RESEARCH ARTICLE

REVISED Combined vitrectomy, near-confluent panretinal endolaser, bevacizumab and cyclophotocoagulation for neovascular glaucoma — a retrospective interventional case series [version 2; peer review: 2 approved]

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Abstract

Background: Neovascular glaucoma (NVG) is a severe, potentially blinding disease and a therapeutic challenge. The purpose of this study was to evaluate the safety and efficacy of an integrative surgical approach to neovascular glaucoma.
Methods: Retrospective analysis of a one-year follow-up of a consecutive interventional case series of NVG. Eyes underwent transscleral cyclophotocoagulation, pars plana vitrectomy, near-confluent panretinal photocoagulation, and intravitreal bevacizumab. Phakic eyes underwent concomitant cataract surgery. Best-corrected visual acuity (BCVA, logMAR), intraocular pressure (IOP, mmHg), number of glaucoma medication, visual analog pain scale (VAPS, 0-10) were recorded at baseline, and 1, 3, 6, and 12 months. Blind eyes were excluded.
Results: Seventy-seven eyes of 77 patients (45 male, 32 female, mean age 73.6±12.2 years) were included. NVG underlying conditions included retinal vein occlusion (41.6%), proliferative diabetic retinopathy (35.1%), central retinal artery occlusion (19.5%), and ocular ischemic syndrome (3.9%). Mean IOP decreased postoperatively from 46.3±10.1 mmHg to 14.5±7.9 mmHg ($p<0.001$), glaucoma medication from 4.7±1.3 to 1.8±1.8 ($p<0.001$), and VAPS from 6.0±1.8 to 0. BCVA remained unchanged. Postoperative intraocular inflammation had resolved in all eyes at the one-month follow-up. 71.4% (55/77) eyes did not require additional major interventions during follow-up.
Conclusions: A single, comprehensive surgery session lowered IOP significantly, reduced GMS, and controlled pain.

Open Peer Review

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Keywords
Neovascular glaucoma, integrative surgical approach, iris neovascularization

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REVISED **Amendments from Version 1**

We are grateful for the opportunity to improve our manuscript. We appreciate the helpful comments and have provided our replies below. We trust that we were able to address the concerns that were raised.

In the Introduction, second paragraph, we changed the phrasing. "In 1994, Miller *et al*. showed that laser occlusion of all branch retinal veins in a primate could lead to CRVO and subsequent retinal ischemia."

In the Results "arterial hypertension" was changed to hypertension as this is the currently accepted terminology.

In Table 1 and in the manuscript– we changed "R stadium" to "NVI stage"

We clarified in the results, that all 3 patients with a retinal detachment consecutively developed a painless phthisis bulbi.

To provide comparison to our study we added a literature overview (Table 3) of different surgical approaches.

In the Discussion regarding NVI stage and interventions, we added, that "there was **no** difference between stage 2 and stage 3". Further we added more details on trabeculectomy in NVG.

Any further responses from the reviewers can be found at the end of the article

Introduction

Neovascular glaucoma (NVG) is a serious complication of a variety of ocular and systemic conditions. Neovascularization is the formation of abnormal blood vessels in an abnormal location triggered by an imbalance of anti-angiogenic and proangiogenic factors caused by retinal ischemia[1]. NVG accounts for 3.9 to 9.2% of all new glaucoma diagnoses[2–4]. According to the Federal Statistical Office of Germany, NVG's age-specific incidence in Germany in the age group from 45 to 64 years is 8 per 100,000. It increases to 24 per 100,000 in subjects older than 64 years[5]. The incidence of NVG varies depending on the etiology of retinal ischemia. For central retinal vein occlusion (CRVO) the reported incidence is 16%[6], for proliferative diabetic retinopathy (PDR) 21.3%[7], for central retinal artery occlusion (CRAO) 14.5%[8], and ocular ischemic syndrome (OIS) 12.9%[9], respectively. Carotid artery obstructive disease and fistulas are additional, extraocular vascular causes of retinal ischemia[10]. Early recognition and treatment of NVG are imperative to prevent aggressive evolution with severe vision loss and intractable pain that can require enucleation within a few months[11]. NVG also carries a poor prognosis for general health: remarkably, the expected lifespan of patients with NVG decreased by 52% compared to an age-correlated normal population, which corresponds to 6.5 years. In diabetics with NVG, the expected lifespan was reduced even more significantly by 72% (5.1 years in this subgroup)[12].

In 1994, Miller *et al.* showed that retinal laser coagulation of primates could lead to CRVO and subsequent retinal ischemia with iris neovascularization[13]. In this model, neovascularization was mediated by vascular endothelial growth factor (VEGF) and correlated to its concentration. Several members of the VEGF family have since been identified, including VEGFA, VEGFB, VEGFC, VEGFD, and the placental growth factor (PLGF) with specific receptor-binding patterns. VEGFA primarily binds to VEGFR2, the activation of which stimulates neovascularization, relevant to NVG, and angiogenesis, the formation of normal blood vessels in normal development. In the eye, VEGF-A is produced by the retinal pigment epithelium, retinal ganglion cells, astrocytes, the endothelium, photoreceptors, and Müller cells[14–17]. Retinal hypoxia upregulates VEGF primarily via the hypoxia-inducible factor (HIF-1α and HIF-2α). The concentration of HIF increases when hydroxylases are inhibited during hypoxia so that HIF is not degraded by the proteasome[18]. HIF binds to the hypoxia-responsive element (HRE) of the VEGF gene in the nucleus leading to its upregulation[19].

Although the mechanism by which NVG emerges is hence relatively well understood, there is no consensus on how to best initiate treatment to address the different aspects. Treatment steps include lowering of IOP (topical and systemic glaucoma medications, glaucoma drainage implants, cyclodestruction)[20–24], anti-inflammatory treatment (topical or intraocular steroids), reduction of retinal ischemia (panretinal photocoagulation (PRP))[25,26], and inhibition of VEGF[27–29]. Vitrectomy with PRP and silicone oil tamponade may also reduce IOP in eyes with NVG[30,31].

Here, we evaluated the safety and efficacy of an integrative combined surgical approach for evolving NVG that combined pars plana vitrectomy, near-confluent full-scatter panretinal photocoagulation, off-label use of intravitreal bevacizumab, and transscleral cyclophotocoagulation in a single surgical session. We hypothesized that such a combined surgical approach for NVG would reduce IOP, medication, pain, reduce the number of necessary outpatient visits, and prevent the necessity of further surgeries.

