Peripapillary Microvascular Improvement and Lamina Cribrosa Depth Reduction After Trabeculectomy in Primary Open-Angle Glaucoma

Joong Won Shin,1 Kyung Rim Sung,1 Ki Bang Uhm,2 Jaehyuck Jo,1 Yeji Moon,1 Min Kyung Song,1 and Ji Yoon Song3

1Department of Ophthalmology, College of Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea.
2Department of Ophthalmology, College of Medicine, Hanyang University, Seoul, Korea
3Seoul International School, Seongnam-si, Gyeonggi-do, South Korea

Correspondence: Kyung Rim Sung, Department of Ophthalmology, University of Ulsan, College of Medicine, Asan Medical Center, 388-1 Pungnap-2-dong, Songpa-gu, Seoul 138-736, Korea; sungeye@gmail.com.

Submitted: August 10, 2017
Accepted: October 30, 2017

Purpose. To evaluate peripapillary microvascular changes in patients with primary open-angle glaucoma (POAG) after trabeculectomy using optical coherence tomography (OCT) angiography, and to determine the influence of lamina cribrosa (LC) displacement on changes in peripapillary microvasculature.

Methods. The peripapillary retinal microvasculature and LC were imaged using OCT angiography and OCT-enhanced depth imaging, respectively. The microvasculature and LC depth (LCD) were measured before, and 1 week, 1 month, and 3 months after trabeculectomy. The microvascular improvement was arbitrarily defined as a reduction >30% of the area of vascular dropout (blue/black areas with <20% vessel density on the color-coded vessel density map). LCD was determined as the mean of vertical distance between the anterior LC surface and a reference plane of Bruch’s membrane.

Results. Thirty-one eyes of 31 POAG patients were included. At 3 months postoperatively, intraocular pressure (IOP) and LCD were significantly decreased from 26.3 ± 11.8 mm Hg to 12.5 ± 3.6 mm Hg, and 501.1 ± 130.2 µm to 455.8 ± 112.7 µm, respectively (all P < 0.001), compared with baseline. The microvascular improvement was observed in 19 eyes (61.3%) at 3 months after trabeculectomy. The maximal reductions in IOP and LCD were significantly greater in eyes with improved microvasculature compared to eyes without improvement (P = 0.020 and P = 0.005). The microvascular improvement was significantly associated with maximal reduction in LCD (odds ratio, 1.062; P = 0.026).

Conclusions. Trabeculectomy can improve peripapillary retinal microcirculation in patients with POAG. This finding suggests that the reduction of LCD induced by lowering IOP may affect peripapillary microvascular improvement in eyes with POAG.

Keywords: glaucoma, trabeculectomy, intraocular pressure, optical coherence tomography angiography, lamina cribrosa.
the glaucoma clinic of Asian Medical Center (Seoul, Korea), between October 2016 and April 2017. The Institutional Review Board of Asian Medical Center approved this study, and the study design was executed in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all individuals who underwent trabeculectomy before participation.

At the initial evaluation, all subjects underwent a comprehensive ophthalmologic examination, including a review of medical history; best-corrected visual acuity assessment; refraction test; slit-lamp biomicroscopy; Goldmann applanation tonometry; gonioscopy; central corneal thickness assessment (DGH-550; DGH Technology, Inc., Exton, PA, USA); axial length measurement (IOLMaster; Carl Zeiss Meditec, Dublin, CA, USA); fundoscopic examination; stereoscopic optic disc photography; red-free photography; standard automated perimetry (Humphrey Field analyzer with Swedish Interactive Threshold Algorithm standard 24-2 test; Carl Zeiss Meditec); spectral-domain (SD)-OCT (Avanti RTVue-XR; Optovue, Inc., Fremont, CA, USA); and OCT-A (AngioVue; Optovue Inc.).

