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Evaluation of corneal endothelial cells density after viscotrabeculotomy in primary open angle glaucoma

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Short title: CECD after viscotrabeculotomy in POAG.

Abstract:

Purpose: The aim of the study was to evaluate the effect of viscotrabeculotomy on corneal endothelial cells density in patients with primary open angle glaucoma.

Design: a prospective interventional uncontrolled study.

Patients and Methods: This study included 42 eyes of 42 patients diagnosed with POAG attending Mansoura ophthalmic center in the period of January2021-December2021. They underwent viscotrabeculotomy. Indirect specular microscopy (Tomey EM3000 corporation, Nagoya, Japan) was performed on central corneas and endothelial images were acquired. Endothelial cell density, area and cell counts were analyzed.

Results: Corneal endothelial cell density decreased in the 1st week postoperative with a statistically significant difference (P<0.001). The mean±SD was 2398.7± 222.8 at 1st week and preoperatively was 2492.7±183.7. At 2nd week follow up there was stability in CECD with no further decrease till 3rd month visit. Mean±SD was 2406.6±221.9 and 2402.9±203.7 at 2nd week and 3rd month respectively.

Conclusion: In our study there was no statistically significant change in corneal endothelial cell density after viscotrabeculotomy at the mean follow-up of 3 months duration.

Keywords: Corneal endothelial cells density, Viscotrabeculotomy, Open angle glaucoma

INTRODUCTION:

Corneal endothelium is the innermost layer of human cornea, which is critical in maintaining a healthy and clear cornea by a mechanism known as the pump-and leak hypothesis[1]**.** Damage to the corneal endothelium is irreversible which can occur as a consequence of intraocular surgery, trauma or diseases such as glaucoma[2]**.** At the early stage of endothelial damage, neighboring cells swell and/or migrate to compensate for the cell loss, which results in an increase in cell size (polymegatheism) and/or alteration of cell shape (polymorphism). Progression of cell loss further compromises corneal transparency and causes corneal edema, bullous keratopathy and impaired visual acuity[3]**.**

Glaucoma is a group of diseases characterized by a specific pattern of optic nerve neuropathy and retinopathy[4]. There is increasing evidence of glaucoma-associated corneal endothelial changes. Endothelial cell loss is attributed to both glaucoma itself and treatment that lowers intraocular pressure (IOP). A direct-compression mechanism due to elevated IOP has been proposed in corneal endothelial cells (CEC) loss in acute angle-closure glaucoma. In addition, cell toxicity after long-term exposure to preservatives in ocular hypotensive

drugs is considered another possible mechanism for endothelial damage. Moreover, endothelial cell loss caused by glaucoma surgery has been reported in patients after application of antiproliferative medications in filtration surgery and aqueous shunt implantation[5].

Viscotrabeculotomy is a surgical intervention performed to control intraocular pressure in patients with open-angle glaucoma. Reduction of IOP depends on aqueous humor filtration using Trabeculotome which is a surgical device that ablates an arc of trabecular meshwork[4]**.** Being less invasive, viscotrabeculotomy is expected to have less damaging effect on corneal endothelium. So, this study was conducted to evaluate the effect of Viscotrabeculotomy on corneal endothelial cells in patients with primary open angle glaucoma

PATIENTS AND METHODS:

This was a prospective interventional uncontrolled study conducted on a total of 42 patients with uncontrolled primary open angle glaucoma who underwent Visco-trabeculotomy. Patients were collected from Mansoura ophthalmic center within the period from January 2022 to December 2022 and followed the tenets of the declaration of Helsinki. Written consent was obtained from each participant before involvement. The study was approved by Institutional Research Board (IRB) (MS.22.03.1927), Faculty of Medicine, Mansoura University.

Patients with POAG were diagnosed based on presence of open angle on gonioscopy with glaucomatous optic nerve damage (NRR notching, thinning or NFL defect) that correspond to visual field defect. Patients with IOP >21mmHg not controlled with maximum tolerated medical treatment were included in this study.

Cases with closed angle glaucoma, secondary glaucoma, concomitant eye disease (e.g keratitis, uveitis, dry eye, ocular surface disease) and patients with history of previous ocular surgery or trauma were excluded from the current study. Detailed history was taken including demographic data, and past history of medical or surgical problems. Duration of glaucoma and number of anti-glaucoma medications were recorded.

