

Trabeculectomy for neovascular glaucoma in proliferative diabetic retinopathy, central retinal vein occlusion, and ocular ischemic syndrome: Surgical outcomes and prognostic factors for failure

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Purpose: To evaluate the outcomes of trabeculectomy in the eyes with neovascular glaucoma (NVG), caused by proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO), and ocular ischemic syndrome (OIS). **Methods:** A retrospective review of NVG eyes that underwent trabeculectomy between 1991 and 2019. Complete success was defined as intraocular pressure (IOP) between 6 and 21 mmHg without antiglaucoma medications (AGM). The risk factors were analyzed by Cox's proportional hazard model. **Results:** The study included 100 eyes of 100 subjects with a mean age of 58 ± 9.8 years and a median follow-up of 1.27 years (interquartile range: 0.63, 2.27). The cause of NVG was PDR in 59 eyes (59%), CRVO in 25 eyes (25%), and OIS in 16 eyes (16%). Trabeculectomy with mitomycin-C was performed in 88 eyes and trabeculectomy in 12 eyes. The cumulative complete success probability of trabeculectomy in PDR was 50% (95% confidence interval [CI]: 38, 65) at 1 year, 8% (1, 46) at 3–5 years. In OIS, it was 64% (43, 96) from 1 to 5 years. In CRVO, it was 75% (59, 94) at 1 year, 45% (23, 86) from 2 to 5 years. The PDR was associated with a higher risk of surgical failure compared to OIS ($P = 0.04$) and CRVO ($P = 0.004$). Other significant risk factors were increasing age ($P = 0.02$), persistent neovascularization of iris (NVI) ($P = 0.03$), higher number of anti-vascular endothelial growth factor (VEGF) injections prior to trabeculectomy ($P = 0.02$), and delay in performing trabeculectomy ($P = 0.02$). **Conclusion:** Compared to CRVO and OIS, the eyes with NVG secondary to PDR had poor success with trabeculectomy. Older age, persistent NVI, need for a higher number of anti-VEGF injections, and delayed surgery were associated with a higher risk for trabeculectomy failure.

Key words: CRVO, NVG, OIS, PDR, trabeculectomy

Neovascular glaucoma (NVG) is a secondary glaucoma that occurs as a result of abnormal new vessel formation in the anterior chamber angle resulting in elevated intraocular pressure (IOP). The three common etiologies of NVG are proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO), and ocular ischemic syndrome (OIS).^[1,2]

In patients with diabetes, the retinopathy worsens due to poor glycemic control leading to ischemia and neovascularization of the posterior and anterior segment resulting in NVG. In the eyes with ischemic CRVO, NVG occurs suddenly within 3–4 months (rarely up to 2 years) of the vein occlusion.^[3] In the eyes with OIS, NVG occurs over time, secondary to vascular insufficiency either to the uveal tissue alone or to the retinal tissue also. The presentation of NVG in OIS may be delayed as the findings vary either due to the hyposecretion of the aqueous with normal or low IOP despite completely closed angles or with elevated IOP.^[4,5]

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Received: 03-Jun-2021

Revision: 03-Aug-2021

Accepted: 17-Aug-2021

Published: 29-Oct-2021

Access this article online

Website:

www.ijo.in

DOI:

10.4103/ijo.IJO_1516_21

Quick Response Code:



The treatment of NVG includes the treatment of the underlying retinal ischemia, systemic control of the underlying disease, and also IOP control.^[6,7] The management of NVG is difficult and treatment outcomes are variable, based on the etiology of NVG, visual potential, and systemic comorbidities.^[1,8,9] Over 50% of the eyes with NVG need surgery for IOP control.^[10] The success rates of trabeculectomy with mitomycin-C in the eyes with NVG secondary to PDR vary from 62.6 to 81.2% at 1 year and reduce to 51.3 at 5 years.^[8,11] Trabeculectomy with mitomycin-C, use of intravitreal anti-vascular endothelial growth factor (VEGF) agents, and aggressive panretinal photocoagulation (PRP) has improved the success rates of trabeculectomy.^[8,12-16] Unlike the other types of secondary glaucomas, persistent new vessels, hyphema, or vitreous hemorrhage,^[17] may contribute to the long-term failure of trabeculectomy in NVG.

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Cite this article as: Senthil S, Chary R, Ali MH, Cherukuri JR, Rani PK, Krishnamurthy R, *et al.* Trabeculectomy for neovascular glaucoma in proliferative diabetic retinopathy, central retinal vein occlusion, and ocular ischemic syndrome: Surgical outcomes and prognostic factors for failure. Indian J Ophthalmol 2021;69:3341-8.

