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Efficacy of modified diode transscleral cyclophotocoagulation in patients with painful neovascular glaucoma secondary to retinal vein occlusion

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Purpose: *To assess the efficacy (success rate) of modified diode transscleral cyclophotocoagulation (TSCPC) in patients with painful neovascular glaucoma (NVG) secondary to retinal vein occlusion (RVO).*

Material and Methods*: This prospective, single-center cohort study included 62 patients (62 eyes) with NVG secondary to RVO. Best-corrected visual acuity (BCVA), the number of intraocular pressure (IOP)-lowering medications, laboratory characteristics and pain scores were assessed. A diode laser TSCPC with a fiber optic G-probe was performed at a power of 1,000 mW for duration of 1.5 s (corresponding to 1.5 J/pulse). Post-TSCPC measures of success included IOP between 10 and 21 mmHg or a reduction in IOP of ≥ 30% from baseline IOP, no ocular pain and improvement in or maintenance of BCVA.*

Results: *At 12 months after TSCPC, the IOP decreased by 48% (p = 0.000). Eight (13%), 18 (29%), and 7 (11%) eyes received two, three, and four CPC sessions, respectively. Post-TSCPC complications included long-term inflammation was noted in 6 eyes (9.7%) and hyphema in 1 eye (1.6%). Multivariate regression analysis demonstrated that TSCPC success depended on the baseline IOP (p = 0.01), number of local IOP-lowering medications (p = 0.03), and presence of preoperative complications (p = 0.02), and was associated with a D-dimer value < 0.55 mg fibrinogen equivalent units/l (p = 0.01). Panretinal laser photocoagulation performed early (within 3 months) after RVO and combined with antiangiogenic therapy did not prevent NVG, but contributed to the success of TSCPC for NVG.*

Conclusion: *The success rate of modified diode TSCPC in patients with painful NVG secondary to RVO at 12 months was 71%. Modified diode TSCPC in painful NVG secondary to RVO appears to be safe in terms of the absence of serious complications (hypotony and phthisis bulbi). TSCPC success depends on the presence of ophthalmic and systemic complications which should be treated.*

Keywords:

diode laser, transscleral cyclophotocoagulation, neovascular glaucoma, retinal vein occlusion

Introduction

Neovascular glaucoma (NVG) is one of the most difficult to manage complications of retinal vein occlusion (RVO) which may result in disastrous visual loss or blindness [1]. In the management strategy, the first priority should be to try to prevent its development by appropriate management of the causative diseases. Management of NVG primarily consists of controlling the high intraocular pressure (IOP) by medical and/or surgical means to minimize the visual loss [1]. The most common surgical approaches for NVG include trabeculectomy, tube shunt surgery, and cyclodestructive procedures. Most surgical procedures for this condition are aimed at decreasing the IOP by increasing aqueous outflow. Cyclodestruction decreases the IOP by decreasing aqueous production and has been found to be highly effective in NVG [2]. Diode transscleral cyclophotocoagulation (TSCPC) is the most commonly used cyclodestructive procedure [3].

Currently, no consensus exists regarding the selection of the most appropriate laser energy in TSCPC for providing a balance between IOP reduction and the risk of dangerous complications. Thus, standard TSCPC techniques cause collateral damage to ciliary body and scleral structures due to their non-selective nature, which has been associated with complications of laser treatment (persistent hypotony with phthisis bulbi, hyphema, intraocular inflammation, and cystoid macular edema with vision loss) [3, 4]. The rate of hypotony post TSCPC for glaucoma may be as high as 18% - 39% (first and foremost, in cases with NVG) [5,

6]. Moreover, the success rates in the published literature are widely variable (36.7–94.4%), likely due to differences in the approach to the selection of diode laser energy settings and other factors (form of glaucoma, definition of success, and follow-up duration).

Concerns with regard to the efficacy and safety of TSCPC performed with conventional laser energy settings gave rise to the emergence of new approaches. Duerr and colleagues [7] compared the outcomes of standard pop-titrated TSCPC (a starting power of 1.75 W and 2.0-second duration) and slow-coagulation TSCPC (1.25 W and 4.0 to 4.5-second duration for dark or light brown irises, and 1.5 W and 3.5 to 4.0-second duration for other iris pigmentation). They concluded that the former technique and the latter technique resulted in similar VA and IOP outcomes and comparable complication profiles, although the former technique had a higher incidence of prolonged inflammation postoperatively. A prospective double-blinded randomized controlled trial is being conducted to compare two TSCPC techniques, the experimental technique using 1250 mW for 4 seconds and the conventional technique using 2000 mW for 2 seconds [8].