Preoperative assessment was done including uncorrected and best corrected visual acuity (UCVA & BCVA) assessment using Landolts broken rings chart then converted to LogMAR.. Refraction was done–using automated refractometer (Topcon RM-800). Anterior segment assessment and fundus examination were done using slit lamp bio microscopy (Haag Streit BP 900). Evaluation of anterior chamber angle by gonioscopy, IOP measurement using goldmann applanation tonometer, assessment of optic nerve head appearance (increased optic disc cupping, thinning of the neuro-retinal rim, focal notching,splinter haemorrhage) using spectral domain OCT (3D, DRI, OCT Triton, Topcon, Oakland, NJ), ,corresponding visual field (VF) changes typical to glaucoma with standard automated perimetry(Zeiss Humphery instrument).Assessement of corneal endothelial cell density was performed using noncontact specular microscopy (Tomey EM3000 corporation, Nagoya, Japan).IOP lowering medication for all patients and only those with failed IOP control underwent surgical intervention.

Viscotrabecolotomy VT

All surgeries were performed by the same experienced surgeon (ASE.) under general anesthesia. Exposure of the operative field was done by a corneal traction suture (vicryl 6/0) placed superiorly followed by a superotemporal fornix based conjunctival flap creation (fig1, A). After adequate hemostasis, a partial thickness sclera flap was fashioned and dissected forward till the limbus (fig1, B). Radial incision was done gently to reach Schlemm's canal which was identified by minimal oozing of aqueous humor. (fig1, C, D). High-viscosity sodium hyaluronate (Healon GV, Pfizer, NY, USA) was injected (using a standard 30G viscocanalostomy cannula) through the ends of Schlemm's canal gradually after its deroofing (fig1, E). This was followed by inserting the angled Harms trabeculotome with a handle (Geuder Instruments, Heidelberg, Germany) into the canal of Schlemm along its path for the entire probe's length. Then, the probe was rotated into the anterior chamber and withdrawn through the incision. (fig1, F). This was repeated for the canal on the opposite side (fig1, G). A little amount of Healon GV was

again injected through the ends of Schlemm's canal into the anterior chamber to deepen it and to prevent further extension of hyphema. Closure of the scleral flap was then done with nylon sutures (10/0), followed by conjunctival securing using nylon sutures (10/0) (fig1, H).

