Clinical Profile and Treatment Outcomes of Patients with Neovascular Glaucoma in a Tertiary Hospital in the Philippines

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ABSTRACT

Objective: To report the clinical profile and treatment outcomes of neovascular glaucoma (NVG).

Methods: A retrospective cohort study was done in a single tertiary hospital. Medical records of patients diagnosed with NVG from January 2000 to August 2018 were reviewed and pertinent data were collected. Study outcomes included visual acuity (VA) and intraocular pressure (IOP) and were analyzed for eyes that received any of the following: intravitreal bevacizumab (IVBe), pan-retinal photocoagulation (PRP), trabeculectomy with mitomycin (trab-MMC), or diode laser cyclophotocoagulation (DLCP) with at least 1 month of follow-up.

Results: There were 162 patients (181 eyes) diagnosed with NVG. Mean age at the time of diagnosis was 55.6 ± 14 years. Diabetic retinopathy (DR) was observed in 81 (45%) eyes and central retinal vein occlusion (CRVO) in 48 (27%) eyes. Baseline VA was hand movement in 67 (37%) eyes and no light perception (NLP) in 49 (27%) eyes. Only 60 (33%) eyes had ≥1 month of follow up (mean of 73 ± 119.1 weeks) after procedures were done. IVBe was done in 22 (37%) eyes, trab-MMC in 20 (33%), PRP in 22 (37%), and DLCP in 24 (40%) eyes. IOP decreased from 45 to 20 mmHg ($p<0.001$) but VA decreased from LogMAR 1.7 to 2.1 ($p<0.01$). There was significant VA decrease in eyes that underwent a single procedure ($p<0.02$) but none in eyes that underwent 2 or 3 procedures. Nonetheless, there was significant IOP decrease ($p<0.05$) when one procedure was done. Of the 49 eyes that had baseline sight, 19 (41%) converted to NLP ($p<0.01$).

Conclusion: Most patients presenting with advanced NVG had DR and CRVO. Procedures led to better IOP but not VA and some lost vision. Aggressive screening for NVG among high-risk groups is warranted to institute treatment early.

Keywords: bevacizumab, central retinal vein occlusion, diabetic retinopathy, neovascular glaucoma, trabeculectomy

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Neovascular glaucoma (NVG) is a blinding disease characterized by intraocular pressure (IOP) elevation and anterior chamber neovascularization.[1,2] In Asian population-based studies, NVG accounts for 0.7-5.1% of all glaucomas.[3,4] Locally, there is limited available data. NVG was a common secondary glaucoma in the two local clinic-based retrospective studies, accounting for 7.4 and 4.8% of all glaucomas in a private and a government hospital, respectively.[5,6] In another local study, NVG was more frequently observed in government hospitals versus private hospitals: 73.8 versus 26.2%, respectively.[7] These studies did not include detailed demographics, clinical characteristics, and responses to treatment which could help drive local health policies. The objective of our study was to describe demographic profiles, clinical characteristics, and treatment outcomes of NVG in a tertiary public eye center.

METHODS

This was a retrospective cohort study conducted at an eye center of a tertiary, urban, government hospital. This study was approved by the Institutional Ethics Review Board of the East Avenue Medical Center and adhered to the tenets of the Declaration of Helsinki.

Medical charts of patients diagnosed with NVG from January 2000 to August 2018 were retrieved and reviewed. Demographic data (sex, age), risk factors, clinical characteristics including presenting symptoms, NVG stage, baseline and final IOPs and visual acuities (VA), initial glaucoma medications, and lens status were collected. Description of the management and statistical analysis were done on patients who underwent at least one of the following procedures and who had at least one month of follow-up after the procedure: intravitreal bevacizumab injection (IVBe), pan-retinal photocoagulation (PRP), trabeculectomy with mitomycin C (trab-MMC), and/or diode laser cyclophotocoagulation (DLCP). Primary outcome measures were VA in the LogMAR scale and IOP. Patients who underwent phacoemulsification during the follow up period were excluded from the study. The treatment outcomes of patients who did not undergo any procedure were not analyzed.