Methods

Ethical statement

Our retrospective study was reviewed and approved by the Ethics Committee of the University of Würzburg (reference: 9/17-sc, dated February 3, 2017) and a clearance certificate for retrospective data evaluation was issued (reference: 20180108 02, dated January 30, 2018). For retrospective anonymized data analysis, patient's consent was not necessary. The Declaration of Helsinki, the Good Clinical Practice (GCP) guidelines and applicable data protection regulations were complied with.

Study design

We included all patients between October 2014 and August 2019 with NVG who met the inclusion criteria in this consecutive interventional case series.

Inclusion criteria were: 1) neovascularization of iris (NVI) or neovascularization of the angle (NVA), 2) IOP > 21 mmHg, 3) best-corrected visual acuity (BCVA, logMAR) ≧ light perception, and 4) 18 years or older.

All patients were treated at the University Eye Hospital in Würzburg, Germany. The combined intervention was part of routine patient care at our clinic and all patients with decompensated neovascular glaucoma and preserved visual

function received this intervention. BCVA, intraocular pressure (IOP, mmHg), the number of glaucoma medication, visual analog pain scale (VAPS, 0-10) was recorded at baseline and at follow-up visits at one, three, six, and 12 months as part of routine care. Iris and anterior chamber neovascularization were graded using the Weiss and Gold rubeosis grading system[32]. Hypotony was defined as IOP ≤ 5 mmHg with hypotonous maculopathy, choroidal folds, or optic neuropathy[33]. Phthisis bulbi[34] was defined as IOP ≤ 5 mmHg in a shrunken eye with worse than hand motion vision with or without pain containing atrophic and disorganized intraocular structures. Success was defined as lOP ≤ 21 mmHg or IOP reduction ≥ 30% from baseline, with or without glaucoma medication and without vision loss[35].

All patients underwent decimal visual acuity testing, which was converted to a logMAR scale. Counting fingers (CF), hand movements (HM), light perception (LP), and no light perception (NLP) were converted into logMAR units 1.9, 2.3, 2.7, and 3.0, respectively[36].

We retrospectively analyzed all patients treated with neovascular glaucoma at our clinic via the electronic hospital information system SAP®. The medical records of the treated patients were analyzed individually. The initial diagnosis of neovascular glaucoma and hospitalization served as the starting point. The cardiovascular risks were taken from the anesthesia premedication form.

Patient treatment and follow-up

Surgical technique. All eyes underwent transscleral cyclophotocoagulation (810 nm diode laser, 360 degrees treatment to pop threshold with 20 spots and leaving out 3 and 9 o'clock), standard 3-port 23 gauge pars plana vitrectomy with a detachment of the posterior vitreous if not already present, near-confluent full-scatter panretinal photocoagulation (PRP) applied under indentation in all four quadrants from the vascular arcades to the ora serrata, intravitreal application of 0,1 mL of bevacizumab (Avastin® 25 mg/1 mL, Roche Pharma, Switzerland), and air tamponade. Phakic eyes underwent concomitant cataract surgery. The operation was carried out either with a retrobulbar block or general anesthesia.

Retreatment. At follow-up, all eyes with elevated IOP were treated following an escalation scheme. First, glaucoma medications were increased to what was maximally tolerated. Eyes were then treated with transscleral cyclophotocoagulation (810 nm diode laser, 360 degrees treatment to pop threshold with 20 spots). Eyes that failed to respond to cyclophotocoagulation with a significant IOP reduction and had retained ambulatory visual acuity underwent tube shunt surgery. Repeated vitrectomy, including fill-in PRP, transscleral cyclophotocoagulation, and off-label use of intravitreal bevacizumab was applied to eyes with elevated IOP and dense vitreous hemorrhage. Fill-in PRP was applied when PRP could not be completed during surgery in eyes with extensive intraretinal hemorrhage. Further intravitreal injections of VEGF inhibitors were only applied for clinically significant non-ischemic macular edema and BCVA ≥1.1 logMAR.

Patients lost to follow-up. All patients who failed to attend follow-up visits completed a standardized telephone survey that contained the following questions: What was the main reason for not following up? What is your current vision function? How many glaucoma drops are you using? Do you have any eye pain? Are you overall satisfied with the outcome of the treatment?

Statistical methods

Data analysis was performed using Statistica 13.1 (Tulsa, Oklahoma, United States). The frequency of observations described categorical variables. Continuous variables were described as mean with standard deviation (SD) or median with range (minimum-maximum). Friedman test and Wilcoxon signed-rank test were used to compare data measured on an ordinal scale and continuous variables with non-normal distribution. Evaluation of data normality was performed using the Shapiro-Wilk test. Welch's t-test for unequal variances was used for IOP between pain versus no-pain group comparison. Categorical variables of the relationship between neovascularization stage and type of intervention were compared using the $\chi 2$ test with odds ratio (OR) measurement. Kaplan–Meier curve and log-rank test were used for success analysis. P-values <0.05 were considered significant.

An earlier version of this article can be found on medRxiv (doi: https://doi.org/10.1101/2020.01.19.20017889)

Results

All 77 patients (45 male, 32 female, mean 73.6±12.2 years, range 29–91 years) completed a one-year follow-up and were included in the retrospective analysis (Figure 1). Conditions that lead to NVG included CRVO 41.6% (32/77), PDR 35.1% (27/77), CRAO 19.5% (15/77), and ocular ischemic syndrome 3.9% (3/77)[37] (Table 1).

The most common cardiovascular risk factor was hypertension 87.0% (67/77), followed by hyperlipidemia 67.5% (52/77), diabetes mellitus 59.7% (46/77), and smoking 11.7% (9/77). While one patient did not have any cardiovascular risk factors, 24.7% (19/77) had at least one risk factor, and 74.0% (57/77) had multiple risk factors.

The mean body mass index (BMI kg/m²) for the study group was 28.7±5.0 (underweight ≤ 18.5, normal weight = 18.5–24.9, overweight = 25–29.9, obesity ≥ 30[38]). 1.3% (1/77) were underweight, 24.7% (19/77) had a normal weight, 40.3% were overweight (31/77) and 33,8% (26/77) obese.