Given the promising results of our previous studies [9, 10], we decided to assess the efficacy and safety of low-intensity diode TSCPC with selective thermal effects on the ciliary epithelium in patients with NVG, and assess the impact of various preoperative factors (ophthalmic and associated systemic complications) on the efficacy of TSCPC for NVG secondary to RVO.

The study purpose was to assess the efficacy (success rate) of modified diode TSCPC in patients with painful NVG secondary to RVO.

Material and Methods

Population under study

This prospective, single-center cohort study is part of the research program by the Filatov Institute of Eye Diseases and Tissue Therapy (registration number № 0122U001490). The study was conducted in accordance with the standards expressed in the Helsinki Declaration and was approved by the Filatov Institute ethics committee (Minutes no. 4, 2024). Written informed consent was obtained from all study patients.

Inclusion criteria included NVG secondary to RVO (Fig.1-A, 1-C), ocular pain and an IOP ≥ 30 mmHg despite maximal hypotensive medication.

Patients were excluded if they had NVG secondary to other disorder, severe general systemic disease, or no eye pain.

Examination at presentation and follow-up visits

Patients were evaluated at presentation (V0) and at 1, 6 and 12 months (V1, V6 and V12) after the first session of TSCPC. They underwent best-corrected visual acuity (BCVA) assessment, biomicroscopy, ophthalmoscopy, and gonioscopy. In addition, the number of local IOP-lowering medications used was recorded, and laboratory blood parameters, D-dimer (mg fibrinogen equivalent units (FEU)/l) and low-density lipoprotein cholesterol (LDL-C, mmol/L) were assessed.

A repeat TSCPC was performed if there was a loss of hypotensive effect.

After treatment, eyes were dichotomized into three groups based on whether their BCVA improved, did not change or worsened postoperatively.

A Numerical Rating Scale (NRS) questionnaire was administered to patients to assess their pain [11]. The pain NRS is an 11-point numeric scale, with 0 representing one pain extreme (e.g., “no pain”) and 10 representing the other pain extreme. NRS pain scores were categorized as mild (0 to 4), moderate (5 to 6) or severe (7 to 10) [12].

TSCPC procedure

Epibulbar anesthesia with ophthalmic propacaine hydrochloride 0.5% and either peribulbar or retrobulbar anesthesia with lidocaine hydrochloride 0.5% were administered before the onset of the TSCPC. An 810-nm diode laser TSCPC was applied using a fiber optic G-probe connected to the Vitra 810 (Quantel Medical Instruments, Cournon d’Auvergne Cedex, France), and was performed with a laser power of 1,000 mW and exposure duration of 1.5 s (corresponding to 1.5 J/pulse). The footplate of the G-probe was held parallel to the visual axis, with the laser fiberoptic placed over the pars plicata that was visualized with infrared diaphanoscopy [13]. Repeat TSCPC was performed at 1 month if there was a loss of hypotensive effect. TSCPC was performed concentrically in a circular fashion, with care taken to avoid the 3- and 9-o’clock positions (to prevent damage to the long ciliary nerves and arteries), areas of sclera thinning and sites of failed filtering blebs and glaucoma drainage devices. Post-TSCPC treatment included ophthalmic preservative-free dexamethasone 1 drop (1 mg/1 ml, three times daily) over two weeks to prevent inflammation [14] and a course of non-steroidal anti-inflammatory drug (bromfenac ophthalmic solution) over a month to reduce cyclooxygenase activity and inhibit prostaglandin synthesis [9].

TSCPC efficacy measures

Post-TSCPC measures of success included IOP between 10 and 21 mmHg (or a reduction in IOP of ≥ 30% from baseline IOP), no ocular pain and improvement in or maintenance of BCVA.

Failure was defined as IOP of ≥ 22 mmHg despite maximal hypotensive medication, the development of any complications or the need for glaucoma surgery.

Arterial hypertension was defined as a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg, and/or self-reported current treatment for arterial hypertension with antihypertensive medication.

Given that the study sample was composed of patients with RVO and 85% of the sample had a cardiovascular disease, it became necessary to assess the blood coagulation system and the intensity of pathological processes taking place in the course of fibrinolysis. D-dimer and LDL-C were assessed.