Data collected from the patients' charts were encoded in Microsoft Excel Spreadsheets. SPSS version 25.0 statistical software (IBM Corporation, New York, USA) was used for data analysis. Descriptive statistics (frequency, percentage, median, mean, and standard deviation) were used to describe the baseline characteristics of patients.

Wilcoxon test was used to compare the primary outcome measures at baseline and last clinic visit. One-way z-test of proportion was used to compare the VA conversion to NLP. Mann-Whitney U test was used to compare variables such as patients with and without IVBe injection and diabetic retinopathy (DR) versus CRVO. Kruskall Wallis test was used to compare patients with 1 to 3 procedures: IVBe versus DLCP versus trab-MMC. Hypothesis tests were accepted at a significance level of less than 0.05 ($p<0.05$).

RESULTS

This study included 181 eyes of 162 patients diagnosed with NVG. Baseline demographics and risk factors are listed in Table 1. The mean age of the patients was 55.6 ± 14 years and majority (60%) were males. Most patients were diagnosed with diabetes mellitus (51%) and hypertension (38%). Diabetic retinopathy and central retinal vein occlusion were observed in 81 (45%) eyes and in 48 (27%) eyes, respectively (Table 1).

Table 1. Baseline demographics and risk factors

	N = 162 subjects
Age ± SD, in years	55.6 ± 13.68
Sex, n (%)	
Male	98 (60%)
Female	64 (40%)
Risk factors, n (%)	
Diabetes mellitus	82 (51%)
Hypertension	62 (38%)
Renal condition	8 (5%)
Trauma	8 (5%)
Cardiovascular accident	7 (4%)
Others*	18 (11%)
Unknown	36 (22%)
Predisposing diagnosis, n (%)	n = 181 eyes
Diabetic retinopathy	81 (45%)
Central retinal vein occlusion	48 (27%)
Other vaso-occlusive disease	15 (8%)
Branch retinal vein occlusion	5 (3%)
Eale's disease	4 (2%)
Others†	13 (7%)
Unknown	21 (12%)

*retinal detachment/retinal detachment surgery, heart disease, pulmonary tuberculosis, Eale's disease, high myopia, asthma, prematurity, Coat's disease, chronic obstructive pulmonary disease
†retinal detachment, uveitis, Coat's disease, dropped lens, fungal infection, retinopathy of prematurity

Table 2 shows the clinical characteristics of the patients. Most patients (n=119 or 66%) presented with blurring of vision or loss of vision. Eye pain was observed in 54 (30%). Baseline VA of hand movement was observed in 67 (37%) eyes and no light perception (NLP) was observed in 49 (27%) eyes (Table 2). Most of the eyes (n=101 or 56%) were in the closed angle stage of NVG and were phakic (n=148 or 82%). Unilateral involvement was observed in 142 (88%) eyes (Table 2). Majority (n=10 or 52%) of patients with bilateral eye involvement had diabetic retinopathy.

Table 2. Clinical characteristics of 181 eyes.

Presenting signs and symptoms, n (%)	
Blurring of vision/ Loss of vision	119 (66%)
Eye Pain	54 (30%)
Redness	13 (7%)
Referral for elevated IOP	8 (4%)
NVG stage, n (%)	
Pre-glaucoma	8 (4%)
Open-angle	33 (18%)
Closed-angle	101 (56%)
Laterality in 162 subjects, n (%)	
Unilateral	142 (88%)
Bilateral	19 (11%)
Initial visual acuity, n (%)	
Better than or equal to 5/400	32 (18%)
Counting Fingers	22 (12%)
Hand Movement	67 (37%)
Light Perception	12 (7%)
No Light Perception	49 (27%)
Initial number of glaucoma medication/s, n (%)	
None	54 (30%)
1-2	57 (32%)
3-4	70 (39%)
Mean initial IOP + SD in mmHg, n (%)	47.3 ± 17.1, 178 (98%)
Lens status	
Phakic	148 (82%)
Pseudophakic	22 (12%)

NVG - neovascular glaucoma; IOP - intraocular pressure; SD - standard deviation

Ninety-eight (98) eyes underwent at least one procedure and the average number of procedures done was 1.5 ± 0.7 per eye. Among eyes that received procedures, only 60/98 (61%) had at least 1 month of follow-up and did not undergo cataract surgery (Figure 1). The mean length of follow-up after a non-medical intervention was 73 ± 119.1 weeks. In this group, IOP decreased from baseline of 45 to 20 mmHg (p=0.000) but VA declined from 1.70 to 2.06 LogMAR (p=0.009) (Table 4).