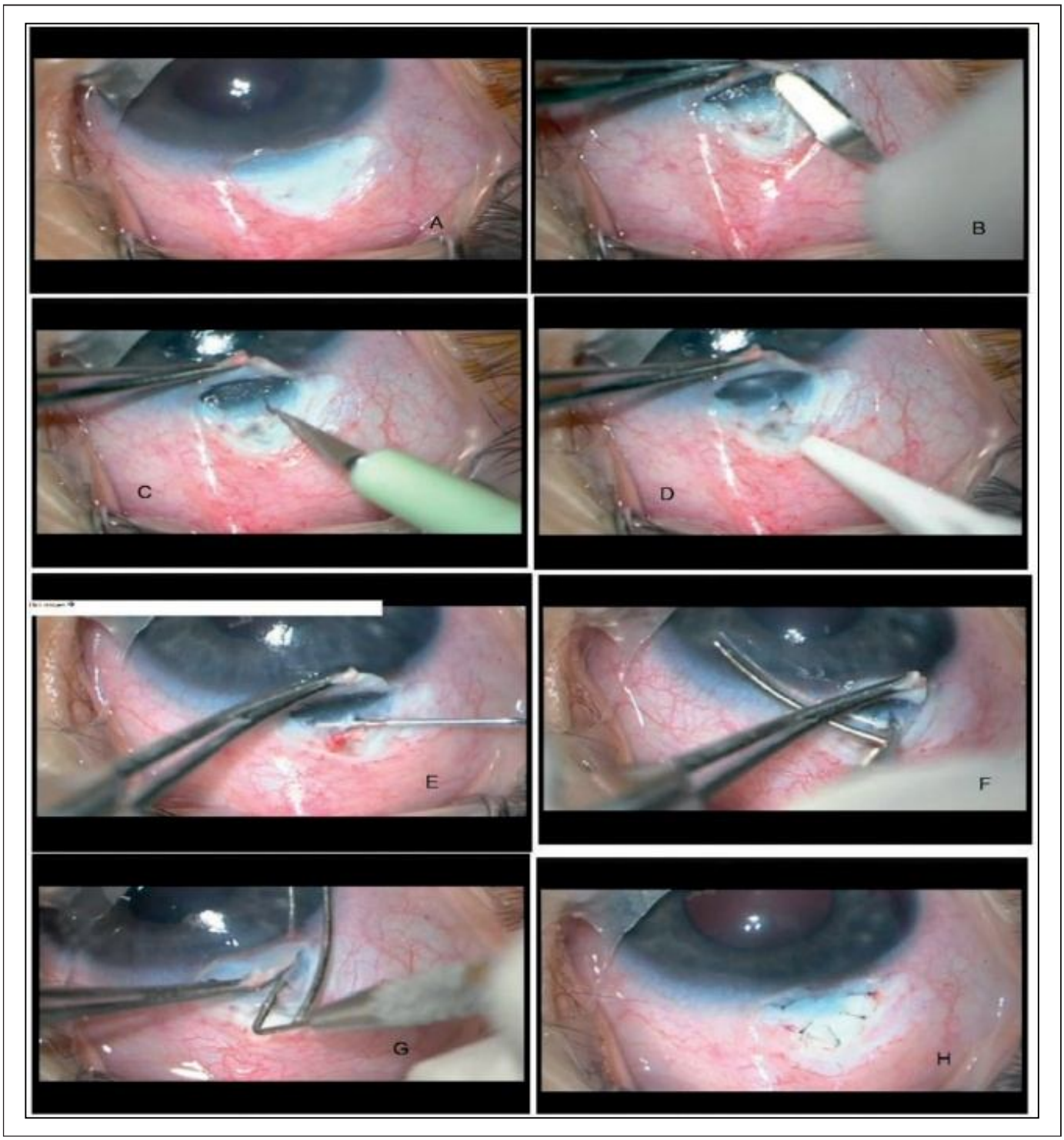

Figure 1: Steps of viscotrabeculotomy. (a: Fornix-based conjunctival peritomy, b: scleral flap dissection, c and d: locating Schlemm's canal, e: injection of viscoelastic material, f and g: trabeculotomy, h: closure of scleral flap.)

Postoperative treatment included topical antibiotic (ofloxacin) eye drops and topical steroids (dexamethasone) which were administered five times a day then tapered gradually over 1 month. Cycloplegics (cyclopentolate) were applied three times a day in the first week. Patients were examined on the first post-operative day and then postoperative follow up visits were scheduled at weeks 1 and 2 then months 1, 2 and 3.

Success was defined as complete success as IOP ≤ 18 mmHg (criteria 1), an IOP ≤ 16 mmHg (criteria 2), IOP ≤ 14 mmHg (criteria 3) and ≤ 12 mmHg (criteria 4) and/or IOP reduction by ≥ 30% of baseline IOP (last IOP measurement immediately before surgery) without IOP lowering medications. Qualified success was defined as IOP controlled according to the same criteria with/without IOP lowering medications, without the need for further surgery for IOP reduction and without any vision threatening complications or hypotony (IOP ≤ 5 mmHg)[6].

Statistical analysis:

Data was entered and analyzed using IBM-SPSS software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) Repeated measure ANOVA and pairewise comparison tests were used to compare the preoperative and postoperative variables. . Effect size was calculated as partial η^2 which was used to compute Cohen's f by using G Power software (version 3.1.9.7). Effect size was considered small, moderate, and large if Cohen's f equals .1, .24, and .4, respectively.

Friedman's test was used if assumptions for using a parametric test were violated. For all tests, a p value of less than 0.05 was considered significant.

