

**Corrected Distance Visual Acuity** The preoperative CDVA was 0.7±0.5 logMAR in the ExPress group and 0.5±0.4 logMAR in the Trab group ( $P=0.302$ ). Throughout the entire follow-up period, the CDVA did not change significantly; by the end of the follow-up period, the scores were 0.7±0.5 logMAR and 0.5±0.4 logMAR in the ExPress and Trab groups, respectively ( $P=0.284$ ).



**Figure 2 Mean IOP at 1<sup>st</sup> week after ExPress implantation and trabeculectomy** The IOP was maintained more stably in the ExPress implantation group. The number indicate the postoperative day, A indicated the IOP measured at 9 a.m., and P indicated the IOP measured at 5 p.m.



**Figure 3 Histogram of eyes with large IOP fluctuation across 12mo** Large IOP fluctuation was defined as 3 mm Hg or greater. The trabeculectomy patients were more likely to show large fluctuations during follow up. <sup>a</sup>Statistically significant difference between the groups.

**Table 2 Comparison of IOP in ExPress implantation and trabeculectomy groups at specific times postoperatively** mm Hg

| Time                | ExPress (n=17) | Trabeculectomy (n=23) | P     |
|---------------------|----------------|-----------------------|-------|
| Preop.              | 27.1±10.1      | 25.8±6.4              | 0.607 |
| 1 <sup>st</sup> wk  | 9.4±3.0        | 10.5±4.5              | 0.793 |
| 1 <sup>st</sup> mo  | 11.3±4.8       | 12.8±5.7              | 0.437 |
| 2 <sup>nd</sup> mo  | 12.5±4.5       | 12.9±5.9              | 0.889 |
| 3 <sup>rd</sup> mo  | 12.7±4.9       | 13.4±6.0              | 0.841 |
| 6 <sup>th</sup> mo  | 12.0±4.1       | 12.4±4.3              | 0.807 |
| 9 <sup>th</sup> mo  | 12.8±6.3       | 14.0±5.3              | 0.515 |
| 12 <sup>th</sup> mo | 12.1±4.2       | 15.5±6.2              | 0.212 |

P value by Mann-Whitney U test.

**Table 3 Comparison of antiglaucoma medication amount in ExPress implantation and trabeculectomy groups at specific times postoperatively**

| Time                | ExPress (n=17) | Trabeculectomy (n=23) | P     |
|---------------------|----------------|-----------------------|-------|
| Preop.              | 2.75±0.45      | 2.55±0.74             | 0.609 |
| 1 <sup>st</sup> mo  | 0.06±0.24      | 0.04±0.21             | 0.935 |
| 3 <sup>rd</sup> mo  | 0.06±0.24      | 0.17±0.58             | 0.871 |
| 6 <sup>th</sup> mo  | 0.12±0.33      | 0.30±0.82             | 0.892 |
| 9 <sup>th</sup> mo  | 0.41±0.71      | 0.74±1.01             | 0.551 |
| 12 <sup>th</sup> mo | 0.53±0.80      | 0.78±1.13             | 0.705 |

P value by Mann-Whitney U test.

**Table 4 Comparison of long-term IOP fluctuation (in mm Hg) between ExPress implantation and trabeculectomy groups during follow-up period**

| Time | ExPress (n=17) | Trabeculectomy (n=23) | P     |
|------|----------------|-----------------------|-------|
| 1wk  | 2.4±0.8        | 4.2±2.7               | 0.027 |
| 3mo  | 2.4±2.0        | 3.6±2.2               | 0.074 |
| 6mo  | 2.4±1.7        | 3.5±1.9               | 0.074 |
| 12mo | 2.6±1.8        | 2.9±1.6               | 0.448 |

P value by Mann-Whitney U test.

**Table 5 Comparison of corneal ECD in ExPress implantation and trabeculectomy groups at postoperative 12mo**

| Parameters        | ExPress (n=17) | Trabeculectomy (n=23) | P     |
|-------------------|----------------|-----------------------|-------|
| ECD preop.        | 1906.6±605.8   | 2186.7±367.9          | 0.241 |
| ECD 12mo          | 1739.2±620.9   | 1671.1±331.3          | 0.606 |
| ECD 12mo loss (%) | 10.0±7.0       | 18.2±13.3             | 0.050 |

ECD: Endothelial cell density; ECD loss (%): Endothelial cell density loss (%); P value by Mann-Whitney U test.