Hyung *et al.*,^[18] reported poor success of trabeculectomy in CRVO compared to DR. Takihara *et al.*,^[8] however, did not find the etiology of NVG to be a risk factor for the failure of trabeculectomy ($P = 0.93$). Mermoud *et al.*^[9] reported better success with Molteno implant in the eyes with NVG secondary to DR compared to those with a CRVO ($P = 0.003$).

Since the reported outcomes of glaucoma surgery in NVG eyes with various etiologies are contradictory, we aimed to evaluate the outcomes of trabeculectomy in the eyes with NVG caused by PDR, CRVO, and OIS.

Methods

We retrospectively reviewed records of NVG patients who underwent trabeculectomy with or without mitomycin-C between October 1991 and November 2019. The Institutional Review Board approval was obtained and the study adhered to the tenets of the Declaration of Helsinki. The consecutive patients with NVG secondary to PDR, CRVO, and OIS who underwent trabeculectomy with a minimum 3-month postoperative follow-up were included. The eyes with no light perception, <3-month follow-up, NVG due to other causes, eyes with prior transscleral cyclophotocoagulation (CPC), or any other concomitant intraocular procedure were excluded. The eyes with prior cataract surgeries were included.

Diagnostic criteria for PDR, CRVO, and OIS: The diagnoses were clinical based on one or more of these findings. The eyes with PDR had either new vessels over the optic disk (NVD), or new vessels elsewhere (NVE), or combined pre-retinal/vitreous hemorrhage/tractional retinal detachment. The CRVO eyes had disk edema, peripapillary hemorrhages, flame-shaped hemorrhages in multiple quadrants, dilated tortuous veins with or without the presence of macular edema. The OIS eyes had microaneurysms, narrowed retinal arteries, dilated and beaded veins (non-tortuous), and occasional or multiple intraretinal hemorrhages in the region of the mid-peripheral retina.

NVG was diagnosed in the presence of visible neovascularization of the iris (NVI) and/or angle neovascularization (NVA) with IOP >21 mmHg. NVI is thin twigs of vessels present on the iris surface or at the pupillary margin. In the eyes with OIS, the NVI may be extensive, flat, arborizing, and present over the iris surface with grooves/tracks.^[9] NVA is identified gonioscopically as thin vessels that cross the scleral spur and branch/arborize over the trabecular meshwork.

Main outcome measures: A complete success was defined as IOP between 6 and 21 mmHg without any AGM (antiglaucoma medications), and qualified success was defined as the need for topical AGM for IOP control. Failure was defined as IOP >21 mmHg with AGM, or IOP ≤5 mmHg, or loss of light perception.

Surgical procedure: The trabeculectomy surgery was performed by experienced glaucoma specialists. Antifibrotic agent, mitomycin-C (MMC) was used at 0.04% for 1–4 min according to the surgeon's preference. The conjunctival opening was either limbal-based or fornix-based depending on the surgeons' preference.

The data collected include age, gender, angle status, NVI and NVA, systemic comorbidities, cause of NVG, the status of the retina, prior panretinal photocoagulation (PRP), anti- VEGF

injections, pre-and post-operation details (IOP, number of AGM, best-corrected visual acuity [BCVA]), complications, and additional interventions if any. The visual acuity (in LogMAR) was considered stable when the postoperative vision was within ±2 lines of preoperative vision; improved when there was a gain in >2 lines; and worsened when there was a loss of >2 lines. Persistent new vessels caused NVI despite good posterior segment treatment with retinal photocoagulation and anti-VEGF injections.

Statistical analysis: Statistical analysis was performed using the software STATA v14.2 (StataCorp, College Station, TX, USA). The categorical data were described in proportions. The parametric data were described in mean ± standard deviation and non-parametric data were described in median and interquartile range (IQR). The Kaplan–Meier survival analysis was used to estimate the probability of trabeculectomy success. Comparisons between preoperative and postoperative continuous data were performed using the Wilcoxon's signed-rank test, Kruskal–Wallis, or Analysis of variance (ANOVA). To analyze the risk factors for trabeculectomy failure, the equality of survivor functions was assessed by the log-rank test. The risk factors were assessed using a multivariate Cox proportional hazards model. A P value of < 0.05 was considered statistically significant.

Results

Demographic and clinical features: The analysis included 100 eyes of 100 subjects with NVG that satisfied the inclusion criteria. The clinical and demographic details are shown in Table 1. The cause of NVG was PDR in 59 eyes (59%), followed by CRVO in 25 eyes (25%), and OIS in 16 eyes (16%). Gonioscopically, the angles were closed in 63 eyes and open in 37 eyes. Persistent NVI was observed in 77 eyes and NVA in 63 eyes. The glaucoma surgery performed was trabeculectomy with mitomycin-C in 88 eyes and trabeculectomy in 12 eyes. The mean age of the subjects was 58 ± 9.8 years with a median follow-up of 1.27 years (0.63, 2.27).