RESULTS:

This study included 42 eyes of 42 patients presented with and operated upon for POAG at Mansoura Ophthalmic center, Mansoura University, Mansoura, Egypt from January 2022 to December 2022 uncontrolled. Details of demographic data, preoperative examination and investigations are illustrated in tables 1 & 2. The mean age was 52.23±9.59 with 33 male patients (78.6%) and 9 female patients (21.4%). Brimonidine tartarate 0.15% (Alphanova) is the most commonly used medication (82.7%) followed by combined dorzolamide hydrochloride 2%+ timolo l0.5% (twinzol :75%.). Preoperatively, the UCVA and BCVA were 0.95 ± 0.63 and 0.77 ± 0.69, respectively. The mean IOP was 29.29±2 with and C/D ratio was 0.75±0.11. Additionally, preoperatively, the most common finding in OCT was superior and inferior thinning (59.5%), and in VF it was superior and starting inferior arcuate scotoma (n=25, 59.5%). Corneal endothelial density (CED) was 2492.7±183.7, central corneal thickness (CCT) measured 520.7±35.79 and coefficient of variance (CV) was 39.21±3.86.

Table (1): Socio-demographic and history distribution among studied cases:

	N=42	**%**
Age /years		
mean±SD	52.23±9.59	
(Min-Max)	(40-65)	
Sex		
Male	33	78.6
Female	9	21.4
Glaucoma duration (months**)** median **(**range)	2.0 (0.08-14.0)	
Anti-glaucoma medications	n(%)	
Simbrinza	2 (5.0)	
Dutrav	2 (5.0)	
Cosopt	7(17.5)	
Alphanova	33(82.5)	
Twinzle	30(75.0)	
Ioprost	9(22.5)	

Table (2): Preoperative Examination and investigations:

Preoperative UCVA	*0.9525 ± 0.6324*
Preoperative BCVA	0.7757 ± 0.6999
Preoperative IOP	29.29 ± 2.003
Preoperative C/D ratio	0.752±0.112 (0.60—0.97)
Preoperative OCT (n, %)	
Superior and inferior thinning	25 (59.5%)
Sever thinning in all quadrants	15 (35.7%)
Total atrophy	2 (4.7%)
Preoperative Visual field (n, %)	
Superior and starting inferior arcuate scotomas	25 (59.5%)
Double arcuate scotomas	13 (30.9%)
Constricted field	4 (9.5%)
Preoperative Specular microscopy	
CED	2492.7 ± 183.7
CCT	520.07 ± 35.791
CV	36.21 ± 3.867

Postoperatively, there was a decrease in UCVA at 1st and 2nd weeks with statistically significant difference (p<0.001) then it improved starting from 1st month to became nearly similar to baseline value at 3rd month (0.9457, P=1.00). Similarly BCVA decreased at 1st week with statistically significant difference (P<0.001) and it improved at 2nd week (P=1.00) that maintained at all follow up visits. Also, there was a statistically significant reduction in IOP throughout the follow up visits to reach 11.64

+0.983 (P<0.001) at 3rd month. On the other hand, there were no statistically significant changes regarding refraction (P=.149) Details of postoperative UCVA, BCVA, IOP and refraction are shown in tables 3 & 4, fig2.

On endothelial cell analysis, CED shows a significant reduction from 2492.7±183.7 preoperatively to 2415 + 222.8 at 1st week, after that it showed non-significant reduction to reach 2402.9 ± 302.7 at 3rd month. Regarding CCT there was a significant increase at 1st and 2nd week (P<0.001) then it became nearly similar to pre-operative result at 3rd month (516.68 + 30.373, P= 1.00). Also, CV showed a slight decrease at 1st week then it became nearly similar to baseline at 3rd month (36.29 +2.949, P=1.00). Details of postoperative endothelial cell analysis are illustrated in table 5.fig 3,4,5

Table (3): Postoperative UCVA, BCVA and IOP:

