Changes in Macular Perfusion after Trabeculotomy Operation in Primary Open Angle Glaucoma by Optical Coherence Tomography Angiography

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Received:27-10- 2022, Accepted: 10-11-2022, Published online:16-12-2022

EJO(MOC) 2022;4:228-237.

Short Title: Changes in Macular Perfusion after Trabeculotomy Operation in POAG by OCTA.

Abstract:

Purpose: The aim of study is to evaluate changes in macular vessel density after trabeculotomy operation and reduction of intra ocular pressure (IOP) in primary open angle glaucoma (POAG) by optical coherence tomography angiography (OCTA).

Methods: The study included 28 eyes presented by POAG who were treated at an Ophthalmic Center in Egypt between February 2018, till august 2019. All studied eyes underwent visco-trabeculotomy operation. Macular vessel density (VD) was evaluated by OCTA pre-operative and then for 3 months postoperative.

Results: The mean age of the study patients was 55.96 ± 10.43 years. They included 23 males (82.1%) and 5 females (17.9%). The mean preoperative IOP was 26.55 ± 7.279. At 3 months follow up the mean IOP was 13.20 ± 4.69 with P< 0.001. There was a significant improvement in mean foveal VD from 15.04 ± 4.23 preoperatively to 18.47 ± 4.71 at 3 months postoperatively with p< 0.001. The mean superior macular zone also showed significant improvement from 45.55 ± 4.54 preoperatively to 48.84 ± 5.80 at 3 months with p=0.027. Mean inferior macular VD showed improvement from 46.69 ± 5.62to 49.95 ± 7.10 three months post operatively with P=0.031. There was no significant change in nasal macular density, while in temporal macular vessel density there was early reduction in the mean VD from 45.01 ± 3.79 to 43.27 ± 3.97 two weeks postoperatively. However, it returned to near preoperative value in the next follow ups to 45.04 ± 5.19 at three months.

Conclusions: The current study showed changes in macular vessel density after trabeculotomy operation in patients with primary open angle glaucoma correlated with IOP reduction. However, it has yet to be evaluated whether these changes have a significant clinical significance in long-term follow-up.

Key Words: open angle glaucoma, visco-trabeculotomy, optical coherence tomography angiography.

INTRODUCTION

Glaucoma is one of the most important causes of blindness in humans, affecting 2% of the population. There is wide variation of the prevalence of different types of glaucoma according to the geographic region all over the world. Primary open-angle glaucoma (POAG) is one of the most prevalent types of glaucoma which is characterized by progressive destruction of retinal ganglion cell death, optic nerve head excavation and visual field loss[1].

Persistently elevated intra ocular pressure (IOP) in addition to IOP fluctuations are the major risk factors for progression of glaucoma. In cases with advanced glaucoma, it has been reported that a 40% decrease in IOP is required for stopping the disease progression. However, even with maximum medical therapy, this reduction couldn't be achieved. Moreover, short- and long-term fluctuations in IOP may also occur with medical therapy. Control of peak diurnal or long-term IOP fluctuations is of a great importance as soon as there are structural or functional progression observed in a patient with low office measurement of IOP. Poor patient compliance may also be a problem for maintaining medical treatment[2].

Abnormalities of the blood flow and vessel autoregulation were reported to play major role in the

pathogenesis and progression of POAG. Various types of ocular hemodynamic deficits were reported in many studies in eyes with POAG, including reduction of the choroidal and retrobulbar blood flow in eyes with more advanced glaucoma[3].

Ocular hemodynamic changes after IOP reduction surgeries have been reported in many studies. Most of these studies reported that, following trabeculectomy, there is a significant decrease of IOP with subsequent an increase in ocular blood flow parameters[4].

Improvement of the retinal microcirculation is also expected, yet this was not confirmed. In the last few years, the use optical coherence tomography angiography (OCT-A) allows visualization of the microvascular networks of the retinal capillaries. Using this technique helps to provide reproducible, noninvasive and quantitative data of the peripapillary and macular retinal microvasculature[5].