Table 1: Demographic and preoperative and postoperative clinical profile of the entire cohort (n=100 eyes of 100 subjects)

Parameter	Mean±SD	Range (min, max)
Preoperative parameters		
Age (years)	58±9.8	32, 81
LogMAR visual acuity at presentation	0.83±0.7	0, 3
IOP at presentation (mmHg)	36.5±12.7	4, 68
Number of AGM at presentation	2.09±1.4	0, 4
Number of preoperative AGM	2.78±1.5	0, 5
Number of PRP	1.84±1.2	0, 6
Number of anti-VEGF injections	0.72±1.2	0, 9
Postoperative parameters		
IOP at LFU (mmHg)	16.5±6.2	0, 40
Number of AGM at LFU	0.96±1.1	0, 4
Median follow-up in years	1.27 (0.63, 2.27)	0.32, 14

SD: Standard deviation, LogMAR: Logarithm off minimal angle of resolution, IOP: Intraocular pressure, AGM: Antiglaucoma medications, PRP: Panretinal photocoagulation, VEGF: Vascular endothelial growth factor, LFU: Last follow-up

Comparison of preoperative clinical features in PDR, CRVO, and OIS: The comparison of the baseline and clinical features of the three different etiologies causing NVG are shown in Table 2. The mean age in the three groups was similar ($P = 0.99$). There were more men compared to women in the three groups. There was no significant difference in the preoperative IOP ($P = 0.64$), LogMAR visual acuity ($P = 0.57$), and the preoperative AGM ($P = 0.53$) in the

three groups. About 60–70% of all the eyes had closed angles on gonioscopy ($P = 0.85$). The NVA ($P = 0.85$) and NVI ($P = 0.96$) were persistent in two-thirds of all the eyes in the three groups. Before trabeculectomy, the number of sittings of PRP ($P = 0.69$) and the number of anti-VEGF injections (bevacizumab) ($P = 0.3$) were similar in the three groups. The majority of the eyes in all the three groups underwent trabeculectomy with MMC, 90% eyes in PDR, 100% eyes in OIS, and 76% eyes in

Table 2: Comparison of preoperative and postoperative clinical parameters in the NVG eyes caused by different etiologies, PDR, CRVO, and OIS

Parameter	PDR (n=59)	CRVO (n=25)	OIS (n=16)	P
Age in years, mean (SD)	57.9 (8.9)	57.9 (9.5)	58.2 (13.9)	0.99 [®]
Gender, Male: Female	47:12	21:4	12:4	0.78 [§]
Preoperative LogMAR VA, median (IQR)	0.7 (0.4,1.1)	0.8 (0.3,1.3)	0.5 (0.3,0.8)	0.57 [*]
Preoperative IOP, mean (SD)	35.5 (13.4)	37.6 (11.8)	38.4 (11.5)	0.64 [®]
Number of AGM preop, median (IQR)	3 (3,4)	3 (1,4)	3.5 (1.5,4)	0.53 [*]
Gonioscopy				
Closed angle	36 (61%)	16 (64%)	11 (68.8%)	0.85 [§]
Open angle	23 (39%)	9 (36%)	5 (31.2%)	
NVA				
Present	36 (61%)	16 (64%)	11 (68.8%)	0.85 [§]
Absent	23 (39%)	9 (36%)	5 (31.2%)	
NVI				
Present	46 (78%)	19 (76%)	12 (75%)	0.96 [§]
Absent	13 (22%)	6 (24%)	4 (25%)	
Lens status				
Clear	7 (12%)	9 (36%)	5 (31%)	0.02 [#]
Cataract	34 (58%)	14 (56%)	5 (31.25%)	0.19
Pseudophakia	18 (30%)	2 (8%)	6 (37.5%)	0.05
Prior PRP median (IQR)	2 (1,3)	2 (1,3)	2 (0.8,3)	0.69 [*]
Preoperative anti-VEGF injections, median (IQR)	0 (0,1)	1 (0,1)	0 (0,1)	0.38 [*]
Type of surgery				
Trabeculectomy	6 (10.2%)	6 (24%)	0 (0%)	0.08 [#]
Trab MMC	53 (89.8%)	19 (76%)	16 (100%)	
Median time from diagnosis to glaucoma surgery	55 (28,137)	32 (13,72)	42 (25.5,102)	0.16 [*]
IOP at LFU, median (IQR)	18 (14,19)	15 (12,18)	15 (11.5,18.8)	0.16 [*]
Number of AGM at LFU, median (IQR)	1 (0,2)	0 (0,1)	0 (0,1.2)	0.34 [*]
Postoperative LogMAR VA, median (IQR)	1.3 (0.7,2.3)	1.5 (0.8,2.3)	0.5 (0.2,1.4)	0.04 [*]
Duration of postoperative FU in months, median (IQR)	16 (8,28.5)	15 (7,32)	12.5 (7.5,23)	0.58 [*]
Additional interventions				
Needling	2	1	1	0.79 [#]
Bleb repair	1	1	0	0.65
Bleb resuturing	1	0	0	1.00
AGV	0	0	1	0.16
CPC	2	0	0	1.00
Repeat Trab MMC	1	1	0	0.65
Complications				
Hyphema	18 (30.5%)	3 (12%)	1 (6%)	0.06 [#]
Bleb leak	0	0	1	0.16
Conjunctival buttonhole	1	0	0	1.00