Mean logMAR BCVA was 1.9±0.7 at baseline,1.7±0.8 at one month, 1.8±0.8 at three months, 1.8±0.8 at six months, and 1.8±0.8 at 12 months (p=0.47, Figure 2). At baseline, 35.1% (27/77) of patients and at 12 months, 45.5% (35/77) of patients had an ambulatory visual acuity (≥ logMAR 1.7), respectively, but was not statistically significant (p=0.0931). One eye worsened from LP to NLP at one week, three eyes at six months, and three eyes at 12 months.

IOP decreased significantly from 46.3±10.1 mmHg at baseline to 21.4±10.9 mmHg at one month, 18.6±10,7 mmHg at three

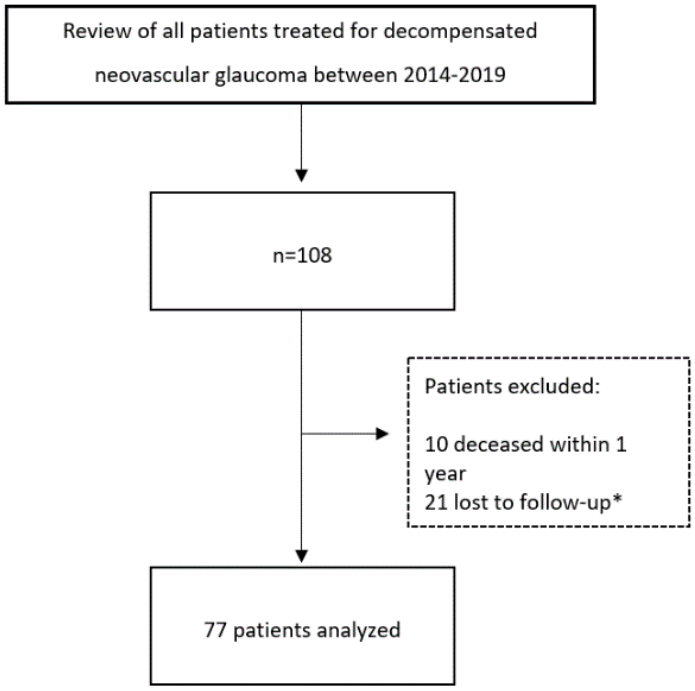

Figure 1. Flow chart. Eyes with no light perception and patients with a history of glaucoma other than neovascular glaucoma were excluded. *Telephone survey with all patients lost to follow-up.

Table 1. Demographic characteristics of neovascular glaucoma patients.

Variables	n = 77
Age (years)	73.6±12.2 (range 29–91)
Gender	n (%)
Female	32 (41.6)
Male	45 (58.4)
Laterality	n (%)
Right	34 (44.2)
Left	43 (55.8)
Diagnosis	n (%)
CRAO	15 (19.5)
CRVO	32 (41.6)
PDR	27 (35.1)
OIS	3 (3.9)
BMI (kg/m²)	n (%)
<18.5	1 (1.3)
18.5-24.9	19 (24.7)
25-29.9	31 (40.3)
30-34.9	19 (24.7)
>35	7 (9.1)
NVI stage	n (%)
Stage 1	0 (0)
Stage 2	9 (11.7)
Stage 3	26 (33.8)
Stage 4	42 (54.5)

BMI, body mass index; CRAO, central retinal artery occlusion; CRVO, central retinal vein occlusion; PDR, proliferative diabetic retinopathy; OIS, ocular ischemic syndrome.

months, 15.1±7.6 mmHg at six months, and 14.5±7.9 mmHg at 12 months (p<0.001; Figure 3). At one-year follow-up, 89.6% (n=69) of patients had an IOP ≤ 21 mmHg. IOP ≤ 5 mmHg was found in 7.8% (n=6) and tolerated without complications. 96.1% (n=74) presented at baseline with IOP≥30 mmHg. The number of glaucoma medication decreased from 4.7±1.3 at baseline to 1.9±1.9 at one month, 1.8±1.7 at three months, 1.8±1.5 at six months, and 1.8±1.8 (p<0.001; Figure 4) at 12 months.

While 32.5% (n=29) of patients complained of ocular pain at baseline (VAPS: 6.0±1.8), all patients were without pain at all follow-up visits. Patients with pain had a significantly higher baseline IOP of 49.9±9.0 mmHg than patients without pain 44.1±10.3 mmHg (p<0.01).