There are many reports of good intraocular pressure control via trabeculotomy in POAG[6]. Therefore, we established this study to assess the changes in macular perfusion after trabeculotomy operation in primary open angle glaucoma

METHODS

A prospective, noncomparative, interventional study was done including 28 eyes of patients with POAG presented to Mansoura Ophthalmic Center in Mansoura, Egypt, between February 2018, till august 2019. The study was conducted after approval from institutional review board (IRB MS.18.03.55. R1.R2.R3), Faculty of Medicine of Mansoura University and was carried out in accordance with the Decleration of Helsinki, after obtaining a written informed consent from all the participants before their inclusion in the study after explaining all possible risk factors.

Inclusion criteria included Patients with primary open angle glaucoma based on the optic nerve head appearance typical to glaucoma (increased optic disc cupping, thinning of the neuroretinal rim, focal notching, splinter haemorrhage), corresponding visual field loss typical to glaucoma together with an elevated IOP above 21 mmHg and a gonioscopically open angle in the absence of any cause for secondary glaucoma.

Anti-glaucoma medications were initiated for all patients and only those patients in whom the IOP control failed (as evidenced by progressive optic nerve head damage and/or visual field deterioration) and the decision for surgery to lower the IOP was taken were enrolled in the study. Patients above 40 years of age fulfilling these criteria were enrolled.

While exclusion criteria included media opacity that does not permit optical coherence tomography acquisition with good signal strength, poor papillary dilatation, history of previous intraocular surgery, high myopic fundus and patients with macular pathology. Full history was obtained from each case including demographic data (age, sex) and related medical history (eg, systemic diseases such as diabetes and hypertension, neurologic or metabolic diseases). All patients underwent full ophthalmic examination including best corrected visual acuity (BCVA) assessment. VA was measured with Landlot's broken rings chart, and converted to Log MAR for statistical analysis using Snellen chart (auto chart projector CP 670; Nidek Co., Ltd, Gamagori, Japan), Anterior segment slit lamp examination (Topcon SL-7F Slit Lamp - Alternup Medical, France), central corneal thickness using pachymetry and measurement of IOP using Goldmann applanation tonometer (Tono-Pen XL Medtronic Solan, Jacksonville, FL, USA). Gonioscopy was used to asses the anterior chamber angel and Volk lens 78 diopter was used for fundus examination.

All patients then underwent Visco-Trabeculotomy operations by one surgeon (Prof. Dr. A. Elwehidy), starting with a fornix based conjunctival incision. Then a 4 × 4 mm triangular sclera double flap was created at the limbus. After identification of Schlemm's canal, a scalpel was used to cut its outer wall followed by excised with fine scissors. Then injection of high-viscosity sodium hyaluronate (Healon GV) was slowly performed and in the form of repeated boli then repeating this procedure on the other side. U-shaped probes (Harms trabeculotomy probe) were then inserted into both ends of the opened canal and rotated 90 degrees against the trabecular meshwork and toward the anterior chamber to achieve a 120-degree opening of the trabecular meshwork. After removal of the inner flap, the scleral flap was closed with three 10–0 nylon sutures. Conjunctival sutures were then placed. Follow ups were at 2 weeks, 1 month and 3

months by anterior segmen examination and aseesment of IOP, BCVA, C/D ratio and fundus examination.

Post operative follow up was done first day, one week, 2 weeks, 1 month and 3 months postoperative. Postoperative treatment consisted of topical steroids (dexamethasone) and antibiotic (ofloxacin) five times daily with gradual taper over a 5 week period. Cycloplegic drops (cyclopentolate) was used 3 times daily for the first postoperative week and then discontinued.

All patients were scanned preoperatively then 2 weeks, 1 month and 3 months postoperative with Swept source optical coherence tomography (DRI-OCT1 Atlantis system, Topcon, Tokyo, Japan) (SS-OCT) for macular vessel density.

Statistical analysis

Data were entered, analyzed and tabulated by using Statistical Package for the Social Sciences (SPSS 23, IBM/SPSS Inc., Chicago, IL) software for analysis. Basal criteria of the cases were presented as frequencies and percentages (%) or mean values and standard deviations (SD) (after testing of normality by Kolmogorov-Smirnov and Shapiro-Wilk's tests). For comparison of quantitative data between two related groups (in comparison with their basal values), paired-samples t-test. or Wilcoxon test were used for parametric and non-parametric data respectively. For all tests, P values <0.05 are considered significant.