Statistical tests used: [#]Fisher's exact test, ^{*}Kruskal-Wallis test, [§]Chi-square test, [®]ANOVA *F*-test. SD: Standard deviation, IQR: Interquartile range, LogMAR: Logarithm of minimal angle of resolution, VA: Visual acuity, IOP: Intraocular pressure, AGM: Antiglaucoma medications, PRP: Panretinal photocoagulation, AGV: Ahmed glaucoma valve, LFU: Last follow-up, NVI: New vessels of iris, NVA: New vessels of the angle, Trab MMC: Trabeculectomy with mitomycin-C, CPC: transscleral cyclophotocoagulation. PDR: proliferative diabetic retinopathy, CRVO: central retinal vein occlusion, OIS: Ocular ischemic syndrome

CRVO ($P = 0.08$). The eyes that were pseudophakic were the highest in PDR ($P = 0.05$) and significantly more eyes had clear lens in CRVO ($P = 0.02$).

Comparison of postoperative clinical features in PDR, CRVO, and OIS, Table 2: Postoperatively, there was a significant decrease in IOP at the final follow-up. In the eyes with PDR, the IOP decreased from 35.5 (13.4) to 18 (14, 19) mmHg, $P < 0.001$; in the eyes with CRVO, it decreased from 37.6 (11.8) to 15 (12, 18) mmHg, $P < 0.001$; and in eyes with OIS from 38.4 (11.5) to 15 (11.5, 18.8) mmHg, $P < 0.001$. However, the last follow-up IOP was not significantly different between the three groups ($P = 0.16$). There was a significant reduction in postoperative AGM at the final follow-up, from a median of 3–1 in PDR, 3–0 on CRVO, and 3.5–0 in OIS, ($P < 0.0001$). The median number of AGMs at the final follow-up was similar in the three groups ($P = 0.34$). The duration of the postoperative follow-up was also similar in the three groups ($P = 0.58$).

Visual outcomes

The postoperative visual acuity (VA) was significantly better in the eyes with OIS (median VA of 20/60) compared to PDR (median VA of 20/400) and CRVO (median VA of 20/620), ($P = 0.04$), while the preoperative visual acuity was not significantly different ($P = 0.57$). Overall, the vision was stable in 18 eyes, improved in 21 eyes, and worsened in 61 eyes. The improved (or stable lines) vision was observed in 34% (20) of the eyes in PDR, 36% (9) of the eyes in CRVO, and 63% (10) of the eyes in OIS. Decreased vision was observed in 66% (39) of the eyes in PDR, 64% (16) of the eyes in CRVO, and 37% (6) of the eyes in OIS. At the last follow-up, four eyes had no perception of light (PL) vision - 2 eyes due to high IOP and advanced glaucomatous damage (1 PDR and 1 CRVO) and two eyes due to hypotony and phthisis bulbi (1 OIS and 1 PDR).

Postoperative complications

The most common postoperative complication noted was hyphema, which was present in a greater proportion of the eyes in PDR (30.5%) compared to CRVO (12%) and OIS (6%).