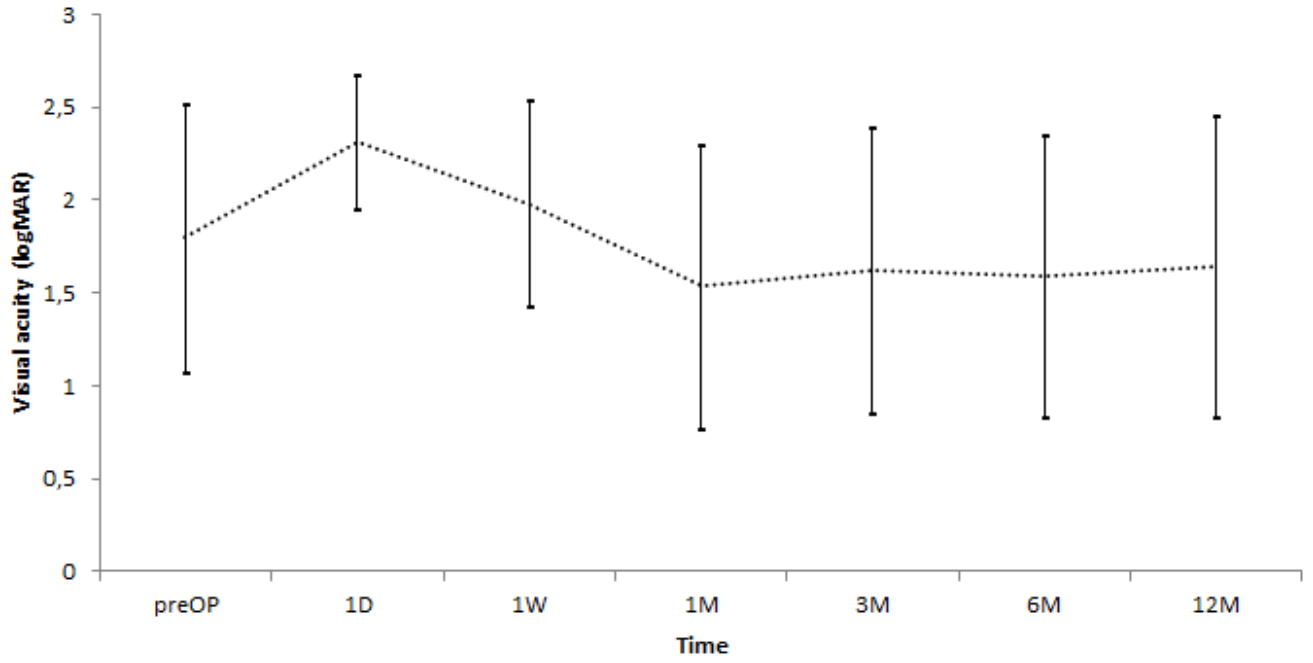

Figure 2. **Visual acuity during follow-up (mean ± SD) (p=0.47).**

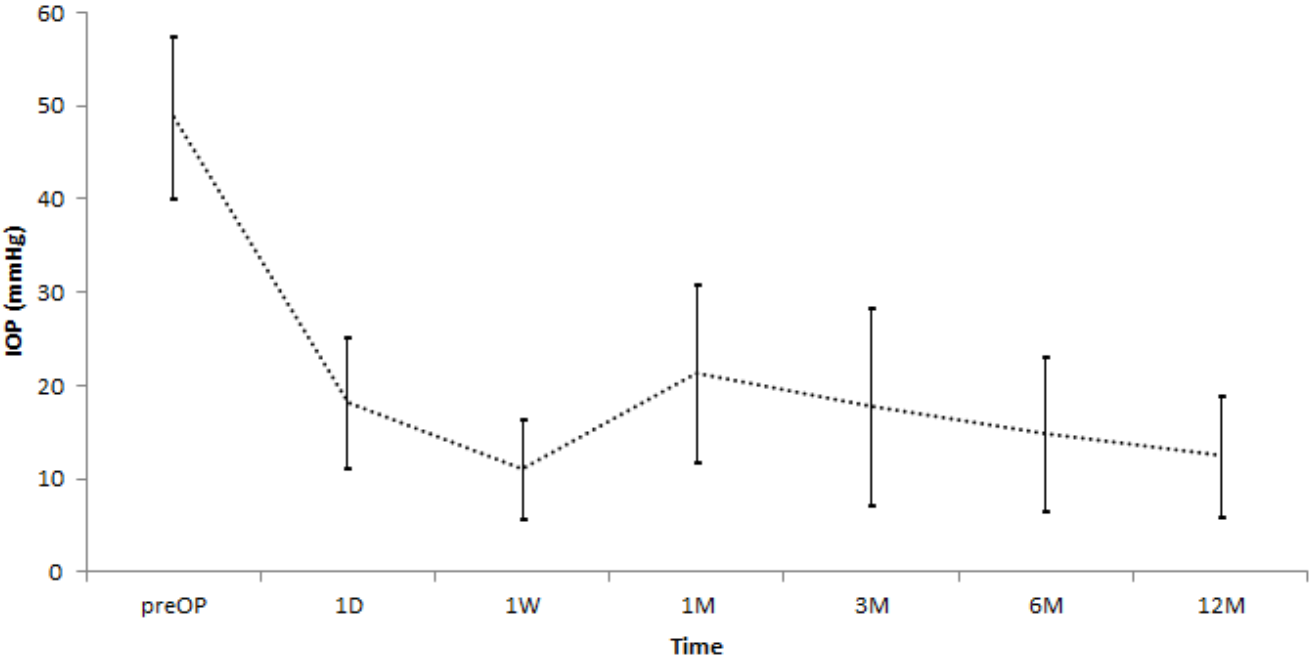

Figure 3. **Intraocular pressure (IOP) during follow-up (mean ± SD) (p<0.001).**

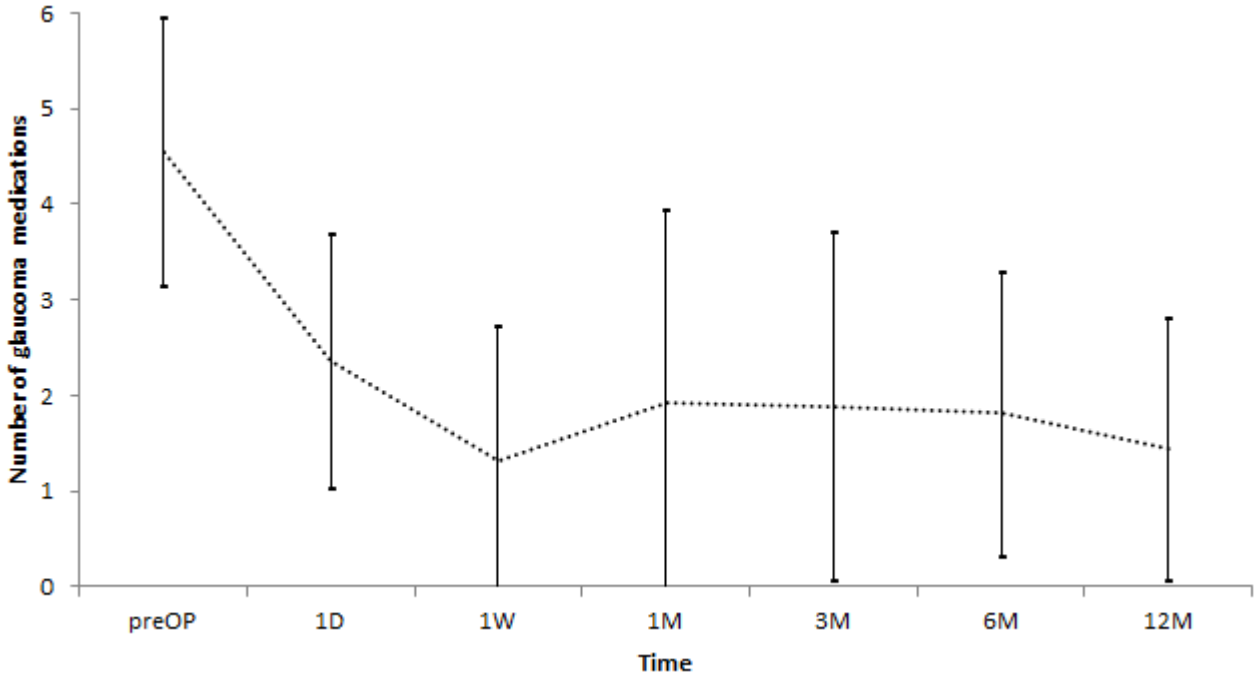

Figure 4. Number of glaucoma medication during follow-up (mean ± SD) (p<0.001).