RESULTS

The study included 28 eyes of patients presented by POAG who were treated at Mansoura Ophthalmic Center in Mansoura, Egypt. The patient demographics and medical history are presented in Table 1.

Table 1. Demographic data of the Studied patients

		All patients (n= 28)
		Mean & SD
Age		55.96 ± 10.43
Gender	**Male**	82.1% (23)
	Female	17.9% (5)
DM		28.6% (8)
HTN		35.7% (10)
Hepatic		7.1% (2)
Hyperthyroidism		10.7% (3)

Data is expressed as mean and standard deviation or percentage and frequency.

The mean preoperative BCVA in logMAR in studied patients was (0.52 ± 0.40). It showed significant reduction 2 weeks postoperatively into (0.65 ± 0.43). However, It improved again to (0.58 ± 0.34) one month and (0.47 ± 0.40) three months postoperatively (Table 2).

Table 2. Comparison between Preoperative and postoperative best corrected visual acuity:

BCVA	**All patients (n= 28)**			
	Preoperative	**Two weeks postoperative**	**One month postoperative**	**Three months postoperative**
Mean & SD	0.52 ± 0.40	0.65 ± 0.43	0.58 ± 0.34	0.47 ± 0.40
P	-	**0.013**	0.073	0.267

Data is expressed as mean and standard deviation. P value is generated by comparing each reading to the basal value. P is significant when < 0.05.

The mean preoperative IOP was (26.55 ± 7.279) mmHg. It showed significant reduction two weeks post operatively to (12.18 ± 3.10) mmHg, with continued reduction during follow ups into (13.40 ± 5.84) mmHg and (13.20 ± 4.69) mmHg in the following one month and three months respectively (Table 3) (Fig 1).

Table 3. Comparison between preoperative and postoperative intra-ocular pressure:

IOP	**All patients (n= 28)**			
	Preoperative	**Two weeks postoperative**	**One month postoperative**	**Three months postoperative**
Mean & SD	26.55 ± 7.279	12.18 ± 3.10	13.40 ± 5.84	13.20 ± 4.69
P	-	**< 0.001**	**< 0.001**	**< 0.001**

Data is expressed as mean and standard deviation. P value is generated by comparing each reading to the basal value. P is

significant when < 0.05.