	Time	Mean± SD	P	F	Partial η^2	Cohen's f
UCVA	**Baseline**	0.9525±0.63240		69.645	.629	1.302
	1 week	1.2764±0.57853	0.00			
	2 week	1.2093±0.57667	0.00			
	1 month	0.9457±0.62071	1.00			
	2month	0.9457±0.62071	1.00			
	3 month	0.9457±0.62071	1.00			
BCVA	**Baseline**	0.7757±0.69991		33.661	.451	0.906
	1 week	0.9064±0.70173	0.00			
	2 week	0.6843±0.66469	0.085			
	1 month	0.6843±0.66469	0.085			
	2 month	0.6843±0.66469	0.085			
	3 month	0.6843±0.66469	0.085			
IOP	**Baseline**	29.29±2.003		928.304	.958	4.776
	1 week	13.14±1.201	0.00			
	2 week	12.07±.894	0.00			
	1 month	11.68±.843	0.00			
	2 month	10.57±2.751	0.00			
	3 month	11.64±.983	0.00			

UCVA: Uncorrected visual acuity, BCVA: Best corrected visual acuity, IOP: Intraocular pressure, SD = standard deviation. Sig. = significance (p-value). Partial eta squared (and Cohen's f) are estimates of effect size. Cohen's f (0.1 = small, 0.25 = medium, 0.4 = large effect size). The test of significance is one-way repeated measures ANOVA. P: difference between baseline and every reading.

Table (4): Postoperative Refraction

Time	Median	Q1, Q2	X^2	Sig.
Baseline	-1.000	-3.25, 1	8.13	P.149
First week	-1.625	-4.00, 1.75		
Second week	-1.625	-4.00, 1.5		
First month	-1.2150	-3.25, 1		
Second month	-1.1250	-3.25, 1		
Third month	-1.1250	-3.25, 1		

Notes: Q1-Q3 = 25^{th} – 75^{th} percentiles. Sig. = significance (p-value). The test of significance is Friedman's test.

Table (5): Postoperative Endothelial cell analysis

Time	**Mean± SD**	**p**	**F**	**Partial η^2**	**Cohen's f**
CED					
Baseline	2492.7±183.7		14.348	.259	.591
1 week	2415.5±222.8	0.00			
2 week	2406.6±221.9	0.01			
1 month	2400±201.1	0.00			
2 month	2406.2±200.14	0.00			
3 month	2402.9±203.7	0.00			
CCT					
Baseline	520.07±35.791		34.863	.460	.923
1 week	532.43±29.123	0.000			
2 week	527.43±29.537	0.159			
1 month	517.71±29.991	1.000			
2 month	516.50±30.334	1.000			
3 month	516.68±30.373	1.000			
CV					
Baseline	36.21±3.867		4.520	.099	.331
1 week	35.29±3.256	0.035			
2 week	36.29±3.188	1.00			
1 month	36.57±2.881	1.00			
2 month	36.14±2.935	1.00			
3 month	36.29±2.949	1.00			

CED: Corneal endothelial density, CCT: Central corneal thickness, CV: Coefficient of variance, SD = standard deviation. Sig. = significance (p-value). Partial eta squared (and Cohen's f) are estimates of effect size. Cohen's f (0.1 = small, 0.25 = medium, 0.4 = large effect size). The test of significance is one-way repeated measures ANOVA. P: difference between baseline and every reading.

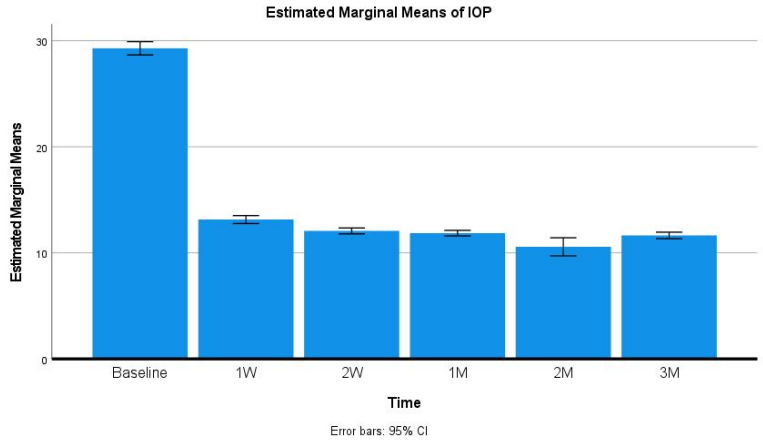

Figure (2): Changes in IOP during 3 month follow up.