Early postoperative complications (day 1 to four weeks) included intraocular fibrin 67.5% (52/77), hyphema 20.8% (16/77), choroidal detachment 16.9 (13/77), and corneal erosion 14.3% (11/77). Late postoperative complications (> 1 months) included retinal detachment in 3.9% (3/77) and consecutively a painless phthisis in these 3 cases (Table 2).

At the one-year follow-up, surgical intervention was required in 16.9% (22/77) eyes. Of these eyes, 63.6% (14/22) received vitrectomy, 22.7% (5/22) a Baerveldt glaucoma drainage implant, 4.5% (1/22) a trabeculectomy with mitomycin C and 4.5% (1/22) a keratoplasty. One painful and blind eye needed enucleation.

Repeat transscleral cyclophotocoagulation was performed in 11.6% (15/77). 3.9% (5/77) of patients with a mean BCVA 1.1±0.3 logMAR received an additional 4.0±0.8 anti-VEGF injections.

At baseline, 11.7% (9/77) had neovascularization of the iris (NVI) stage of 2, 33.8% (26/77) stage 3 and 54.5% (42/77) stage 4. The combined average stage was 3.4±0.7 (range 2–4). Patients with stage 4 needed significantly more major interventions compared with stage 3 (OR 25.0, 95% CI 3.09-201.7, p=0.003) and stage 2 (OR 19.0, 95% CI 1.03-347.3, p=0.047). There was no statistically significant difference between the number of interventions required at stage 2 and stage 3 (OR 0.89, 95% CI 0.03-23.9, p=0.9471).

Table 2. Early postoperative inflammation and postoperative complications.

Complications	n (%)
Early inflammation/complications	
Extensive fibrin	52 (67.5)
Hyphema	16 (20.8)
Choroidal swelling	13 (16.9)
Corneal erosion	11 (14.3)
Late complications	n (%)
Retinal detachment and Phthisis bulbi	3 (3.9)

Kaplan-Meier analysis showed a probability of success of 65% at one-year follow-up (Figure 5).

Lost to follow-up

21 patients were lost to follow-up. 10 patients died during the one-year follow-up period. All 21 patients lost to follow-up completed a telephone survey. The main reasons for missed visits were general health issues in 52.4% (11/21), long-distance to our clinic 38.1% (8/21), and family-related reasons in 9.5% (2/21). 57.1% (12/21) of patients had retained at least ambulatory vision. 71.4% (15/21) used 1.7±1.2 glaucoma eye drops. 95.2% (21/22)

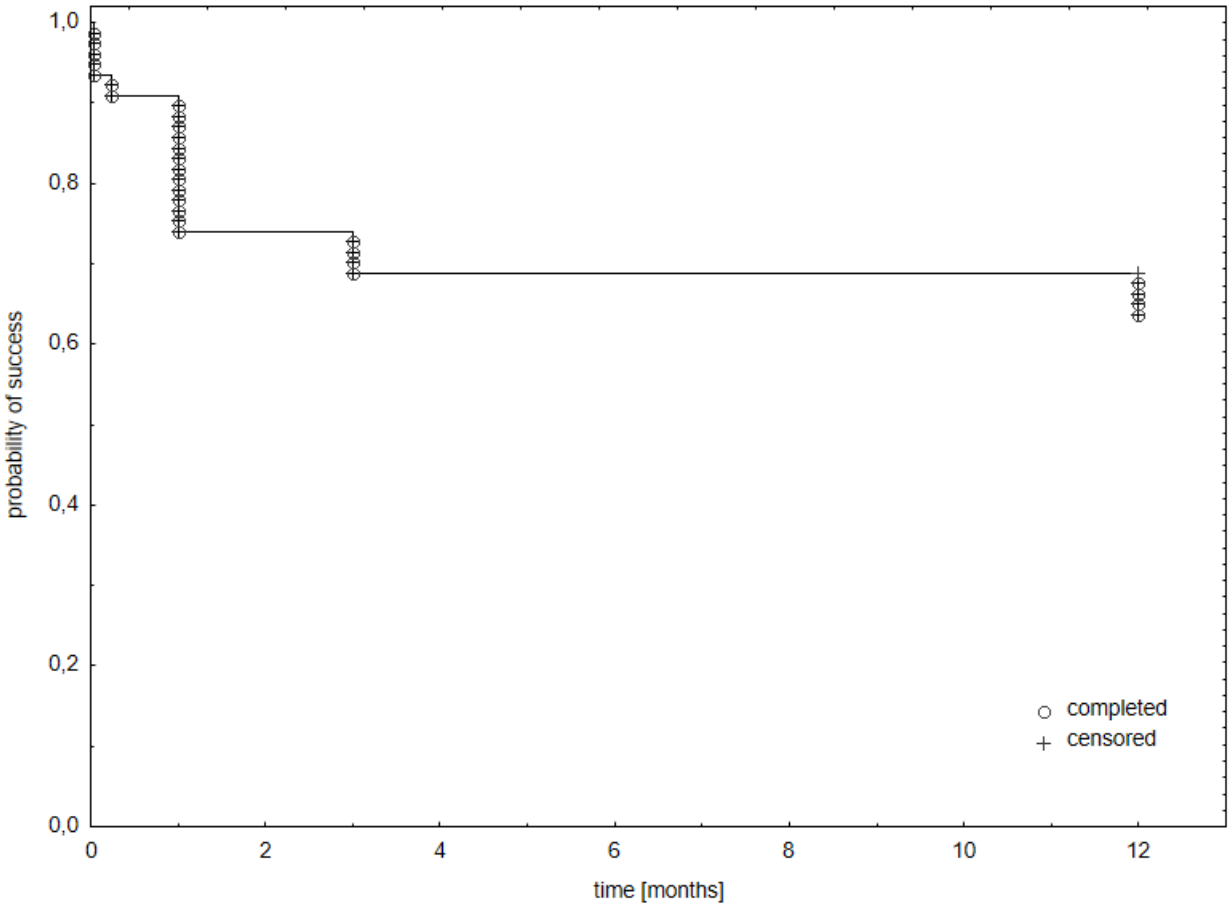

Figure 5. Kaplan-Meier univariate estimates of the probability of success: intraocular pressure (IOP) ≤ 21 mmHg or IOP reduction ≥ 30% from baseline, with or without glaucoma medication, without vision loss.

reported overall satisfaction with the treatment. All patients were pain-free.