Patients had a consultation with a general physician or cardiological consultation for the assessment of the status of the cardiovascular system and recommendation of changes in medication treatment.

Statistical analysis

Statistical analyses were performed using the open source software Jamovi (Jamovi, Sydney, Australia). Categorial variables were described using frequencies and percentages. Shapiro-Wilk test was performed to determine normality of data. Non-normally distributed data were described using median and interquartile range (IQR). Changes in continuous variables over time were assessed using the Wilcoxon signed-rank test. Comparisons of frequencies expressed as percentages were made with a calculator for comparison of proportions. Spearman correlation coefficients (rs) were calculated. Multiple regression analysis was used to determine the variables which impact the clinical outcome. P-value < 0.05 was considered statistically significant.

Results

Sixty-two patients (62 eyes) with NVG secondary to RVO were included in this study. Of these, 40 eyes (65%) had pattern vision. All patients had ocular pain. The baseline clinical characteristics of patients (n = 62) with NVG secondary to RVO are presented in Table 1.

Changes in IOP, BCVA, number of IOP-lowering medications and pain score

At 1, 6 and 12 months after TSCPC, the IOP decreased by 23% (p = 0.000), 45% (p = 0.000) and 48% (p = 0.000), respectively (Table 2). Of the 62 eyes, 29 (47%) received one CPC session, whereas other required at least one repeat CPC session due to inadequate IOP reduction: 8 eyes (13%), 18 eyes (29%), and 7 eyes (11%) received two, three, and four CPC sessions, respectively. Of note, there was no loss of vision after any subsequent CPC session compared with after the first session. After TSCPC treatment, long-term inflammation was noted in 6 eyes (9.7%), hyphema in 1 eye (1.6%), and no eye showed hypotony.

In addition, corneal edema significantly improved, with an improvement in BCVA, in 5 eyes (8%). Moreover, in 4 eyes (6.5%), hyphema was noted before treatment, and completely disappeared, with an improvement in BCVA, within a month after TSCPC treatment.

At 12 months, the median (IQR) number of local IOP-lowering medications decreased by 33%, from 3.0 (2-4) to 2.0 (1-2), compared to baseline (p = 0.000).

In addition, the median (IQR) NRS pain score improved to 1 (0-2) in all patients.

The TSCPC success rate at 12 months was 71%. The median total energy per CPC session was 58.5 J, and median total energy for the entire period of treatment (median (IQR) number of CPC sessions, 2.0 (1-3)) was 112.5 (58.5-134.4) J.

Most patients with TSCPC treatment success had a long history of RVO. Of note that patients with a previous history of panretinal laser photocoagulation (PRLP) only, anti-vascular endothelial growth factor (VEGF) only, or PRLP combined with anti-VEGF therapy substantially contributed to the proportion of patients with IOP-lowering success of TSCPC. Of 44 eyes (71%) with CPC success at 12 months, 4 had a previous history of PRLP only, 6 had a previous history of anti-VEGF therapy only, and 12 had a previous history of PRLP plus anti-VEGF therapy (p = 0.049). In addition, 30 eyes (48%) showed improvement in rubeosis and/or anterior chamber angle (Fig. 1 B).

TSCPC treatment for NVG secondary to RVO was effective in eyes of 30 (48%) patients with a D-dimer level < 0.55 mg FEU/l and eyes of 38 (57%) patients with an LDL-C level < 3.0 mmol/l.

Our univariate regression analysis demonstrated that many variables had a significant impact on TSCPC success in NVG secondary to RVO (Table 3).

Our multivariate regression analysis, however, demonstrated that TSCPC success in NVG secondary to RVO depended on the baseline IOP (p = 0.01), number of local IOP-lowering medications (p = 0.03), and presence of preoperative complications (p = 0.02), and was associated with a D-dimer value less than 0.55 mg FEU/l (p = 0.01).