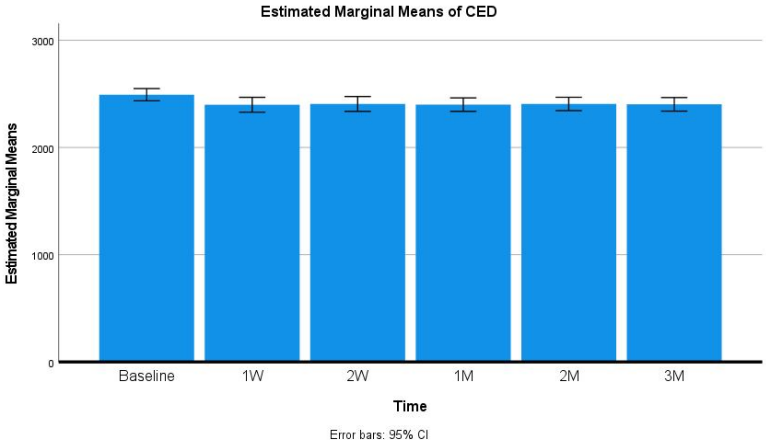

Figure (3): changes in CED during 3 month follow up.

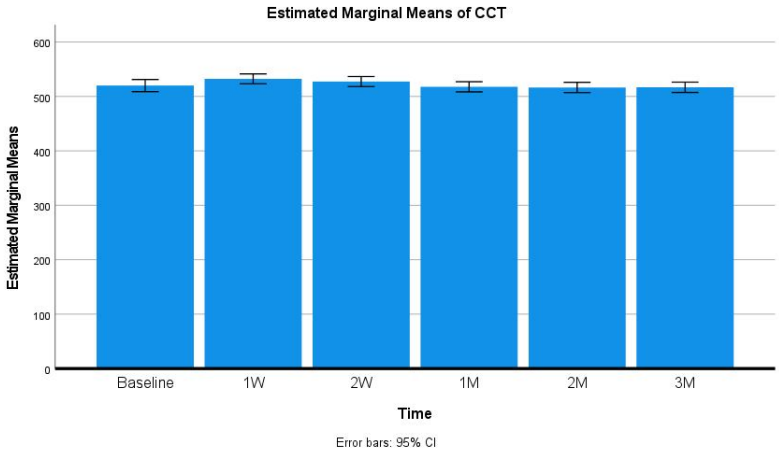

Figure (4): changes in CCT during 3 month follow up.

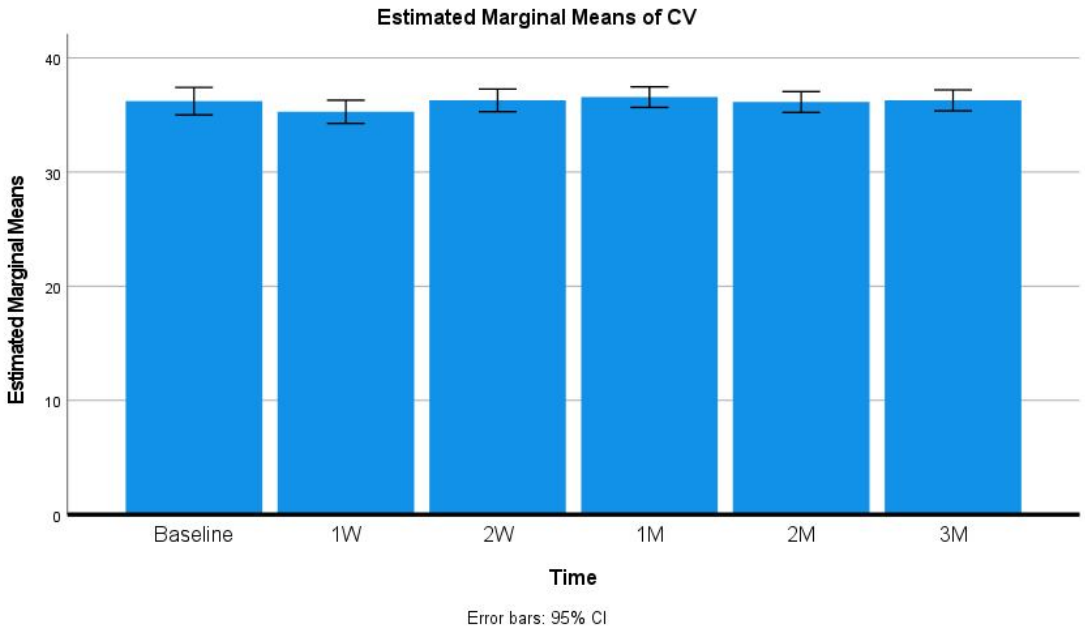

Figure (5): changes in CV during 3 month follow up.