Discussion

By 1871, NVG was known as "glaucoma haemorrhagicum et apoplecticum" and feared as a consequence of ischemia that quickly led to enucleation due to "hefty ciliary neuralgia"[39]. In 1963, using improved equipment, Weiss *et al.* found that emerging neovascularization and fibrovascular membranes of the iris and the angle could be observed well before the onset of advanced NVG[40], hinting at a window to initiate treatment. Today, the ability to detect neovascularization early is complemented by improved interventions that address both the underlying pathology and elevated IOP. However, these interventions need to be implemented during the early stages of the disease because NVG continues to have a rapid evolution and a poor prognosis for both the eye and the patient[12]. One study showed that the expected lifespan of patients with NVG decreased by 52% compared to an age-correlated normal population, corresponding to a loss of 6.5 years. In diabetics with NVG, the lifespan was reduced even more by 72%[12]. In our study, 74% (57/77) of patients had multiple cardiovascular risk factors and were overweight or obese. During follow-up, ten patients died. The high mortality rate is a reminder that any treatment strategy of NVG should aim at keeping the number of necessary follow-up visits and additional interventions at a minimum. We tried to address this need by combining several interventions in a single surgical session.

Retinal ischemia is the primary cause of NVG[10,41]. Accordingly, PRP is the standard of care to reduce posterior pole oxygen demand and angiogenic drive while vitrectomy is performed to increase the partial pressure of vitreous oxygen[42,43]. We performed lens extraction, pars plana vitrectomy, and endoscopic PRP because of significant media opacities and because endoscopic laser through the pars plana approach facilitates the delivery of 360° near-confluent peripheral retinal laser treatment out to the ora serrata. In our clinical experience, even relatively small areas of retinal ischemia may cause further NVG progression. Therefore, we took care to apply 360° PRP to near-confluence up to the ora serrata. Such extensive treatment would be challenging or impossible using standard PRP with an indirect ophthalmoscope or at the slit lamp.

In the healthy eye, the vitreous body and the iris-lens diaphragm form a relative diffusion barrier that maintains a higher

oxygen partial pressure in the posterior chamber than the vitreous overlying the posterior pole. Concurrently, it reduces the diffusion of angiogenic mediators. Recreating a relative diffusion barrier after vitrectomy[44] is beneficial and reduces NVI occurrence[45]. A relative barrier can be achieved with silicone oil[46] that reduces the incidence of NVG[46,47]. Following this concept, Bartz-Schmidt *et al.* treated 32 NVG patients with pars plana vitrectomy, retinal, and ciliary body photocoagulation, and silicone oil tamponade as eyes were left aphakic. This approach controlled IOP (defined as an IOP between 8 and 21 mmHg) in 72% of patients for at least one year[30]. In our study we achieved an IOP control in 77.9% and all eyes were pseudophakic and without silicone oil at the conclusion of the surgery, thereby suggesting that silicone oil as a diffusion barrier may not be necessary[30].

Our success rate of 65%, defined as an IOP <22 mmHg, with or without glaucoma medication and without vision loss after a one-year follow-up, is similar to success rates reported for glaucoma drainage devices, which range from 62% to 66.7%[24,48–50]. One study reported a 73% success rate in 38 eyes that received a glaucoma drainage device and had relatively few postoperative complications[51]. However, this report is the exception as others have found[24,48–50]. (Table 3).

Trabeculectomy has been one of the most important intraocular pressure lowering operations in glaucoma since the 1960s, so this surgical technique was also used in NVG. Different studies have shown a failure rate of up to 80%[52,53]. The use of mitomycin C (MMC) and 5-fluorouracil (5-FU) led to a higher success rate and was 54% after 18 months for MMC used intraoperatively and 55% after 35 months for 5-FU[54]. A combined trabeculectomy and retinal cryotherapy did not seem to improve the surgical success outcome for NVG in diabetic patients[55]. However, in this study patients had received panretinal photocoagulation prior to the surgery and in contrast to our study IOP ≤ 21 mmHg was the only success criteria.

Neovascular glaucoma is a major risk factor for failure of trabeculectomy[56,57]. Chronic blood-retinal barrier insufficiency, for example in advanced diabetic retinopathy, in which endothelial damage and the subsequent release of serum proteins occurs, plays an important role[58]. Retinal ischemia also leads to the production of inflammatory mediators[59], which can lead to filtering bleb scarring and postoperative failure of the trabeculectomy[58].

Our integrative surgical approach avoided tube-specific complications (e.g., tube exposure, retraction, corneal touch, obstruction), ranging from 13% to 26% in NVG over five years[24,48–51]. It delivers both retina and glaucoma treatment in a single surgical session and reduces the patient and health care system burden by simplifying postoperative care and follow-up. Our telephone survey with all patients lost to follow-up revealed that the main reasons for missed visits were other (general) health issues in 52.4% and long distance to the clinic in 38.1% but a high subjective satisfaction rate.

Patients with NVI stage 4 needed significantly more major interventions than stage 3 or stage 2, but there was no difference between stage 2 and stage 3. This finding suggests that early and comprehensive treatment may be more beneficial than a stepwise treatment strategy.

It is worth noting that IOP reduction can also be achieved without cyclodestruction applying only pars plana vitrectomy, lensectomy with a preserved anterior capsule, and panretinal endophotocoagulation as reported by Kinoshita *et al.*[31]. However, this study included only 13 eyes with a lower mean preoperative IOP of 29 mmHg as in our study. By contrast, other

Table 3. Literature overview.