To be included, all subjects were required to have POAG, a best-corrected visual acuity of 20/40 or better, a spherical refraction of 8.0 to 3.0 diopters (D), a cylinder correction 3=3 D, and clear ocular media. POAG was defined as having an open angle on gonioscopy, history of IOP >21 mm Hg, retinal nerve fiber layer defects or glaucomatous optic disc changes (neuroretinal rim thinning, disc excavation, or disc hemorrhage), and corresponding visual field (VF) defects confirmed by at least two reliable VF examinations. Only reliable VF test results (i.e., false-positive errors <15%, false-negative errors <15%, and fixation loss <20%) were included in the study. A glaucomatous VF defect was defined as: the presence of a cluster of 3 nonedge contiguous points on a pattern deviation plot with P < 5% (1 of which had a P < 1%) confirmed by at least two consecutive examinations; a pattern standard deviation with P < 5% or a glaucoma hemifield test result outside normal limits. Patients with any ophthalmic or neurologic disease known to affect the optic nerve head or VF were excluded.

The indications for trabeculectomy were based on the progression of glaucomatous damage (VF and/or optic disc) and/or elevated IOP despite MTMT. All ocular hypotensive medications were continued up to the time of surgery. Patients with hypotony maculopathy or extremely low IOP of less than 6 mm Hg after trabeculectomy were excluded from this study. If both eyes met the inclusion criteria, one eye was randomly chosen for analysis. The IOP measurement, OCT-enhanced depth imaging, and OCT-A imaging were performed at 1 week, and 1 and 3 months after surgery.

**OCT-A Imaging**

The OCTA imaging system (AngioVue; Optovue, Inc.) provides noninvasive visualization of the retinal microvasculature. A split-spectrum amplitude-decorrelation angiography algorithm was used to identify perfused vessels by capturing the dynamic motion of moving particles, such as red blood cells. Details of this algorithm have been previously described. In this study, each patient underwent peripapillary OCT-A imaging of a 4.5 × 4.5 mm region centered on the optic disc. The microvascular information is presented as a vessel density map or color-coded vessel density map in the whole retina layer between internal limiting membrane and retinal pigment epithelium. It also provides a quantitative vessel density (%) measurement, calculated as the percentage of measured area occupied by vessels with flowing blood. Circumpapillary vessel density (cpVD) was measured in a region defined as a 750 μm-wide elliptical annulus extending from the optic disc boundary.

All scans were individually reviewed by two investigators (JWS, KRS) for evaluation of quality. Eyes with poor image qualities were excluded on the basis of the following criteria: signal strength index (SSI) <40; poor-clarity images; localized weak signal caused by artifacts such as floaters; residual motion artifacts visible as irregular vessel patterns or disc boundary on the enface angiogram; or segmentation failure.

**Determination of Microvascular Improvement**

To determine microvascular improvement, the vascular dropout (red regions) was compared between the color-coded vessel density maps before and 3 months after trabeculectomy. The vascular dropout was defined as blue/black areas with <20% vessel density on the color-coded vessel density map. The microvascular improvement was defined as a reduction of >30% of the area of vascular dropout. The postoperative image was registered to the preoperative image, then same regions (green regions) were compared. In this case, the area of vascular dropout was decreased from 6.75 mm² to 4.44 mm² (34.2% reduction) after trabeculectomy and, therefore, is considered to be an improvement.

All scans were individually reviewed by two investigators (JWS, KRS) for evaluation of quality. Eyes with poor image qualities were excluded on the basis of the following criteria: signal strength index (SSI) <40; poor-clarity images; localized weak signal caused by artifacts such as floaters; residual motion artifacts visible as irregular vessel patterns or disc boundary on the enface angiogram; or segmentation failure.
The LC was imaged at 4.5 × 4.5 mm region (304 × 304 A-scans) using the enhanced depth imaging technique with SD-OCT (Avanti RTVue-XR; Optovue, Inc.). Details of this technique to evaluate the LC have been described previously. 22,23 To determine LC depth (LCD) and choroidal thickness, 7 B-scans were selected from the three-dimensional image dataset of SD-OCT. Seven B-scan images spaced equidistantly across the vertical optic disc diameter. The anterior LC surface was delineated manually in all B-scans. The Bruch’s membrane positions were marked at 500 μm from the termination of Bruch’s membrane and used to create reference plane. The LCD was defined as the vertical distance between the anterior LC surface and reference plane. Only the temporal part of the LC from the maximally depressed point was used for LCD measurement. In each B-scan, the average LCD was calculated by the mean of depth measurements with reference plane. The choroidal thickness (white arrows) was measured at every 500 μm from the end of the Bruch’s membrane in each B-scan. Measurements from seven B-scans were averaged and defined as the LCD and choroidal thickness of the eye.