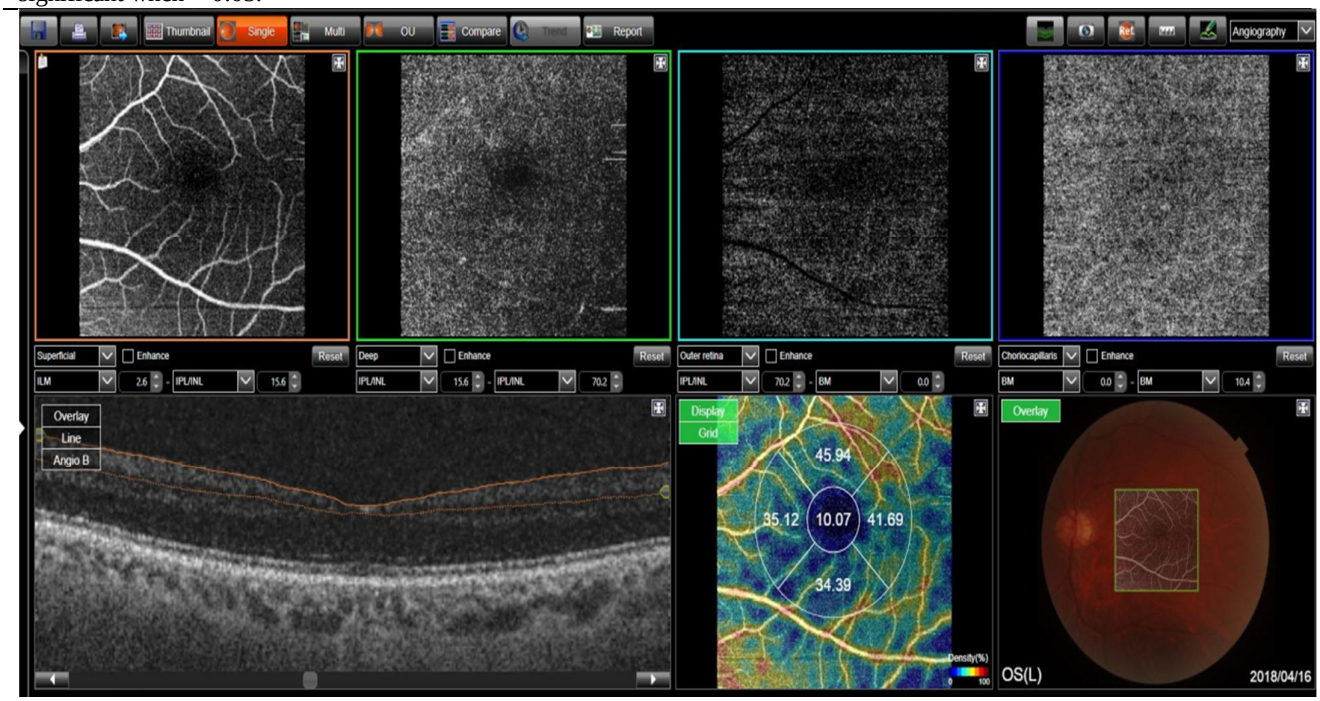

Figure (1): preoperative OCTA

Post operative complications included mild hyphema in 5 cases, which resolved within 1 week. Hypotony and slight transient drop in BCVA in 4 cases , which may be attributed to macular edema.

The mean cup-disc ratio showed insignificant change during postoperative follow up periods from (0.80 ± 0.11) preoperatively to (0.83 ± 0.11), (0.80 ± 0.13) and (0.79 ± 0.13) at 2 weeks, one month and three months postoperatively respectively (Table 4).

Table 4. Comparison between preoperative and postoperative mean cup disc ratio:

C\D ratio	**All patients (n= 28)**			
	preoperative	**Two weeks postoperative**	**One month postoperative**	**Three months postoperative**
Mean & SD	0.80 ± 0.11	0.83 ± 0.11	0.80 ± 0.13	0.79 ± 0.13
P	-	0.070	0.813	0.646

The mean foveal vessel density changed from (15.04 ± 4.23) preoperatively to (17.56 ± 6.81) two weeks postoperatively, with significant increase in the next follow ups to (18.31 ± 5.77) at one month and (18.47 ± 4.71) at three months postoperatively (Table 5).

Table 5. Comparison between preoperative and postoperative foveal vessel density:

Foveal vessel density	**All patients (n= 28)**			
	preoperative	**Two weeks postoperative**	**One month postoperative**	**Three months postoperative**
Mean & SD	15.04 ± 4.23	17.56 ± 6.81	18.31 ± 5.77	18.47 ± 4.71
P	-	0.055	**0.003**	**< 0.001**

Data is expressed as mean and standard deviation. P value is generated by comparing each reading to the basal value. P is significant when < 0.05.

The mean preoperative superior macular vessel density was (45.55 ± 4.54). It changed in the next follow ups to (46.32 ± 5.21) two weeks postoperatively and to (47.73 ± 5.76) one month postoperatively. It also showed significant increase three months postoperatively to (48.84 ± 5.80) (table 6).

Table 6. Comparison between Preoperative and postoperative superior macular vessel density:

Superior macular	**All patients (n= 28)**			
	preoperative	**Two weeks postoperative**	**One month postoperative**	**Three months postoperative**
Mean & SD	45.55 ± 4.54	46.32 ± 5.21	47.73 ± 5.76	48.84 ± 5.80
P	-	0.472	0.091	**0.027**

Data is expressed as mean and standard deviation. P value is generated by comparing each reading to the basal value. P is significant when < 0.05.

The mean preoperative inferior macular vessel density was (46.69 ± 5.62). It changed 2 weeks postoperatively to (47.86 ± 6.45), with significant changes to (48.55 ± 5.78) one month and (49.95 ± 7.10) three months postoperatively (Table 7) (Fig 2).