Authors	Year	Design	Intervention	n	IOP preOP (mmHg)	Success (%)	Vision loss (%)	Phthisis bulbi (%)
Mermoud *et al.*[60]	1993	retrospective	Molteno-Valve	60	42.3 ± 13.2	62	48	18
Every *et al.*[49]	2006	prospective	Molteno-Valve	145	40.1 ± 13.0	72	32	N/A
Yalvac *et al.*[8,48]	2007	retrospective	Ahmed-Valve vs Molteno-Valve	38/27	39.5 ± 4.5 vs 39.3 ± 3.9	63 vs 37	23-33	7.9-14.8
Takihara *et al.*[56]	2009	retrospective	Trabeculectomy + MMC	101	35.9 ± 11.3	62.6	12.9	5.0
Netland *et al.*[51]	2010	retrospective	Ahmed-Valve ± NVG	38/38	39.1 ± 11.2 vs 43.8 ± 11.0	89.2 vs 73.1	23,7	13,2
Shen *et al.*[61]	2011	retrospective	Trabeculectomy versus Ahmed-Valve	20/20	47.7 ± 10.2 vs 47.8 ± 11.3	70 vs 65	15 vs 30	5.0
Xie *et al.*[50]	2019	retrospective	Ahmed-Valve	66	48.23±8.17	66.7	N/A	N/A
Strzalkowski *et al.*[37]	2021	retrospective	PPV+EL+Avastin+ CPC	77	46.0 ± 10.3	64.6	3.9	5.7

studies that only used anti-VEGF agents as primary treatment[28,62] reported failure rates up to 88%[62]. Anti-VEGF agents may be best used as an adjuvant treatment[29]. Consistent with our findings, a study that used pars plana vitrectomy, endoscopic peripheral panretinal photocoagulation, and endocyclophotocoagulation (ECP) also achieved an IOP reduction which was more effective than panretinal photocoagulation, intravitreal bevacizumab, pars plana vitrectomy, and trabeculectomy with mitomycin C or Ahmed valve placement. However, the authors reported a higher phthisis rate of 7.4%[63].

Because of the underlying ocular disease, visual function remained low in most eyes in our study.

There are limitations to our study. Because the integrative surgical approach described here was the primary practice pattern, there was no control group. This limited us to an intragroup comparison of before versus after treatment data. As a retrospective study, it can only inform on future prospective studies' parameters and design and help formulate, but not answer, hypotheses about associations between treatment and outcomes.

In conclusion, this study shows that NVG can be controlled in most cases by an integrative surgical approach delivered in a single surgical session that combines transscleral cyclophotocoagulation, cataract removal, pars plana vitrectomy, near-confluent full-scatter panretinal photocoagulation, and intravitreal bevacizumab. Patients with advanced iris neovascularization required significantly more additional interventions. The described approach lowered IOP significantly, reduced the number of glaucoma medications, and controlled pain.

Data availability

Underlying data

Open Science Framework: Combined vitrectomy, near-confluent panretinal endolaser, bevacizumab and cyclophotocoagulation for neovascular glaucoma — a retrospective interventional case series. https://doi.org/10.17605/OSF.IO/QTCGV[37].

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Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 17 March 2021

https://doi.org/10.5256/f1000research.54199.r80498

✔ **Andrew W. Eller**
Retina Service, Department of Ophthalmology, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA, USA

Saloni Kapoor
University of Pittsburgh Medical Center, Pittsburgh, USA

The authors have satisfactorily addressed the comments we provided and made all the changes we suggested. They have not provided a regression analysis as they would like to put this forward in another manuscript which we look forward to reading.

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 01 December 2020

https://doi.org/10.5256/f1000research.29684.r75197

✔ **Stefan Dithmar**
Department of Ophthalmology, HELIOS Dr. Horst Schmidt Kliniken, Wiesbaden, Germany

The authors present a very interesting observational study on the therapy of neovascularization

glaucoma. The treatment of this clinical entity is difficult and often unsatisfactory. The authors report on a convincing surgical approach and present retrospective results in a relatively large patient group. The presentation of the results is good and the manuscript is well written.

Taking into account the reviewer report by Andrew W. Eller, I have no further comments to make.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Retina research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 20 November 2020

https://doi.org/10.5256/f1000research.29684.r73906

?

Andrew W. Eller
Retina Service, Department of Ophthalmology, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA, USA

Saloni Kapoor
University of Pittsburgh Medical Center, Pittsburgh, USA

In this study Dr Strzalkowski *et al.* provide a retrospective observational analysis of a single

center's experience with aggressive upfront treatment of neovascular glaucoma (NVG) with combined vitrectomy, near confluent pan retinal endolaser, bevacizumab and transscleral cyclophotocoagulation.

The authors hypothesize that upfront combined treatment would improve outcomes in terms of IOP, antiglaucoma medications, pain, necessity of further surgeries and help reduce follow-up visits. They report baseline characteristics and one-year outcomes for 77 patients with neovascular glaucoma that underwent the combined procedure. We congratulate them on implementing a success strategy in treating these complex cases. Often patients with NVG have disastrous outcomes with poorly controlled IOP and significant loss of vision. In this series, a number of patients were able to maintain reasonable vision. It can often be difficult to "titrate" treatment of IOP, often resulting in hypotony. There were three patients with phthisis bulbi and another six with hypotony for a total of nine or 11.7%. Three patients developed retinal detachment. Perhaps these were the same three patients who developed phthisis bulbi.

The major drawback of this study is the lack of alternate treatments for randomization. This limits our ability to draw any conclusions about optimal management strategies and only hypotheses can be generated. This is appropriately acknowledged by the authors who are careful not to overstate their conclusions.

The authors seemed to have corelated surgical success with the stage of iris neovascularization. In other words, there were more surgical interventions with stage 4, then stages 2 or 3. It is the experience of this reviewer that one can corelate treatment success of NVG with presenting IOP and the immediate response of IOP to medical therapy. In clinic, if the initial IOP is less than 40 mmHg and medical treatment can reduce the IOP into the low 20's, these patients can often be treated with an initial injection of an anti-VEGF medication, followed by PRP laser. In the long term, any residual glaucoma can usually be treated with medical therapy alone. Those patients presenting with an IOP greater than 40 mmHg, and not responding to medical therapy will require more aggressive treatment. If the visual potential is reasonable, this treatment may include anti-VEGF, PRP laser (with vitrectomy if visualization of the retina is poor), and glaucoma surgery. If the visual potential is very poor, then not invasive glaucoma treatment such as transscleral CPC) is advised. Using their data, are the authors able to confirm our observations regarding treatment of NVG.