**Surgical Success** Kaplan-Meier survival curves of the ExPress and Trab groups are plotted in Figure 4. Complete success was achieved in 65% and 61% of the patients, respectively (P=0.810), while qualified success was achieved in 82% and 78% of patients, respectively (P=0.757).

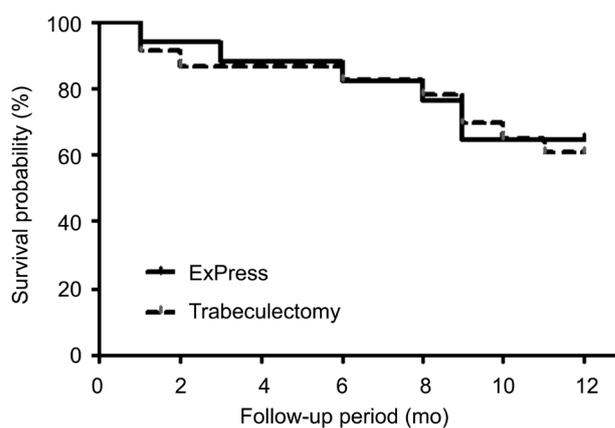
**Complications and Additional Procedures** Laser suturelysis was performed in 3 patients from the ExPress group (17.6%) and in 5 patients from the Trab group (21.7%) (P=0.537). There were 1 (5.8%) and 5 (21.7%) bleb needling procedures performed in the ExPress and Trab groups, respectively. The difference is not statistically significant (P=0.216).

The postoperative complication profiles are summarized in Table 6. Complications in the ExPress group included wound leakage (5.9%), bleb fibrosis (5.9%), and choroidal detachment (5.9%). Trab group patients, meanwhile, experienced complications such as hyphema (8.7%), bleb fibrosis (8.7%), early hypotony (13.0%), and choroidal detachment (8.7%).

**DISCUSSION**

In recent years, several new IOP-lowering procedures have been developed as alternatives to standard trabeculectomy. ExPress implantation, for example, is a new means of standardizing trabeculectomy that shows outcomes quite similar to those of trabeculectomy<sup>[6,11]</sup>.

In the present study, the ExPress group relative to the Trab group had similar IOP-lowering and success rates but a lower rate of IOP fluctuation. Throughout the follow-up period, good IOP control was achieved in both groups. A trend toward lower mean IOP in the ExPress group was observed, though this did not represent a statistically significant difference relative to the Trab group. The number of antiglaucoma medications used postoperatively was not significantly different between the two groups.



**Figure 4 Kaplan-Meier survival curves after ExPress implantation and trabeculectomy** The rates of complete success for the ExPress and trabeculectomy groups were 82% and 83% at 6mo and 65% and 61% at 12mo, respectively. The differences between the 2 groups' survival curves were not statistically significant (P=0.845). Complete success was defined as 5<IOP<21 mm Hg without antiglaucoma medication.

**Table 6 Postoperative complications after ExPress implantation and trabeculectomy**

| Complication         | ExPress | Trabeculectomy |
|----------------------|---------|----------------|
| Hyphema              | 0       | 2 (8.7)        |
| Wound leakage        | 1 (5.9) | 0              |
| Bleb fibrosis        | 1 (5.9) | 2 (8.7)        |
| Early hypotony       | 0       | 3 (13.0)       |
| Choroidal detachment | 1 (5.9) | 2 (8.7)        |

Our results are in accordance with those of a prospective, case control study by Wagschal *et al*<sup>[11]</sup>. The rate of complete success was 70% after ExPress implantation compared with 57% after trabeculectomy at the 1y follow-up. There were no differences between the 2 groups in IOP, success rates, complications or additional intervention.

Dahan *et al*<sup>[12]</sup> reported the results of a prospective comparison between ExPress implantation and trabeculectomy. As in the present study, both treatment groups demonstrated significant IOP decrease from the baseline: 44% for the ExPress group, and 48% for the trabeculectomy group. Unlike our result however, the eyes receiving ExPress implantation had a significantly higher probability of complete success. This might be partially explained by their lower, <18 mm Hg IOP cut-off point.