DISCUSSION:

Primary open angle glaucoma (POGA) is an optic neuropathy characterized by progressive damage to the neuro-retinal rim associated with a corresponding VF defect where elevated intra ocular pressure (IOP) is supposed to be the main modifiable predisposing factor, with anatomically open angle and no other cause[4].

Corneal endothelium is the inner most layer of the cornea consisting of hexagonal cells which play a critical role in regulating corneal hydration and transparency. Corneal endothelium has limited proliferating capacity and can't regenerate. It compensates for any trauma or loss by increasing in size(polymegazism) or change in shape (polymorphism). Many studies showed that patients with glaucoma have decreased number of corneal endothelial cells (CEC)[3,5] .

Furthermore, antiglaucomatous medication may have toxic effect on CED due to toxicity and preservative preparations especially with higher concentrations and longer exposure[6].

Additionally, CECL had been observed in various types of glaucoma surgery including glaucoma drainage device and the micro invasive glaucoma surgeries (MIGS)[7]. Even with trabeculectomy which is considered the gold standard operation performed for OAG over the last 50 years, CEC loss had been associated[8].

Other postoperative problems including hyphaema, fibrinous uveitis, shallow anterior chamber and hypotony (with the risk of choroidal detachment and maculopathy) have been recorded as risk factors on CEC[9].

In a parallel attempt to reduce these complications and achieve higher success rate and better control different modalities are being performed throughout the years[10]. One of these modalities is viscotrabeculotomy which is considered a modification of traditional trabeculotomy surgical intervention by using a high density visco elastic substance[11]. The viscoelastic material persists inside the Schlemm's canal for about4–6 days, guarding against the collapse of the canal and acting as a barrier against the migration of fibrinogen secreted by the ciliary body through the operation and thereby inhibiting the fibroblastic proliferation.

Moreover, injection of the viscoelastic material into the anterior chamber helps in reduction of postoperative inflammation and hence impedes the cicatrization process[4]. Also, being less invasive than standard trabeculectomy, theoretically it will be less traumatizing to ocular tissue especially corneal endothelium.

The current study was a prospective interventional study to evaluate the effect of viscotrabeculotomy on CECD on 42 patients presenting to and operated upon Mansoura ophthalmic center with complete success 100% where all the patients achieved IOP less than 16 mmHg throughout the study duration. Elwehidy et al[4] conducted a retrospective study of five-year duration on uncontrolled uveitic glaucoma (24eyes), the success rate following VT syncolysis was 83.3%. At the same year Elwehidy et al[11] also reported the success rate of a prospective study conducted on 74 patients representing with POAG underwent VT and it was 90.5% compared to 74 patients underwent conventional trabeculectomy the success rate was 86.5% . In the current study there were no major complications in any case, transient hyphema was noticed in most cases and resolved completely before the first follow up visit in all cases. Studying the demographic data of the recent study revealed male predominance as reported in many previous studies[12]. The average age of the patients was (40-65) The preoperative clinical characteristics of the study eyes demonstrate the importance of surgery when polypharmacy fails[22]. Poor adherence to medications is reported[14,15]. The advanced C/D ratio (0.752±0.112) in the studied eyes classifies the glaucoma as moderate to severe and justifies the importance to provide these eyes with the lowest and safest IOP attainable, in an attempt to control disease progression, as recommended[16].