Table 7. Comparison between Preoperative and postoperative inferior macular vessel density:

Inferior macular	**All patients (n= 28)**			
	Preoperative	**Two weeks postoperative**	**One month postoperative**	**Three months postoperative**
Mean & SD	46.69 ± 5.62	47.86 ± 6.45	48.55 ± 5.78	49.95 ± 7.10
P	-	0.279	**0.048**	**0.031**

Data is expressed as mean and standard deviation. P value is generated by comparing each reading to the basal value. P is significant when < 0.05.

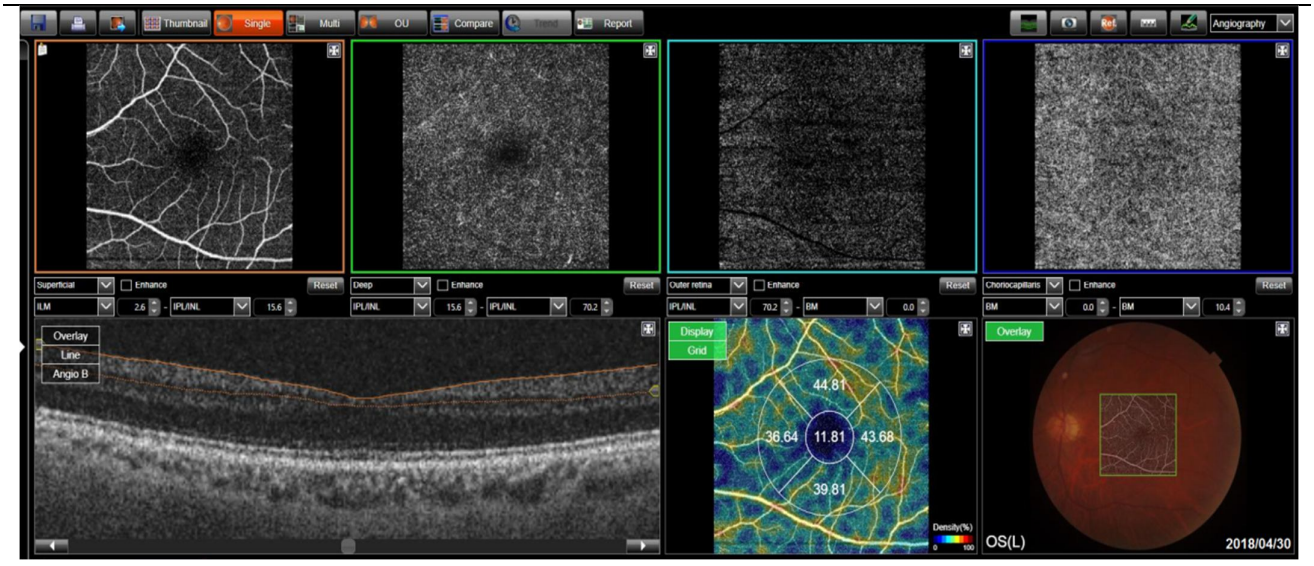

Figure (2): two weeks postoperatively

The mean nasal macular density changed from (43.99 ± 4.57) preoperatively to (43.95 ± 3.87) two weeks, (43.88 ± 3.51) one month and (43.79 ± 5.72) three months postoperatively (table 8).

Table 8. Comparison between preoperative and postoperative nasal macular vessel density:

Nasal macular	**All patients (n= 28)**			
	Preoperative	**Two weeks postoperative**	**One month postoperative**	**Three months postoperative**
Mean & SD	43.99 ± 4.57	43.95 ± 3.87	43.88 ± 3.51	43.79 ± 5.72
P	-	0.957	0.896	0.868

Data is expressed as mean and standard deviation. P value is generated by comparing each reading to the basal value. P is significant when < 0.05.

The mean preoperative temporal macular vessel density was (45.01 ± 3.79). It showed significant reduction two weeks postoperatively to (43.27 ± 3.97). However, it improved again in the next follow ups to (45.04 ± 4.70) one month and (45.04 ± 5.19) three months postoperatively (Table 9) (Fig 3 & 4).