Microvascular Change After Trabeculectomy

To determine LCD, seven B-scans (green line) were selected from the three-dimensional image dataset of SD-OCT. Seven B-scan images were spaced equidistantly across the vertical optic disc diameter. The Bruch’s membrane position was marked at 500 μm from the termination of Bruch’s membrane and used to create reference plane (red dotted lines). The LCD was defined as the vertical distance between the anterior LC surface and reference plane. Only the temporal part of the LC from the maximally depressed point was used for LCD measurement. In each B-scan, the average LCD was calculated by the mean of depth measurements with reference plane. The choroidal thickness (white arrows) was measured at every 500 μm from the end of the Bruch’s membrane in each B-scan. Measurements from seven B-scans were averaged and defined as the LCD and choroidal thickness of the eye.

Measurement of LC Depth and Choroidal Thickness

The LC was imaged at 4.5 × 4.5 mm region (304 × 304 A-scans) using the enhanced depth imaging technique with SD-OCT (Avanti RTVue-XR; Optovue, Inc.). Details of this technique to evaluate the LC have been described previously. 22,23 To determine LC depth (LCD) and choroidal thickness, 7 B-scans were selected from the three-dimensional image dataset of SD-OCT. Seven B-scan images spaced equidistantly across the vertical optic disc diameter. The anterior LC surface was delineated manually in all B-scans. The Bruch’s membrane positions were marked at 500 μm from the termination of Bruch’s membrane and used to create reference plane. The LCD was defined as the vertical distance between the anterior LC surface and reference plane. Only the temporal part of the LC from the maximally depressed point was used because the maximally depressed point was often close to the central vessel trunk of which the shadow obscured the LC. In each B-scan, the average LCD was calculated by the mean of depth measurements with reference plane; subsequently, seven B-scans were averaged and defined as the LCD of the eye (Fig 2). The choroidal thickness was measured at every 500 μm from the end of the Bruch’s membrane in each B-scan; subsequently, seven B-scans were averaged and defined as the choroidal thickness of the eye. For follow-up measurements, sets of B-scans were selected to correspond to those that had been selected for the baseline measurements. The LCD and choroidal thickness were measured by two examiners (JWS, MKS) and the intraclass correlation coefficient (ICC) was calculated.

Statistical Analysis

Normality of the data was confirmed in all continuous variables by the Kolmogorov-Smirnov test. The clinical characteristics were compared between eyes with improved and non-improved peripapillary microvasculature after trabeculectomy using the independent t-test for continuous variables and χ2 test for categoric variables. The preoperative and postoperative IOP, LCD, and cpVD values were compared using repeated measures analysis of variance (rANOVA) in the improved and nonimproved groups, respectively. Univariate logistic regression analysis was used to determine the factors associated with the improved peripapillary microvasculature after trabeculectomy. Then, stepwise multivariate logistic regression was performed for variables with a P value < 0.10 in the univariate analysis. Statistical analysis was performed using statistical software (SPSS version 20; IBM Corp., Armonk, NY, USA). P value ≤ 0.05 was considered to be statistically significant.