The statistically significant IOP-fluctuation difference (to the advantage of the ExPress group) observed in the early postoperative period in our study is noteworthy. There have been no reports in the literature on the rate of IOP fluctuation in cases of ExPress implantation in glaucoma patients. The importance of IOP fluctuation nonetheless was identified in the pointwise linear regression analysis of AGIS patients reported by Nouri-Mahdavi *et al*<sup>[13]</sup>. Indeed, in their study, IOP

fluctuation remained a significant predictor of VF worsening despite inclusion of mean IOP and number of glaucoma interventions as independent covariates in their regression models.

As for the present study, although good IOP control was achieved in both groups, IOP fluctuation was significantly lower after ExPress implantation in the early postoperative period from week 1 to month 3. In contrast to trabeculectomy, ExPress implantation does not require either sclerostomy or peripheral iridectomy. This might reduce the variability of results among ExPress implantation patients relative to trabeculectomy cases. This might also reduce postoperative inflammation, which is a very desirable effect<sup>[14]</sup>. One possible explanation for the present result is that the small lumen of the ExPress device provided additional resistance to aqueous flow during the early postoperative period. In fact, aqueous flow through that small lumen probably is more constant than that through the wide sclerectomy of trabeculectomy, even when both apertures are secured by overlying scleral flaps.

During the immediate postoperative period, there was a greater need for postoperative manipulation (specifically, laser suturelysis) in the Trab group than in the ExPress group. The Trab group's higher rate of IOP fluctuation during the first week might be associated with this finding.

In this study, trabeculectomy resulted in a higher rate of postoperative complications (39%) than ExPress implantation (17%). Most notably, hyphema and early hypotony were observed only in the Trab group. These results are in accordance with Dahan and Carmichael's<sup>[15]</sup> study, which reported a lower rate of postoperative complications in the ExPress group (20% vs 33%). These and other such results are the reason that ExPress implantation has been proposed and promoted as a less invasive procedure than trabeculectomy, given particularly its lower rate of complications resulting from postoperative hypotony.

The results of studies on the impact of trabeculectomy on ECD vary greatly: for example, from 1.6% to 54.8% in investigations conducted by Smith *et al*<sup>[16]</sup>. There have been no reports in the literature on the long-term effects of ExPress shunt on endothelial cells. In our analysis, the ECD loss % was significantly higher in the Trab group.

The exact mechanics of endothelial damage by trabeculectomy are unknown. There are, however, hypotheses, that such damage is caused by a postoperative inflammatory reaction in the anterior chamber or by hypoxia directly or indirectly induced by persistent IOP elevation<sup>[7,17]</sup>. As noted earlier in these pages, ExPress implantation, in the present study, induced a lower rate of postoperative IOP fluctuation. ExPress implantation, furthermore, does not require a large sclerectomy or an iridectomy, which can reduce operative time and, thus too, postoperative inflammation. These differences might also

tend toward reduced postoperative endothelial cell loss in ExPress compared with Trab patients.

Another unfavorable factor with respect to postoperative endothelial damage is the use of antimetabolites and viscoelastics substances during surgery. Antimetabolites' corneal endothelial cytotoxicity has been demonstrated in previous studies<sup>[18-19]</sup>. Remnant viscoelastic material in the anterior chamber, meanwhile, can interfere with aqueous outflow, thereby inducing IOP spikes in the early postoperative period. Anterior chamber collapse during sclerostomy or peripheral iridectomy also can damage corneal endothelial cells.

The major limitations of our study are its small sample size (40 eyes) and retrospective design. Notwithstanding, this small group was sufficient to show statistically significant differences between the compared procedures, particularly in IOP fluctuation and the rate of endothelial cell loss. In any case, further studies with longer follow-up periods and larger numbers of subjects are required.

In summary, ExPress implantation, as compared with trabeculectomy, is a more predictable and reproducible technique that is less subject to variability. Especially, it appears to have early-postoperative advantages such as reduced rates of IOP fluctuation and corneal endothelial cell loss. ExPress implantation also is an effective treatment in cases of low-ECD advanced-stage glaucoma for which stable IOP reduction is essential.

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**Authors' Contributions:** Lee GY conceived of the study, and was major contributor in writing the manuscript. Lee CE participated in its design and coordination and helped to draft the manuscript. Lee KW conducted the study, and help to collect the data. Seo S made substantial contributions to analysis and interpretation of data and give final approval of the version to be published. All authors read and approved the final manuscript.

**Conflicts and Interest:** Lee GY, None; Lee CE, None; Lee KW, None; Seo S, None.

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