Discussion

We have previously reviewed current treatments for NVG and assessed the role of laser cylodestruction methods with different energy settings for the control of IOP in NVG [15]. Potential complications of standard TSCPC (laser power, 2 W; exposure time per burn, 2 s; energy, 4 J)) for NVG have been noted [5, 6, 16]. Ramli and colleagues stressed that underlying diagnosis of NVG is a significant risk factor for hypotony post TSCPC and noted the unpredictable dose-response relationship of these eyes with TSCPC and higher risk of hypotony [6]. Compared to other types of glaucoma, eyes with NVG exhibit disproportional resistance to aqueous outflow due to the presence of fibrovascular membrane and ischemia-induced uneven production of the aqueous humor. Therefore, any cyclodestruction procedure can result in imbalance between the resistance to aqueous outflow and aqueous secretion, thus leading to hypotonia [6, 17-19]. In the current study, we assessed the efficacy and safety of low-intensity diode TSCPC as a first-line or second-line treatment for patients with NVG secondary to RVO who experienced an IOP increase above 30 mmHg, neovascularization of the iris (Fig. 1A) and anterior chamber angle, ocular pain, and in whom previous medical or surgical treatment did not result in adequate IOP decrease.

We supposed that a decrease in laser energy settings in TSCPC would result in reduced rates of severe complications (inflammation, hypotony, and phthisis bulbi), which is in line with opinions of other researchers [7, 20]. Khodeiry and colleagues [21] reported on no major complications and minimal non-major complications after slow coagulation TSCPC (with lower power and longer exposure time settings and avoidance of producing a pop sound) for post-vitrectomy patients with silicone oil-induced glaucoma [21]. This is in agreement with the

Table 1. Clinical characteristics of patients with painful neovascular glaucoma secondary to retinal vein occlusion

No	Baseline characteristics	Values
		Median (interquartile range) or n (%)
1	Age, years	63 (62; 66)
2	Gender (males/females)	30 (48%) / 32 (52%)
3	IOP, mmHg	40 (36-44)
4	Number of local IOP-lowering medications	3.0 (2–4)
5	Oral acetazolamide, YES	60 (97%)
6	NRS pain scores	10 (9-10)
7	BCVA V0 0 (zero) 0.001-0.2	0.02 (0.01; 0.05) 22 (35%) 40 (65%)
8	Ophthalmoscopic evidence V0: Ocular inflammation (marked mixed injection) Corneal edema Keratopathy Hyphema/Vitreous hemorrhage	19 (30.6%) 6 (9.6%) 5 (8.1%) 4 (6.5%) 3 (4.8%) /1 (1.6%)
9	History of interventions: PRLP only Anti-VEGF therapy only Anti-VEGF therapy + PRLP	29 (47%) 9 (15%) 7 (11%) 13 (21%)
10	Time period after anti-VEGF therapy, months	13 (10;18)
11	Time period after RVO, months No treatment After treatment with: PRLP only Anti-VEGF therapy only Anti-VEGF therapy + PRLP	6 (4; 14) 4.0 (3-6) 16 (10-18) 12 (8-21) 18 (8-26)
12	Glaucoma surgery, YES	20 (32%)
13	Cataract/Pseudophakia	47 (76%) / 15 (24%)
14	Cardiovascular pathology, YES	53 (85%)
15	Systolic blood pressure, mmHg	145 (140; 155)
16	Diastolic blood pressure, mmHg	80 (80; 85)
17	LDL-C, mmol/l <1.8 high risk; < 2.6 moderate risk; <3.0 low risk;	2.5 (2.0;3.4) 5 (8.1%) 26 (41.9%) 31 (50%)
18	D-dimer, mg FEU/l (reference values, <0.55 mg FEU/l) 0.5 (0.42; 0.5) 0.75 (0.66-1.05)	 38 patients (61%) 24 patients (39%)
19	Smoking, YES	17 (33%)

Note: BCVA, best-corrected visual acuity; FEU, fibrinogen equivalent units; IOP, intraocular pressure; LDL-C, low-density lipoprotein cholesterol; NRS, numeric rating scale; RVO, retinal vein occlusion;

Table 2. IOP and BCVA values, number of IOP-lowering medications, NRS pain score before and after transscleral cyclophotocoagulation

No.	Characteristic	Baseline	After CPC session		
			V1	V6	V12
		Median (interquartile range)			
1	IOP, mmHg	40.0 (36; 44)	31.0 * (23; 33)	22.0 * (20; 28)	21.0 * (19; 24)
2	BCVA	0.02 (0.01; 0.05)	0.02 (0.01; 0.04)	0.05 (0.02; 0.08)	0.05 (0.02; 0.07)
3	Number of local IOP-lowering medications	3.0 (2-4)	3.0 (2-3)	2.0 (1-2)	2.0 (1-2)
4	NRS pain score	10 (9-10)	3 (2-6)	3 (2-6)	1 (0-2)