RESULTS

A total of 45 eyes of 45 POAG patients who underwent trabeculectomy were initially enrolled. Of these, 11 subjects were excluded due to poor image quality and 3 were excluded due to extremely low postoperative IOP. A total of 31 eyes of 31 POAG patients (20 male, 11 female) who underwent trabeculectomy were included in the final analysis. At the baseline examination, the mean age, refractive error, axial length, central corneal thickness, IOP, and VF MD were 56.1 years, −1.46 ± 2.53 D, 24.71 ± 1.65 mm, 54.9 ± 30.2 mm, 26.3 ± 11.8 mm Hg, and −17.25 ± 11.79 dB, respectively. The interobserver ICCs for measurement of the LCD and choroidal thickness was 0.942 (95% confidence interval [CI] 0.898–0.981; P < 0.001) and 0.960 (95% CI 0.931–0.985; P < 0.001), respectively.

At 3 months postoperatively, the IOP and LCD were significantly decreased from 26.5 ± 11.8 mm Hg to 12.5 ± 3.6 mm Hg and 501.1 ± 130.2 μm to 455.8 ± 112.7 μm, respectively (all P < 0.001, rANOVA). Although the cpVD and choroidal thickness were increased from 44.9% ± 6.0% to 47.0% ± 7.2%, and 130.9 ± 44.4 μm to 138.4 ± 51.9 μm, respectively, this difference was not statistically significant (P = 0.133 and 0.127, respectively).
The peripapillary microvascular improvement was observed in 19 (61.3%) eyes at 3 months after trabeculectomy. Table 1 summarizes the clinical characteristics of eyes with and without microvascular improvement. There were no significant differences in IOP, LCD, choroidal thickness, cpVD, and SSI between eyes with and without microvascular improvement during entire follow-up period. However, maximal reductions in IOP and LCD were significantly greater in eyes with microvascular improvement than eyes without (P = 0.020 and P = 0.005, respectively).

Figure 3 describes the measurements of IOP, LCD, and cpVD at each follow-up visit according to microvascular changes. The IOP was significantly decreased through entire postoperative period compared to preoperative IOP, regardless of microvascular improvement (all P ≤ 0.05). Similarly, a significant reduction in LCD was observed during entire postoperative period, regardless of microvascular improvement (all P < 0.05). The cpVD exhibited a significant increase at 1 and 3 months postoperatively in eyes with microvascular improvement (P = 0.008 and 0.015, respectively).

The results from the logistic regression analysis examining peripapillary microvascular improvement after trabeculectomy are summarized in Table 2. Based on the univariate logistic analysis, microvascular improvement was significantly associated with maximal reductions in IOP (odds ratio [OR], 1.154; P = 0.025) and LCD (OR, 1.049; P = 0.019). Image quality (i.e., SSI) showed borderline significance (OR, 0.941; P = 0.074). The multivariate logistic regression was performed for variables with a P value <0.10 in the univariate analysis. In multivariate analysis, microvascular improvement was significantly associated with maximal reduction in LCD (OR, 1.062; P = 0.026).

**Representative Case**

Figure 4 depicts a representative case involving a 54-year-old woman with POAG (preoperative IOP, 32 mm Hg; VF MD, −21.11 dB) who demonstrated microvascular improvement after trabeculectomy. The postoperative IOP was decreased to 9 mm Hg at 1 week, then gradually increased to 11 mm Hg at 1 month, and 14 mm Hg at 3 months. During the 3-month follow-up period, the retinal microvasculature was gradually improved at the area of vascular dropout with a significant reduction in LCD.

**DISCUSSION**

In the current study, we observed peripapillary microvascular improvement in 61.3% of eyes after trabeculectomy. More importantly, the most relevant factor for microvascular improvement after surgery was the amount of maximal reduction in LCD. The posterior displacement of the LC is
TABLE 2. Factors Associated With Peripapillary Microvascular Improvement After Trabeculectomy