FIGURES LEGENDS

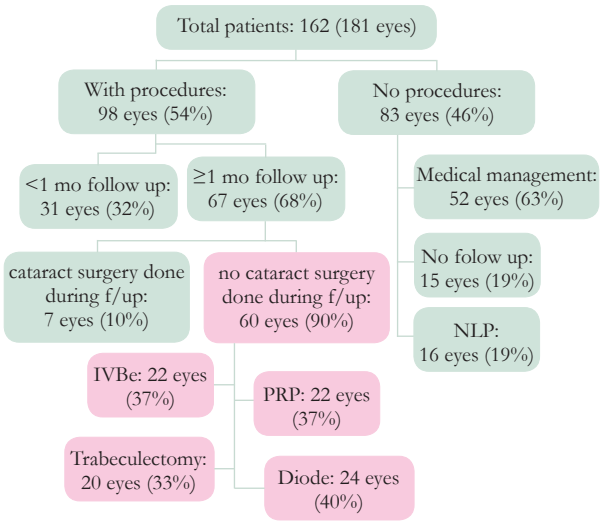

Figure 1. Methods of patient selection. Pink box denotes cohort analyzed for treatment outcomes.

Table 3. Procedures done on eyes of patients with neovascular glaucoma with ≥1 month follow up (n=60 eyes).

Intravitreal bevacizumab injection (IVBe), n (%)	22 (37%)
Trabeculectomy with mitomycin-C (trab-MMC), n (%)	2 (33%)
Time between IVBe and trab-MMC (days)	14 (5-23)
Pan-retinal cyclophotocoagulation (PRP), n (%)	22 (37%)
Diode laser cyclophotocoagulation (DLCP), n (%)	24 (40%)
Mean follow-up duration ± SD, in weeks	73.2 ± 119.2
Mode, in weeks	4

Table 4. Visual acuity and intraocular pressure in neovascular glaucoma eyes with ≥1 month follow up (n=60 eyes)

	Median VA in LogMAR (Range)	Median IOP in mmHg (Range)
Baseline	1.70 (1.50 - 1.93)	45.0 (8.00 - 80.00)
Last follow-up	2.06 (1.68 - 2.11)	20.0 (14.75 - 42.75)
P-value	0.009	<0.001

IOP - intraocular pressure; NVG - neovascular glaucoma; VA - visual acuity

There was a significant decline in VA of those eyes that underwent only one procedure (DLCP only, trab-MMC only, IVBe only) [p=0.012]. There was no significant decline in VA of those eyes that underwent 2 procedures (combination of IVBe with DLCP or IVBe with trab-MMC) and 3 procedures

(combination of IVBe, trab-MMC and PRP, and DLCP, IVBe and PRP) [p=0.409 and p=0.128, respectively). Reductions in IOP in the 3 groups from their respective baselines were significant (p<0.05) (Table 5).

In eyes that underwent trab-MMC, there was significant decrease in VA for IVBe group and significant IOP drop for both the IVBe group and the no IVBe group (Table 6).

When comparing IVBe, trab-MMC and DLCP, VA significantly declined for each group but with significant IOP control (Table 7). Hyphema and choroidal effusion were among the complications noted after undergoing the procedures.

In a subgroup analysis, eyes with CRVO, unlike eyes with DR, revealed a significant decline in VA and significant decrease in IOP after procedures done (Table 8).

Table 5. Visual acuity and intraocular pressure in neovascular glaucoma eyes with ≥ one month follow up stratified according to the number of procedures done (n=60 eyes).