Note: *, as per the Wilcoxon test; ², as per the Fischer exact test; CPC, cyclophotocoagulation; BCVA, best-corrected visual acuity; IOP, intraocular pressure; NRS, numeric rating scale; V1, V6 and V12, follow-up visits at one, six and 12 months after the first session

Table 3. Results of univariate regression analysis for success of transscleral cyclophotocoagulation in patients with neovascular glaucoma secondary to retinal vein occlusion

Characteristic	Adjusted R^2	F (1,60)	β	Standard error of β	p-level
IOP (V0)	0.21	16.79	-0.04	0.01	0.000
Repeated CPC session (2-4)	0.29	25.80	-0.50	0.10	0.000
Number of local IOP-lowering medications	0.10	7.41	-0.18	0.07	0.008
Total energy	0.16	12.71	-0.004	0.001	0.001
PRLC only	0.06	4.92	-0.29	0.13	0.03
Antiangiogenic therapy only	0.12	9.24	0.35	0.12	0.004
PRLC + antiangiogenic therapy	0.06	4.93	0.16	0.07	0.03
NRS pain score (V0)	0.07	5.68	-0.11	0.05	0.02
Complications (V0)	0.16	12.65	-0.14	0.04	0.001
Smoking	0.40	41.55	-0.61	0.09	0.000
Cardiovascular pathology	0.08	6.53	-0.36	0.14	0.01
LDL-C	0.14	11.29	0.227410	0.067676	0.001
D -dimer	0.13	10.50	0.35	0.11	0.002

Note: β, standardized regression coefficient of the equation; F, calculated F-value; IOP, intraocular pressure; LDL-C, low-density lipoprotein cholesterol; NRS, numeric rating scale; p-level, P-value for the null hypothesis of the F test; R^2, coefficient of determination

findings of our previous study on the histopathological features in the rabbit eye after exposure of the distal ciliary body epithelium to selective thermal effects [10]. The current study confirmed safety of the proposed TSCPC technique in patients with NVG secondary to RVO, reporting on isolated complications in the form of edema and long-term inflammation, without persistent hypotony or phthisis bulbi. Of note that the median total energy per CPC session was 58.5 J, median total energy for the entire period of treatment was 112.5 (58.5-134.4) J, and the success rate at 12 months was 71%. In a study by Hwang and colleagues [22], the 12-month success rate for a single session of slow coagulation TSCPC in patients with medically uncontrolled glaucoma was 50.1%, but the proportion of patients with NVG was only 12.3%. Importantly, Hwang and colleagues [22] reported that, after slow coagulation TSCPC, the rate of inflammation as measured with laser flare photometry increased to six-fold at week 1, but gradually decreased thereafter, and was two-fold increased at month 12 compared to baseline.

In the current study, the time from RVO onset to NVG diagnosis was four times longer in patients with a previous history of PRLP than in patients without a previous history of treatment. This finding is in line with the opinion of Hayreh [1] who noted that NVG often presents about 3 months after central RVO, and PRLP does not prevent