As the authors have stated, there are a number of different underlying causes of neovascular glaucoma and they have been combined in this series. This is a fairly large series and we question whether the severity of the NVG and response to treatment may have differed according to the underlying pathology. For example, the iris neovascularization and glaucoma in central retinal vein occlusions (CRVO) tends to progress more rapidly then seen with diabetic retinopathy. Once the retinal ischemia has been addressed in CRVO, it seems these eyes are more likely to develop hypotony. What was the experience of the authors in this study?

The authors cite two studies from the mid-1980's when the use of silicone oil was very much in its early stages of clinical usage. At that time, it was felt that silicone oil reduced or perhaps prevented the flow of VEGF into the anterior chamber and therefore decreased the risk of iris neovascularization and glaucoma. We believe this theory has been discounted as we know that there is a flow of aqueous humor from the posterior segment into the anterior chamber. Retinal detachment alone increases VEGF production and it occurs in cases of proliferative diabetic

retinopathy there can be an even more profound angiogenic effect. An alternative explanation for this observation is that silicone oil improves the outcome in these eyes by simply improving the chances for retinal re-attachment.

In the Introduction, the authors hypothesize that the combined approach would help decrease outpatient visits. This is again emphasized in the Discussion where authors report that patients with neovascular glaucoma have significant comorbidities and lower life expectancy and would therefore benefit from decreased outpatient visits. The counter-argument to be made is that combined aggressive surgical intervention would increase risk of complications and require closer monitoring. No data is provided on the number of follow up visits. Consider adding to results if available. The authors could consider performing a regression analysis to determine which baseline characteristics predicted success with this combined technique. This analysis will help identify patients in whom this technique would be most helpful. It could also show when this technique may be more aggressive than necessary in some cases, and could be more aggressive in others when the addition of a glaucoma drainage device may be beneficial.

Specific comments for revision:

1. In the Introduction, second paragraph, suggest following change. “In 1994, Miller *et al*. showed that laser occlusion of all branch retinal veins in a primate could lead to CRVO and subsequent retinal ischemia.”
2. In the Results, consider rephrasing “arterial hypertension” to hypertension as this is the currently accepted terminology.
3. In Table 1 – consider rephrasing “R stadium” to read “NVI Stage” or Weiss and Gold Rubeosis grading to ensure clarity.
4. In the Discussion, it would be beneficial to see outcomes with staged surgical approach (Incisional surgical management with trabeculectomy/tubes, followed by cryotherapy if poor response) from existing literature to enable some comparison with the combined approach reported in this manuscript.
5. In the Discussion, the authors state “Patients with stage 4 anterior chamber neovascularization needed significantly more major interventions than stage 3 or stage 2, but there was a difference between stage 2 and stage 3”. The data reports NO significant difference between stage 2 and 3. Please clarify.

Overall, a well-organized manuscript with a practical approach to the treatment of neovascular glaucoma with novel data.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ophthalmology, Vitreo-Retinal Diseases and Surgery

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 23 Jan 2021

Piotr Strzalkowski, University Hospital Würzburg, Germany

Dear Reviewers,

We are grateful for the opportunity to improve our manuscript. We appreciate the helpful comments and have provided our replies below. We trust that we were able to address the concerns that were raised.

Thank you,

Piotr Strzalkowski

Reviewers' comments:
Reviewer #1 ("R1" in the following): There were three patients with phthisis bulbi and another six with hypotony for a total of nine or 11.7%. Three patients developed retinal detachment. Perhaps these were the same three patients who developed phthisis bulbi.
Authors: That is exactly correct. We appreciate the thoughtful analysis. All three patients with retinal detachment also developed phthisis bulbi. We added this important information to our manuscript.

R1, 1: As the authors have stated, there are a number of different underlying causes of neovascular glaucoma and they have been combined in this series. This is a fairly large series and we question whether the severity of the NVG and response to treatment may have differed according to the underlying pathology. For example, the iris neovascularization and glaucoma in central retinal vein occlusions (CRVO) tends to progress more rapidly than seen with diabetic retinopathy. Once the retinal ischemia has been addressed in CRVO, it seems these eyes are more likely to develop hypotony. What was the experience of the authors in this study?
Authors: Thank you for sharing your clinical experience. Based on our data we could not find a statistical significant difference in postoperative IOP or hypotony between CRVO and PDR patients.

R1, 2: No data is provided on the number of follow up visits. Consider adding to results if available.
Authors: Information about the number of follow up visits is provided in section "study design": All patients were treated at the University Eye Hospital in Würzburg, Germany. The combined intervention was part of routine patient care at our clinic and all patients with decompensated neovascular glaucoma and preserved visual function received this intervention. BCVA, intraocular pressure (IOP, mmHg), the number of glaucoma medication, visual analog pain scale (VAPS, 0-10) was recorded at baseline and at follow-up visits at one, three, six, and 12 months as part of routine care.

R1, 3: The authors could consider performing a regression analysis to determine which baseline characteristics predicted success with this combined technique. This analysis will help identify patients in whom this technique would be most helpful.
Authors: Regression analysis was not included in this study on purpose because this analysis is part of our ongoing study.

R1, Specific Comments:

- In the Introduction, second paragraph, suggest following change. "In 1994, Miller et al. showed that laser occlusion of all branch retinal veins in a primate could lead to CRVO and subsequent retinal ischemia."
- In the Results, consider rephrasing "arterial hypertension" to hypertension as this is the currently accepted terminology.
- In Table 1 – consider rephrasing "R stadium" to read "NVI Stage" or Weiss and Gold Rubeosis grading to ensure clarity.
- In the Discussion, it would be beneficial to see outcomes with staged surgical approach (Incisional surgical management with trabeculectomy/tubes, followed by cryotherapy if poor response) from existing literature to enable some comparison with the combined approach reported in this manuscript.
- In the Discussion, the authors state "Patients with stage 4 anterior chamber neovascularization needed significantly more major interventions than stage 3 or stage 2, but there was a difference between stage 2 and stage 3". The data reports NO significant difference between stage 2 and 3. Please clarify.

Authors: We have changed the manuscript to include these suggestions.

Competing Interests: No competing interests were disclosed.