However, it was not statistically significant ($P = 0.06$). All eyes with hyphema were managed conservatively, and did not require surgical drainage. The time for resolution ranged from 1 week to 1 month and none had recurrent hyphema. One eye with PDR and NVG had serous choroidal detachment (CD) post-trabeculectomy. The CD resolved with conservative management, and IOP was maintained at 20 mmHg. However, the vision deteriorated from 20/60 to PL +at the end of 5 months, and hence, was considered a failure. One eye with OIS and one eye with PDR had persistent hypotony and the vision deteriorated to PL from 20/60 and 20/80, respectively. These two eyes were considered failures. None had hemorrhagic CD. One eye in OIS had a bleb leak that resolved in 1 month with conservative management. One eye in PDR had a small conjunctival button hole away from the flap and was managed with a 10-0 nylon suture. Bleb needling with MMC was performed in two eyes in PDR, one eye each in OIS and CRVO. Of the four eyes that underwent bleb needling with MMC, three eyes had good IOP control with medications, and one eye had IOP of 24 mmHg despite AGM, and was considered a failure. All these four eyes that needed bleb needling had undergone trabeculectomy with MMC. Thin cystic bleb with late bleb leak was observed in one eye each in PDR and CRVO; and both eyes underwent bleb repair. Five eyes required repeat intervention for IOP control. One eye with OIS underwent Ahmed glaucoma valve, one eye each with PDR and CRVO underwent repeat trabeculectomy with MMC, and two eyes with PDR underwent CPC. The eye with PDR that underwent repeat Trab MMC had IOP of 20 mmHg on two AGMs, and the eye with CRVO had IOP of 14 mmHg on three topical AGMs at the final follow-up.

Complete and qualified survival probability of trabeculectomy is shown in Table 3 and Fig. 1a and b. The cumulative complete success probability of trabeculectomy was significantly less in PDR compared to OIS ($P = 0.05$) [Fig. 1a]. The cumulative qualified success probability was similar between the groups [Fig. 1b].

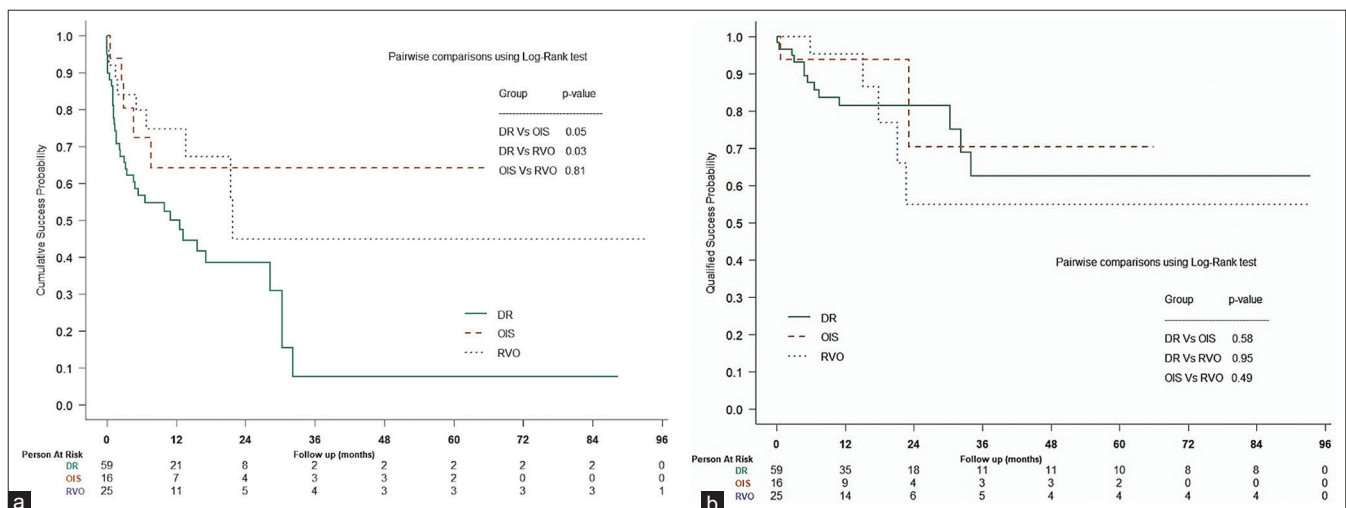


Figure 1: (a) The Kaplan–Meier survival curve showing complete success probability of trabeculectomy in neovascular glaucoma among the eyes with proliferative diabetic retinopathy (DR), ocular ischemic syndrome (OIS), and central retinal vein occlusion (RVO). (b) The Kaplan–Meier survival curve showing qualified success probability of trabeculectomy in neovascular glaucoma among the eyes with proliferative diabetic retinopathy (DR), ocular ischemic syndrome (OIS), and central retinal vein occlusion (RVO)

Table 3: Complete success and qualified success probability of trabeculectomy based on the etiology of neovascular glaucoma