Table 9. Comparison between Preoperative and postoperative temporal macular vessel density:

Temporal macular	**All patients (n= 28)**			
	preoperative	**Two weeks postoperative**	**One month postoperative**	**Three months postoperative**
Mean & SD	45.01 ± 3.79	43.27 ± 3.97	45.04 ± 4.70	45.04 ± 5.19
P	-	**0.043**	0.980	0.982

Data is expressed as mean and standard deviation. P value is generated by comparing each reading to the basal value. P is significant when < 0.05.

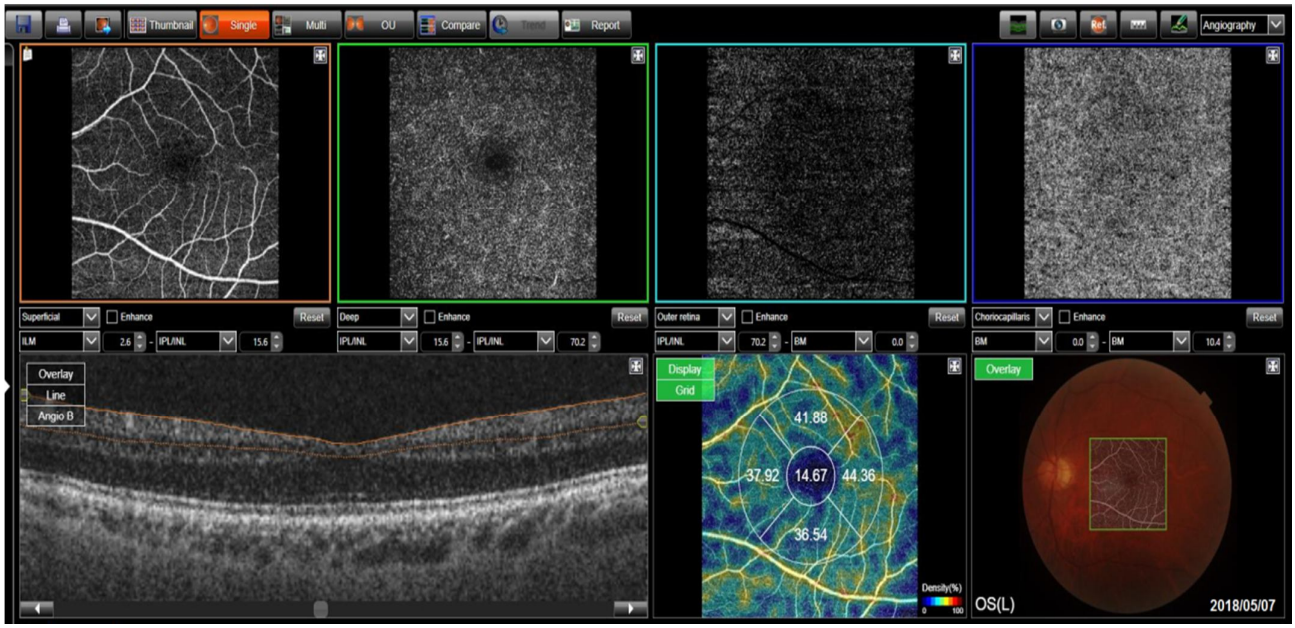

Figure (3) one month postoperatively

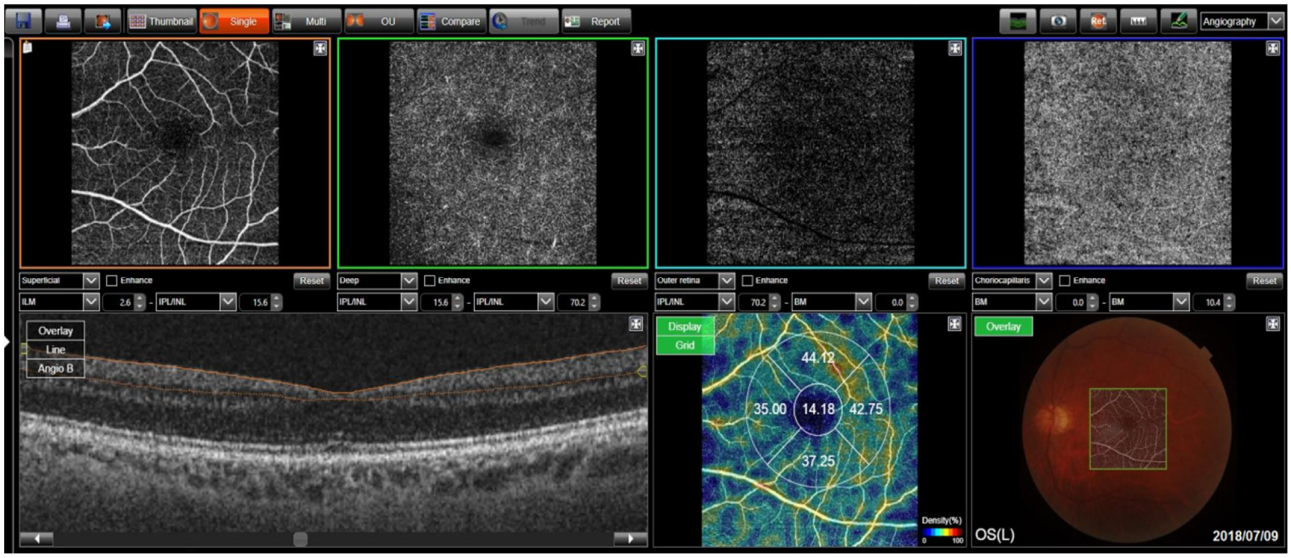

Figure (4) three months postoperatively

DISCUSSION

Open angle glaucoma is a chronic disease which is characterized by damage of the axons within the retinal ganglion cell layer, thinning of the peripapillary retinal nerve fiber layer (RNFL) and loss of fibers of intrapapillary nerve (‘‘cupping’’). Also, posterior displacement of the lamina cribrosa usually occurs in accordance with it. As a result of this anatomical change, the ocular circulation is affected in the form of ischemic insults[7]. IOP reduction generally induces an increase in ocular blood flow in consequence[8].

OCT-angiography (OCT-A) is a new technique that provides highly accurate visualization of retinal microvasculature. Moreover, itallows reproducible quantitative measurement of the vascular networks in the different regions of the retina[9].

Trabeculotomy causes relieve of the resistance to outflow through mechanical cleavage in the trabecular meshwork and the inner layer of Schlemm's canal, the regions mainly involved the resistance to outflow of aqueous humor[10].

This study was carried out at Mansoura ophthalmic center during the period from February 2018, till august 2019 on 28 eyes in 27 patients with POAG who underwent Visco-Trabeculotomy for reduction of IOP.