Group	Median initial VA, in LogMAR (Range)	Median final VA, in LogMAR (Range)	P-value	Median initial IOP, in mmHg (Range)	Median final IOP, in mmHg (Range)	P-value
Single procedure	1.86 (1.60 - 2.11)	2.11 (1.70 - 2.01)	0.012	40 (29 - 59.5)	24 (14 - 50)	0.030
2 procedures	1.70 (1.38 - 1.70)	1.76 (1.45 - 2.01)	0.409	47 (39 - 60)	18 (8 - 28)	0.008
3 procedures	1.55 (1.25 - 1.63)	2.06 (1.68 - 2.11)	0.128	57.5 (39.5 - 61)	24.5 (16.5 - 34.5)	0.036
P-value	0.014	0.529		0.101	0.508	

VA - visual acuity, IOP - intraocular pressure, NVG - neovascular glaucoma

Table 6. VA and IOP in NVG eyes with ≥ one month follow up that underwent trab-MMC with IVBe (n=17 eyes).

Group	Median Initial VA (Range), in LogMAR	Median Final VA (Range), in LogMAR	P-value	Median Initial IOP (Range), in mmHg	Median Final IOP (Range), in mmHG	P-value
IVBe (N=22)	1.65 (1.15 - 1.70)	1.86 (1.63 - 2.11)	0.021	53.5 (40 - 59.8)	19 (15 - 30)	0.017
No IVBe (N=38)	1.91 (1.60 - 2.11)	2.11 (1.70 - 2.11)	0.060	40 (28 - 60)	24 (12 - 45)	0.001
P-value	0.006	0.173		0.241	0.732	

IOP - intraocular pressure, IVBe - intravitreal bevacizumab injection, NVG - neovascular glaucoma, trab-MMC - trabeculectomy with mitomycin C, VA - visual acuity

Table 7. VA and IOP in NVG eyes with ≥ 1 month follow that received specific procedures (n=60 eyes).

Group	Median Initial VA (Range), in LogMAR	Median Final VA (Range), in LogMAR	P-value	Median Initial IOP (Range), in mmHg	Median Final IOP (Range), in mmHg	P-value
IVBe	1.65 (1.15 - 1.70)	1.86 (1.86 - 2.11)	0.003	43.3 (40.0 - 59.75)	19.0 (15 - 30)	0.030
DLCP	1.91 (1.70 - 2.11)	2.11 (02.06 - 2.11)	0.021	40 (30 - 63)	28 (10 - 55)	0.001
Trab-MMC	1.55 (1.25 - 1.63)	2.06 (1.68 - 2.11)	0.021	57.5 (39.5 - 61)	24.5 (16.34.5)	0.001
P-value	0.000	0.866		0.007	0.953	

IOP - intraocular pressure, IVBe - intravitreal bevacizumab injection, DLCP - diode laser cyclophotocoagulation, NVG - neovascular glaucoma, trab-MMC - trabeculectomy with mitomycin C, VA - visual acuity

Table 8. VA and IOP in NVG eyes with DR and CRVO (n=40 eyes).

Group	Median Initial VA (Range), in LogMAR	Median Final VA (Range), in LogMAR	P-value	Median Initial IOP (Range), in mmHg	Median Final IOP (Range), in mmHg	P-value
DM Retinopathy (N=17)	1.7 (1.40 - 2.01)	2.11 (1.60 - 2.11)	0.398	48 (27.25 - 60)	20 (12 - 43)	0.272
CRVO (N=23)	1.7 (0.55 - 1.91)	1.91 (1.70 - 2.11)	0.023	43 (36.5 - 57.8)	20 (16 - 34)	0.004
P-value	0.582	0.679		0.767	0.898	

CRVO - central retinal vein occlusion, DR - diabetic retinopathy, IOP - intraocular pressure, NVG - neovascular glaucoma, VA - visual acuity

Of the 132 eyes who had at least some vision at baseline, 49 eyes had at least one month follow-up and underwent at least one procedure. Of these 49 eyes, 19 eyes (39%) converted to NLP ($p<0.01$). Among those eyes that received procedures and had at least one month of follow up, regardless of baseline vision, 20 (33%) eyes of patients retained or improved VA and 29 (48%) eyes had worsened VA or converted to NLP.