Time period	Complete survival percentage (lower CI, upper CI)	Time period	Qualified survival percentage (lower CI, upper CI)
PDR		PDR	
1 year (n=21)	50 (38, 65)	1 year (n=35)	81 (72, 93)
2 year (n=8)	39 (27, 56)	2 years (n=18)	81 (72, 93)
3 years (n=2)	8 (1, 46)	3 years (n=11)	63 (45, 86)
5 years (n=2)	8 (1, 46)	5 years (n=10)	63 (45, 86)
CRVO		CRVO	
1 year (n=11)	75 (59, 94)	1 year (n=14)	95 (86, 100)
2 years (n=5)	45 (23, 86)	2 years (n=6)	55 (31, 96)
3 years (n=4)	45 (23, 86)	3 years (n=5)	55 (31, 96)
5 years (n=3)	45 (23, 86)	5 years (n=4)	55 (31, 96)
OIS		OIS	
1 year (n=7)	64 (43, 96)	1 year (n=9)	94 (83, 100)
2 years (n=4)	64 (43, 96)	2 years (n=4)	94 (83, 100)
3 years (n=3)	64 (43, 96)	3 years (n=3)	70 (39, 100)
5 years (n=2)	64 (43, 96)	5 years (n=2)	70 (39, 100)

PDR: Proliferative diabetic retinopathy, CRVO: Central retinal vein occlusion, OIS: Ocular ischemic syndrome, CI: Confidence interval, n: Number of eyes

Table 4: Cox's proportional hazard model to evaluate the risk factors for failure of trabeculectomy in the eyes with neovascular glaucoma

	Univariate		Multivariate	
	crude HR (95% CI)	Crude P	HR* (95% CI)	P
Gender: Male vs. Female	0.66 (0.35,1.27)	0.25		
Age	1.01 (0.98,1.04)	0.46	1.04 (1.01,1.08)	0.02
Cause of NVG ref=PDR)				
OIS	0.41 (0.16,1.05)	0.06	0.37 (0.14,0.95)	0.04
CRVO	0.47 (0.22,0.97)	0.04	0.29 (0.13,0.67)	0.004
LogMAR VA at diagnosis	1.06 (0.71,1.56)	0.78		
IOP at first visit	1.00 (0.98,1.02)	0.68		
Number of AGM at first visit	0.94 (0.77,1.14)	0.51		
Angle: Open vs. closed	0.94 (0.53,1.67)	0.83		
NVA: Absent vs present	1.09 (0.61,1.94)	0.76		
NVI: Absent vs. present	0.5 (0.23,1.06)	0.07	0.41 (0.19, 0.9)	0.026
Lens status	0.92 (0.61,1.38)	0.67	0.66 (0.39,1.13)	0.13
Number of preop AGM	1.1 (0.91,1.33)	0.32		
Number of PRP	1.02 (0.83,1.26)	0.85		
No of anti-VEGF	1.18 (1,1.39)	0.046	1.26 (1.04,1.52)	0.02
Glaucoma surgery type: Trab MMC vs. Trab	1.11 (0.49,2.49)	0.81		

HR* Adjusted hazard ratio, SD: Standard deviation, IQR: Interquartile range, LogMAR: Logarithm of the minimal angle of resolution, VA: Visual acuity, IOP: Intraocular pressure, AGM: Antiglaucoma medications, PRP: Panretinal photocoagulation, VEGF: Vascular endothelial growth factor, LFU: Last follow-up, NVI: New vessels of iris, NVA: New vessels of the angle, Trab MMC: Trabeculectomy with mitomycin-C, PDR: Proliferative diabetic retinopathy, CRVO: Central retinal vein occlusion, OIS: Ocular ischemic syndrome, CI: Confidence interval

Risk factors for failure: We evaluated the risk factors for the failure of trabeculectomy [Table 4]. In multivariate analysis, the higher risk for failure was associated with increasing age ($P = 0.02$), presence of persistent NVI ($P = 0.026$), and higher number of anti-VEGF injections before trabeculectomy ($P = 0.02$). Among the three common etiologies, PDR was associated with a higher risk of failure compared to OIS ($P = 0.04$) and RVO ($P = 0.004$). The duration between the

anti-VEGF injection and trabeculectomy (≤ 30 days vs. >30 days; $P = 0.99$) did not seem to affect the survival. Pseudophakia did not affect the survival compared to cataracts or clear lenses ($P = 0.99$). The duration from the diagnosis of NVG to trabeculectomy had a significant effect on the survival of trabeculectomy, odds ratio (95% confidence interval [CI] 1.07 (1.01, 1.14), $P = 0.02$). The postoperative hyphema did not affect the survival of trabeculectomy (the hazard ratio was 0.88;

95% confidence limits: 0.45,1.72; and $P = 0.71$) for complete success and 0.77 (0.26,2.3; and $P = 0.64$) for qualified success.