The results of the current study showed that trabeculotomy was successful in all involved patients in IOP reduction. The mean preoperative intra-ocular pressure was (26.55 ± 7.279)mmHg. It showed significant reduction two weeks post operatively to (12.18 ± 3.10), with continued reduction during follow ups into (13.40 ± 5.84) and (13.20 ± 4.69) in the following one month and three months respectively.

Similar results were reported by Sarkisian et al. who performed 360° ab-interno trabeculotomy in refractory primary open-angle glaucoma and showed significant IOP reduction at all follow ups, with mean IOP changing from 30.2 mmHg preoperatively to 23.2 mmHg at one month and 18.7 mmHg three months post operatively[11].

Also, Razeghinejad et al. who was concerned with Ab Interno Trabeculotomy for POAG in 88 patients the mean IOP dropped from 25.9 6 8.9 mmHg preoperatively to 19.4 6 8.1 mmHg at 1 month and 17.5 6 6.2 mmHg at 3 months[12].

Another study also showed similar results by Cubuk and Unsal. The study performed gonioscopy-assisted transluminal trabeculotomy on 37 patients with POAG. The IOP showed significant reduction also from 25.4 ± 8.4 mmHg preoperatively to 15.7 ± 4.0 mmHg at one month and 14.2 ± 2.2 mmHg at three months postoperatively[13].

As regard best corrected visual acuity, the mean preoperative BCVA in studied patients was (0.52 ± 0.40). It showed significant reduction 2 weeks postoperatively into (0.65 ± 0.43), then it showed improvement again to (0.58 ± 0.34) one month and (0.47 ± 0.40) three months postoperatively.

Similar results were reported by Aktas et al. who performed Transluminal Trabeculotomy in patients with moderate to advanced open angle glaucoma on104 patients.