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P</td>
<td>Odds Ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>1.003 (0.949–1.059)</td>
<td>0.912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axial length</td>
<td>0.804 (0.501–1.312)</td>
<td>0.413</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central corneal thickness</td>
<td>0.989 (0.962–1.041)</td>
<td>0.899</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual field mean deviation</td>
<td>0.974 (0.894–1.062)</td>
<td>0.555</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.034 (0.966–1.108)</td>
<td>0.356</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 1 week</td>
<td>1.092 (0.966–1.316)</td>
<td>0.356</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 1 month</td>
<td>0.962 (0.743–1.246)</td>
<td>0.772</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 3 month</td>
<td>1.024 (0.917–1.142)</td>
<td>0.676</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum change</td>
<td>1.154 (1.008–1.136)</td>
<td>0.025</td>
<td>1.116 (0.980–1.272)</td>
<td>0.099</td>
</tr>
<tr>
<td>Lamina cribrosa depth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.982 (0.937–1.028)</td>
<td>0.437</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 1 week</td>
<td>0.981 (0.934–1.030)</td>
<td>0.446</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 1 month</td>
<td>0.986 (0.916–1.023)</td>
<td>0.252</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 3 month</td>
<td>1.031 (0.896–1.187)</td>
<td>0.668</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum change</td>
<td>1.049 (1.008–1.102)</td>
<td>0.019</td>
<td>1.062 (1.007–1.119)</td>
<td>0.026</td>
</tr>
<tr>
<td>Choroidal thickness, μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.995 (0.978–1.012)</td>
<td>0.549</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 1 week</td>
<td>0.996 (0.981–1.011)</td>
<td>0.572</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 1 month</td>
<td>0.993 (0.979–1.008)</td>
<td>0.383</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 3 month</td>
<td>0.995 (0.978–1.008)</td>
<td>0.340</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum change</td>
<td>0.994 (0.960–1.029)</td>
<td>0.729</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signal strength index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.941 (0.875–1.013)</td>
<td>0.074</td>
<td>1.014 (0.920–1.116)</td>
<td>0.785</td>
</tr>
<tr>
<td>Postoperative 1 week</td>
<td>0.922 (0.843–1.009)</td>
<td>0.154</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 1 month</td>
<td>1.075 (0.966–1.198)</td>
<td>0.186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 3 month</td>
<td>1.097 (0.950–1.266)</td>
<td>0.209</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 4. A representative case involving a 54-year-old woman with POAG exhibiting gradual microvascular improvement (red arrows) after trabeculectomy. The retinal microvasculature was gradually improved at inferotemporal (postoperative 1 week); superonasal (1 month); and superior region (3 months) with reversal of LC. To determine the reversal of LC, the postoperative LCDs (red regions) were compared with the preoperative LCD (green region).
Microvascular Change After Trabeculectomy

This study had several limitations. The small number of patients may limit the generalizability of our findings to the entire population of patients with glaucoma. Our patients were observed for only up to 3 months after trabeculectomy. The IOP-lowering effect decreases gradually after surgery. A long-term sustained IOP reduction has been reported to be associated with a slow rate of progressive RNFL thinning after trabeculectomy rather than early postoperative LCD reduction. Therefore, further research is needed to determine whether microvascular improvement persists over a long-term follow-up period. Recently, it has been reported that LC curvature was reduced after trabeculectomy, and thus it would be interesting to explore the effect of LC curvature change on microvascular improvement in forthcoming study.

In conclusion, we demonstrated microvascular improvement in POAG patients 3 months after trabeculectomy using OCT-A. The maximal reduction in LCD after surgery was significantly associated with microvascular improvement. The recovery of retinal microvasculature using surgical treatment may be supportive evidence of protection from the progression of glaucomatous damage. Further study investigating whether this microvascular improvement persists and whether it provides predictive insights for prognosis of glaucoma patients who undergo filtering surgery should be pursued.

Acknowledgments

Supported by a grant (2016-0411) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, South Korea, and by the Basic Science Research Program through the National Research Foundation of Korea (NRF), which is funded by the Ministry of Education, Science, and Technology (No. NRF-2014R1A1A1A0501089). The authors alone are responsible for the content and writing of the paper.

Disclosure: J.W. Shin, None; K.R. Sung, None; K.B. Uhm, None; J. Jo, None; Y. Moon, None; M.K. Song, None; J.Y. Song, None

References

8. Bungoyme CF, Downs JC, Bellezza AJ, et al. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the...