In our cohort, there were 10 eyes that underwent glaucoma filtering surgery before the year 2000 when the usage of anti-VEGF was not widespread. Four of these 10 eyes underwent trabeculectomy and 6 eyes underwent trabeculectomy MMC. Among these, two eyes with trabeculectomy and two eyes with trabeculectomy MMC survived without the need for antiglaucoma medications. Two eyes with trabeculectomy survived with additional antiglaucoma medications.

There was no difference in trabeculectomy survival before the year 2000 and after when the usage of anti-VEGF became widespread.

Discussion

Two-thirds of all NVGs are caused by three conditions, PDR, CRVO, and OIS.^[20] A majority of the eyes in our cohort had NVG secondary to PDR (59%), followed by CRVO (25%), and OIS (16%). The current study highlights the surgical success of trabeculectomy in the eyes with NVG caused by these three common etiologies. Our results show that the success rate of trabeculectomy in PDR was poor, compared to CRVO and OIS. The progressive retinal disease and the ongoing inflammation in the eyes with PDR could be the contributing factors leading to the scarring and higher rate of trabeculectomy failure. Although there are no direct comparative studies, the available evidence shows contrary results.

Takahara *et al.*^[8] evaluated the outcomes of trabeculectomy with MMC in 101 eyes with NVG. At 1, 2, and 5 years, the success rates were 62.6, 58.2, and 51.7%, respectively. The authors did not find the etiology of NVG to affect the success of trabeculectomy with MMC. Takahara *et al.* in their study included NVG with several etiologies, and most of these (82 eyes) were PDR. The PDR group was combined with 7 eyes of other etiologies of NVG like OIS, uveitis, and others, and the result of 89 eyes was compared with the outcomes of the remaining 12 eyes of CRVO. The grouping together of the etiologies, and smaller sample size of CRVO could have contributed to the lack of difference in the success rates of trabeculectomy in their study. In the current study, the complete success probability of trabeculectomy in PDR was significantly lower compared to the other etiologies. It was 50% at 1 year and 8% at 3–5 years in PDR, compared to 64% from 1 to 5 years in OIS, and 75% at 1 year, 45% at 2–5 years in CRVO. In this NVG cohort, the factors associated with a higher risk of trabeculectomy failure included older age, PDR, persistent NVI, higher number of anti-VEGF injections, and long-time interval between diagnosis and surgery.

In a prospective case series including 30 eyes of 27 patients with a mean follow-up of 17.3 months, Al Obeidan *et al.*^[21] reported a success rate of 80% at the final follow-up after trabeculectomy with MMC in the eyes with full preoperative PRP. A few studies have evaluated the outcomes of trabeculectomy with MMC with and without intravitreal bevacizumab and have shown variable outcomes with success ranging from 50 to 95%.^[11,15,22,23] However, none of these studies have evaluated the outcomes of trabeculectomy based on the etiology of NVG.

The baseline/preoperative clinical characteristics were not significantly different among the three etiologies in our cohort.

There was a significant drop in the median postoperative VA in the PDR eyes, from 20/200 to 20/400; and in the CRVO eyes from 20/125 to 20/630. However, the preoperative VA was maintained in OIS (median, 20/60). The drop in the VA in PDR and CRVO could have been due to progressive retinopathy and maculopathy. The absence of significant posterior segment pathology and timely IOP control could have helped in maintaining the VA in the OIS eyes. While the preoperative VA was better in the OIS cohort (although the difference was clinically significant, and not statistically significant), preserving or maintaining the visual acuity is a challenge. Sivalingam *et al.*^[24] evaluated the outcomes in OIS, and reported that 43% of the eyes with OIS in their study had presenting VA between 20/50 and 20/20. However, half of these eyes had decreased vision to counting fingers in the next 1 year, which was attributed to uncontrolled IOP. Hence, timely control of IOP is important to preserve the pre-existing vision in the eyes with NVG, more so in OIS. Cataract formation also may have contributed to the decrease in vision during follow-up in the eyes with CRVO since a significant number of eyes in this group were phakic. However, the effect of cataract on VA could not be evaluated in this retrospective study.

Two other studies by Mermoud *et al.*^[9] and Downes *et al.*^[25] used drainage implants, and evaluated the outcomes of glaucoma surgery in PDR and CRVO. Both studies reported better outcomes with Molteno implant in NVG caused by PDR compared to CRVO. Mermoud *et al.*^[9] studied 32 eyes with DR and 24 eyes with CRVO and 4 eyes with other causes. The study reported better outcomes in PDR compared to CRVO ($P = 0.003$). The definition of failure in their study included eyes resulting in phthisis bulbi and eyes with loss of light perception, which was noted in 48% of the eyes. Two-thirds of the eyes had a loss of vision due to progressive retinal disease, and one-third lost vision due to progressive glaucoma. It is important to note that almost an equal number of eyes with PDR and CRVO were included in their study; however, they were not matched for baseline features. Less than 50% of the eyes underwent adequate laser photocoagulation, and more eyes in the CRVO group had poor vision before surgery. These factors could have affected the results in their study. Downes *et al.*^[25] also found that eyes with PDR (13/30, 43% success) had better complete success with Molteno implant compared to CRVO (3/15, 20% success). The authors could not explain the reason for the difference in the success between the two etiologies.