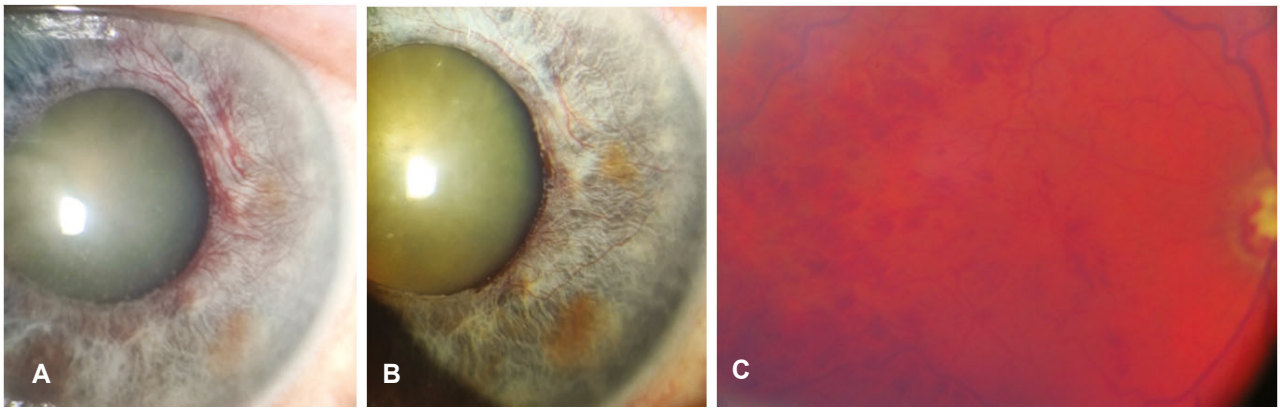

Fig. 1. Photograph of the anterior segment in the left eye in a 62-year-old female patient with neovascular glaucoma secondary to retinal vein occlusion. Note iris neovascularization and complicated cataract at the IOP of 40 mmHg before TSCPC (A); partial regression of neovascularization at the IOP of 24 mmHg at 12 months after 2 TSCPC sessions (B), and intraretinal hemorrhages, glaucomatous excavation and optic disc neovascularization at the pre-treatment fundus photograph (C).

the development of NVG in such patients [1]. It is also an agreement with the opinion of Qu and colleagues [23] who noted the importance of early PRLP for the prevention of NVG.

Other researchers [24, 25] concluded that anti-VEGF injections effectively stabilized iris neovascularization (INV) activity and controlled IOP in patients with INV alone and early-stage NVG without angle closure. In advanced NVG, these injections cannot control IOP but may be used adjunctively to improve subsequent surgical results. In the current study, at presentation, affected eyes in all patients exhibited INV and anterior chamber angle neovascularization. Additionally, 32% of patients had a history of surgery for NVG, whereas others either had somatic contraindications for or refused to have, surgery.

Ehlers and colleagues [26] demonstrated that anti-VEGF therapy combined with PRLP for NVG resulted in more rapid decrease in IOP than PRLP alone. In addition, the combination group had increased frequency and rapidity of regression of neovascularization. This is in agreement with the current study, where history of anti-VEGF therapy combined with PRLP had an impact on the success of TSCPC in 35% of eyes ($p = 0.049$).

Because the majority (85%) of the sample had a cardiovascular disease, we decided to assess the blood coagulation system and the intensity of pathological processes taking place in the course of fibrinolysis in these patients [27, 28]. Fibrin degradation product D-dimer is a marker of clot formation and fibrinolysis and was increased in 39% of patients. We also assessed LDL-C levels; elevated LDL-C is a primary risk factor for atherosclerosis and is associated with increased risk of cardiovascular disease [29]. In the current study, 51% of patients had moderate or high risk of cardiovascular disease and atherosclerosis. Hayreh and co-authors [30] also paid attention to associated systemic abnormalities in patients with RVO. Our univariate regression analysis demonstrated the impact of the presence of cardiovascular disease with high D-dimer and low LDL-C levels on the success of TSCPC. A course of TSCPC was found to be effective in 68% of patients (30 eyes) with reference values of D-dimer (< 0.55 mg FEU/l) and 57% of patients (38 eyes) with LDL-C < 3.0 mmol/l, which stresses the need for the correction of risk factors. Our multivariate regression analysis confirmed that TSCPC success in NVG secondary to RVO not only depended on the baseline IOP, number of local IOP-lowering medications, and presence of ophthalmic complications, but also was associated with a normal D-dimer value. That is, TSCPC success in NVG secondary to RVO depends on the presence of ophthalmic and systemic complications which should be treated.

Limitations of this study included small sample size, the inclusion of patients with a failure of various previous treatment options (due to the refractory nature of NVG and concomitant complications), and the absence of a control group receiving conventional diode TSCPC for NVG for comparison. The last limitation was associated with the risk of developing serious ophthalmic complications and the mechanism underlying the pathogenesis of NVG that requires personalized application of various treatment approaches. Together, these limitations may affect generalizability of the results. This risk for selection bias was mitigated in the study design by determining the inclusion and exclusion criteria.

Conclusion

The success rate of modified diode TSCPC in patients with painful NVG secondary to RVO at 12 months was 71%. Modified diode TSCPC in patients with painful NVG secondary to RVO appears to be safe in terms of the absence of serious complications (hypotony and phthisis bulbi).

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Abbreviations: *BCVA, best corrected visual acuity; CPC, cyclophotocoagulation; IOP, intraocular pressure; NVG, neovascular glaucoma; PRLP, panretinal laser photocoagulation; RVO, retinal vein occlusion; TSCPC, transscleral cyclophotocoagulation.*