The current study demonstrated decrease in UCVA at 1st week and 2nd week follow up visits then improved at 1st month and maintained till the 3rd month (.9457±0.62071). Similarity BCVA worsen at 1st week with statistically significant difference(P<0.001) then increased at 2nd week to (.6843±.6646) till the end of follow up become nearly similar to preoperative measures .Both results may be related to usual post-operative corneal edema and astigmatic scleral sutures which start reliving along early postoperative follow up(1st and 2nd months)

ON the other, hand Refraction showed no statistically significant changes over the follow up period(P=.149) despite being clinically significant with increasing astigmatism. related to post-operative scleral sutures.

In harmony with our results, Elwehidy et al[11] Found a statistically significant improvement in the BCVA (p = 0.001) achieved at the third postoperative month and maintained through the end of follow-up in (VST) group compared trabeculectomy with Ologen implant (Trab-Ologen) group in uncontrolled uveitic glaucoma (UG).

Stability of visual acuity in the participants is an indirect evidence of the relative safety of the procedure[17] also reported on the safety of viscotrabeculotomy.

Projecting on the IOP values at the different follow up time, VT is highly effective in bringing about a significant reduction in the IOP (from 29.29 at baseline to 11.14 after 3rd month) that is sustainable over the follow up duration This is in accordance with the study by Kinoshita-Nakano et al.[6] and Elwehidy et al[4].

The current study revealed increased CCT at 1st and 2nd visits (532.43±29.123 and 527.43±29.537 respectively) then decreased to become nearly similar to preoperative readings and this could be due to postoperative edema and early CECL related to procedure manipulation. At the 3rd month follow up there was no statistical changes in CCT and this is matching with Mustafa Kamal et al[13] study on 113 glaucoma patients who underwent trabeculectomy and assessed for the change in CCT, there was no statistically significant change in CCT after trabeculectomy at the mean follow-up of 12 months. The current study demonstrated no statistically significantly difference in CV at the mean follow up of 3 months duration, and this is an approval of the safety of VT on corneal endothelium.

The current study demonstrated a statistically significant decrease in CED in the 1st week (2398.7±222.8, p<0.001) with baseline). This could be correlated with usual postoperative endothelial loss associated with any ocular surgery. There was no further decrease in CED for the last follow up visits (p=1.00).

In comparison with our study Endothelial cell damage and reducing CED have been observed with glaucoma drainage devices, Statistically significant endothelial cell loss occurs following Ahmed valve implantation it is reported to be

between 7.6% and 11.5% ($p < 0.05$) at six month, between 10.5% and 15.3% ($p < 0.05$) at 12 months and one study reports 15.4% ($p < 0.05$) at 24 months. A five-year retrospective case series reported that the cumulative risk of corneal decompensation following Ahmed valve insertion is 3.3%[18].

Additionally, surgical trauma produced by trabeculectomy and the adjuvant use of mitomycin C (MMC) reduces ECD. Several studies showed that ECD loss after trabeculectomy with MMC was 1.9% to 18%. However, the results were derived from a relatively small number of cases with short postoperative follow-up periods (i.e., most were 12 months). A study with a longer follow-up of 24 months found the mean ECD decrease was 9.3%.[19].

For more comparison with our study, we found a study evaluating CED after deep seclrectomy versus trabeculectomy which reported a significant reduction in ECD between sclerectomy and trabeculectomy, 2.6%vs. 7% in central cornea, this difference is because DS is less invasive than trabeculectomy as it does not penetrate the anterior chamber[20].

Another study prospectively evaluated changes in the CECD in 60 eyes of 60 patients who underwent trabeculectomy and 50 eyes of 45 patients who underwent Ex-press device implantation. The mean CECD in the trabeculectomy group was lower than Ex-press group[21] **.**

There is a limitation of the current study related to small sample size and short duration of follow up, so we recommend for other studies with large sample size and long duration.

CONCLUSION:

Viscotrabeculotomy is a safe procedure as it doesn't affect corneal endothelium or central corneal thickness and postoperative changes were clinically non-significant. It is safe and effective in reducing the IOP with no effect on corneal endothelium.

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Data Availability: The authors declare that all data supporting the findings of this study are available within the article and its supplementary information file.

Competing interests: The authors declare no competing interests.

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Ethics declarations: All procedures performed in the study followed the 1964 Helsinki declaration and its later amendments, University Ethics Committee approved the project.

Conflict of interest

All authors have no conflicts of interest that are directly relevant to the content of this review.

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