A few of the eyes in our series had trabeculectomy without antimetabolites. To look at the effect of MMC use on the surgical results, we compared the outcomes in the three groups with and without MMC, lack of anti-metabolite use in a small cohort did not seem to influence the results.

Increasing age was a significant risk factor for trabeculectomy failure in our cohort. This is contrary to the previous reports in the literature. In a study by Takahara *et al.*^[8] younger age <50 years, was a significant risk factor for failure. One-year survival of trabeculectomy was 35.6% in patients younger than 50 years, compared to 72.2% in patients older than 50 years, $P < 0.0007$). The authors attributed this to a more severe wound healing response and also more severe disease in the younger patients, since the condition has resulted in NVG at

an early age. Mermoud *et al.*^[9] also reported poorer success rates in subjects younger than 55 years. (9% vs. 49%). Factors such as longer duration of diabetes and diabetic retinopathy, poor systemic control of diabetes, and associated systemic comorbidities are more likely to be present in older patients. This could have contributed to a higher risk for trabeculectomy failure as noted in our study.

Persistent NVI and a higher number of anti-VEGF injections before trabeculectomy were also associated with a higher risk of failure in our study. Both these features are probable surrogate measures of the severity of retinal ischemia and probably represent poor control of the ocular and systemic conditions, thus contributing to failure. It may be prudent to perform implant surgery in the eyes with these risk factors. Extensive peripheral anterior synechiae (PAS) was also reported to be a risk factor for failure of trabeculectomy.^[26] Although the proportion of eyes with angle-closure were similar in all the groups, we did not have data on the extent of PAS in these eyes. In our study, the delay in surgery, which was as a risk factor, could be a surrogate for progressive angle-closure with time in these eyes. There was no difference in trabeculectomy survival before and after the year 2000, when the use of anti-VEGF was common. Before intravitreal anti-VEGF use became popular, the commonly followed protocol was to perform a thorough PRP in these eyes, which could have helped with better control of neovascular stimulus.

In the eyes with NVG, with high risk for trabeculectomy failure, glaucoma drainage devices may be indicated. With adequate posterior segment treatment to decrease the neovascular drive, the outcomes of trabeculectomy and glaucoma drainage devices offer similar success in NVG.^[27-29] In a study by Rani *et al.*,^[10] eyes with NVG and VA better than 20/200 at presentation reported similar success rates in the outcomes of trabeculectomy in the Indian eyes compared to the glaucoma drainage device in a UK cohort.

The limitations of a retrospective study apply to our study as well. The study included cases over a long period, hence, six surgeons (trained glaucoma specialists) were involved in the management of these eyes. Twelve of the 100 eyes in our study underwent trabeculectomy without antimetabolite. The decision to use intraoperative MMC during trabeculectomy was at the surgeons' discretion. In the case of thin conjunctiva or sclera, MMC was not used. Although NVG eyes are at a high risk for trabeculectomy failure, in the eyes with mobile conjunctiva with no prior intraocular surgery, the antifibrotic agent was not used for augmenting trabeculectomy. A few cases from an earlier time, when MMC was not routinely used as an adjunct during trabeculectomy, were also included. While this may be a limitation, our sub-analysis and risk factor analysis showed that this factor had no effect on our study results. The study includes subjects from a long time (28 years) and the management protocols for PDR, CRVO, and OIS have changed over time, which may have had an effect on the outcome of trabeculectomy. Several patients were lost to follow-up after 1 year, which is another limitation. The strength of our study is that it has directly evaluated and compared the outcomes of trabeculectomy among the three common etiologies of NVG. The results of our study provide important insights to prognosticate outcomes of glaucoma filtering surgery based on the etiology and the preoperative risk factors.

Conclusion

To conclude, the success of trabeculectomy in NVG eyes was significantly poor in the eyes with PDR compared to CRVO and OIS. In older subjects with NVG, and those with persistent NVI and delayed trabeculectomy, there is a higher risk for the failure of trabeculectomy.

Acknowledgments

Ms. Sreedevi for help with language editing.

Financial support and sponsorship

Hyderabad Eye Research Institute.

Conflicts of interest

There are no conflicts of interest.

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