There was no significant change in VA between the preoperative value (0.51 ± 0.24) and postoperative value in the last follow up (0.47 ± 0.21)[14].

On the other hand, Hasan et al. studied the results of trabeculectomy in POAG in 51 patients. The mean VA dropped from 0.17±0.17 preoperatively to 0.21±0.24 1year postoperatively[15].

The cup-disc ratio showed insignificant change during postoperative follow up periods from (0.80 ± 0.11) preoperatively to (0.83 ± 0.11), (0.80 ± 0.13) and (0.79 ± 0.13) at 2 weeks, one month and three months postoperatively respectively. The lack of improvement may be attributed to the advanced preoperative cupping, age of the patients or the chronic nature of the disease.

Similar results were reported by Paranhos Jr et al. who performed trabeculectomy operation on 22 eyes of patients with chronic open-angle glaucoma, pigmentary glaucoma, pseudoexfoliation syndrome, and low-tension glaucoma. There were no statistically significant changes in cup-disc ratio before and after the operation[16].

Another study by Kotecha, A. et al. who performed trabeculectomy operation on 70 adult patients found that there was significant improvement in the cup only after 2 years while there was no significant change at any point before that[17].

Regarding macular vessel density, in this study there was a significant improvement in vessel density % (VD) in foveal, superior and inferior macular zones with no significant changes in nasal zone. However, in the temporal zone there was a transient reduction in VD two weeks postoperatively, which increased again in the next follow ups.

The foveal vessel density showed a significant improvement from 15.04 ± 4.23 preoperatively to 18.31 ± 5.77 one month postoperatively and to 18.47 ± 4.71 at three months postoperatively.

As regard the superior macular zone VD there was a significant improvement at 3 months postoperatively from 45.55 ± 4.54 preoperatively to 48.84 ± 5.80 at 3 months.

The inferior macular zone showed significant improvement of VD one month and three months postoperatively and changed from 46.69 ± 5.62 preoperatively to 48.55 ± 5.78 at 1 month and 49.95 ± 7.10 at 3 months postoperatively.

On the other hand, there was a reduction in VD in the temporal macular zone from 45.01 ± 3.79 preoperatively to 43.27 ± 3.97 two weeks postoperatively. However, it improved again in the following follow ups to reach 45.04 ± 5.19 at 3 months postoperatively. This reduction could also be attributed to early post operative macular changes as a result of IOP reduction.

Similar results to our study were reported by Ch'nget al. who the studied the effects of surgeries that decrease IOP focused on NFL, foveal avascular zone, peripapillary and macular VD. They observed initial decrease in macular VD during the first month post-operatively, but a significant increase in VD 3 months post-operatively was then reported[18].

Also, Alnawaiseh et al. who studied changes in flow density by OCTA after iStent Insertion in Combination with Phacoemulsification in Patients with OAG, showed postoperative improvement in macular VD postoperatively from 44.6±2.9 to 47.6±4.5[19].

On the contrary, Lommatzschet al. studied changes in OCTA in 19 eyes with POAG before and after trabeculectomy there was no significant change in the macular VD at any postoperative time[20].

For the best of our knowledge to date, only a few studies have been conducted on macular VD changes after glaucoma operations as measured by OCTA.

Conclusions:

The current study showed changes in macular vessel density after trabeculotomy operation in patients with primary open angle glaucoma correlated with IOP reduction. However, it has yet to be evaluated whether these changes have a significant clinical significance in long-term follow-up.

DATA AVAILABILITY

All data are included in this article.

ACKNOWLEDGEMENT

None

Conflict of Interest

Authors declare no conflicts of interest.

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Ethics declarations

Conflict of interest

Ahmed S. Elwehidy, Wafaa T. Abd-Elfattah, Amal A. Abd-Elwahab, Rania K. Farag. all authors have no conflicts of interest that are directly relevant to the content of this review.

Funding: No sources of funding were used to conduct this review.

Reviewer disclosures: No relevant financial or other relationships to disclose.

Declaration of interest: No financial affiliations or financial involvement with any organization or entity with a financial competing with the subject matter or materials discussed in the review.

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