DISCUSSION

The demographics and clinical characteristics of the patients with NVG in this study were similar to other published studies. In Mexico, China and Saudi Arabia, most NVG patients were male, phakic, unilateral, with DR and CRVO/hypertension as the most frequent predisposing conditions.[1,8,9] Most of the eyes of the patients with NVG in our study presented in the late stage of the disease with poor VA, high IOP, and closed-angle glaucoma similar to the other studies.[1,8,9] Thus, many eyes in our study required end-stage procedures such as DLCP, and consequently these eyes were not able to receive the definitive treatment for retinal ischemia such as PRP and IVBe.

We purposely excluded patients who had less than one month of follow-up after the procedure or who had cataract surgery during the procedures or within the follow-up duration so as to remove confounding factors that may influence the last visit VA. Subjecting our NVG patients to procedures (IVBe, PRP, trab-MMC, and DLCP) may have significantly lowered IOP. However, VA significantly worsened in about 1 year average follow-up time. Although not included in the analysis, the progression and complications of concomitant retinal vascular disease due to poor control of co-morbidities (i.e., diabetes mellitus and hypertension) could have resulted to continuous loss of vision. An interesting observation in the subgroup analysis was the significant decline in VA if only a single procedure was done compared to multiple procedures, where the VA change was not significant. IOP, however, whether single or multiple procedures, was significantly lower for both. One reason for this observation could be that those eyes that underwent two or three procedures had already very poor baseline vision and had reached a "floor effect" (the baseline VA for each of the groups depending on the number of procedures done were significantly different, $p = 0.014$).

The addition of IVBe to trab-MMC in our study failed to show any statistical difference in terms of IOP and VA. There was an average of 14 days of IVBe injection prior to trab-MMC which theoretically could improve bleb morphology but has not been proven to lower IOP. A systematic review by Simha *et al.* found that there is no evidence to evaluate statistically the effectiveness of anti-VEGF treatments, even as an adjunct to conventional treatment in reducing the IOP in NVG.[10] Similar findings of no difference were observed in another study where they compared DLCP alone or with IVBe, and trabeculectomy alone or with IVBe, respectively.[11]

Interpretation of results is limited by the retrospective study design and short duration of follow-up and significant drop-out rate. Almost half (46%) of all the eyes did not receive any procedure due to the high drop-out rate. Advanced NVG eyes with serviceable vision definitely need aggressive management more than just topical or oral glaucoma medications to preserve vision. Sixty-three percent (63%) of those who dropped out just received glaucoma medications. Nineteen percent (19%) of those who dropped out had NLP in the NVG eye. It was also noteworthy that in our cohort of NVG patients who had some vision at baseline and underwent at least one procedure with follow-up for at least one month or more, 39% of all the eyes converted to NLP.

Our study also was limited by lack of a standard protocol for managing this disease and the small number of patients who underwent specific procedures which limited our analyses. The outcome parameters (IOP and VA) were not matched at baseline to adequately assess the response to the specific procedure. Furthermore, the treatment outcomes were not analyzed according to the stage of the disease. A prospective study would better assess the efficacy of the specific procedures and would better address the above limitations.

Since prevention is recommended by most studies to approach NVG, a prospective cohort study involving high-risk groups such as patients with DR and hypertension would be worth investigating, correlating risk factors such as glycemic and hypertension control and instituting treatment at an early phase.

In conclusion, NVG seen in our tertiary center usually presented late with advanced NVG and

poor VA. Most of the patients had DR and CRVO. Better IOP control was achieved with combinations of IVBe, DLCP, trab-MMC, and PRP. However, a great percentage of eyes still lost vision despite aggressive measures. Aggressive screening for NVG among high-risk groups such as patients with DR and hypertension/CRVO is warranted to institute treatment at an early phase to prevent vision loss.

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