DOI: 10.66069/ojspub.20542254

Study on the Timing of Combined Anti-VEGF Therapy and Focal Retinal Photocoagulation for Branch Retinal Vein Occlusion

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Abstract: ***Objective:*** *To explore the optimal timing for focal retinal photocoagulation following conventional intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection in patients with macular edema (ME) secondary to branch retinal vein occlusion (BRVO), so as to provide evidence for individualized clinical management.* ***Methods:*** *A retrospective analysis was performed on 65 patients (67 eyes) diagnosed with BRVO complicated with ME admitted to the Department of Ophthalmology, Inner Mongolia Forest General Hospital from January 2020 to December 2022. According to findings of fundus fluorescein angiography (FFA), enrolled subjects were divided into non-perfusion zone group (34 patients, 36 eyes with non-perfusion area ≥5 DD) and neovascularization group (31 patients, 31 eyes). All patients received intravitreal ranibizumab injection followed by focal retinal photocoagulation one week after anti-VEGF treatment. All subjects were followed up for 3 months. Changes in best-corrected visual acuity (BCVA), central retinal thickness (CRT), absorption of retinal hemorrhage and incidence of adverse events were compared between two groups.* ***Results:*** *BCVA was significantly improved and CRT was markedly reduced after treatment in both groups (P<0.05). At 1 month post-treatment, the non-perfusion zone group achieved superior improvements in BCVA (0.60±0.21) and CRT (234.75±54.75 μm) compared with the neovascularization group (P<0.05). The incidence of vitreous hemorrhage was significantly higher in the neovascularization group (16.1%) than that in the non-perfusion zone group (0%, P<0.05). No statistically significant intergroup difference was observed in the absorption rate of retinal hemorrhage (P>0.05).* ***Conclusion:*** *Combined anti-VEGF and focal retinal photocoagulation is safe and effective for BRVO treatment. Early photocoagulation applied at the stage of non-perfusion lesion ≥5 DD facilitates better early visual function recovery and reduces the risk of severe complications such as vitreous hemorrhage, which serves as the preferred timing for clinical intervention.*

Keywords: Branch retinal vein occlusion, Macular edema, Anti-VEGF, Focal retinal photocoagulation, Retinal non-perfusion area, Neovascularization.

1. Introduction

Branch retinal vein occlusion (BRVO) is one of the most prevalent retinal vascular disorders in clinical practice, with an incidence approximately three times higher than central retinal vein occlusion (CRVO). It predominantly affects middle-aged and elderly individuals over 50 years old, and major risk factors include hypertension, arteriosclerosis, diabetes mellitus, hyperlipidemia and hemodynamic disorders [1-3]. Driven by population aging and rising prevalence of chronic systemic diseases, the global prevalence of BRVO has exceeded ten million cases in recent years, posing a severe threat to visual function among aging population.

The core pathogenesis of BRVO originates from venous compression at arteriovenous crossing sites, venous stasis and thrombosis, which disrupt venous outflow and trigger retinal ischemia and hypoxia with elevated vascular permeability. Subsequent pathological manifestations include retinal hemorrhage, exudation, cotton-wool spots, macular edema (ME), capillary non-perfusion and retinal neovascularization, further progressing to vitreous hemorrhage and tractional retinal detachment in advanced cases. ME accounts for the leading cause of central vision loss in BRVO patients with an incidence ranging from 60% to 80%. Extensive retinal non-perfusion area (≥5 DD) acts as an independent high-risk factor for neovascularization with an occurrence rate of 30%–40%. Newly formed fragile neovessels are prone to rupture and bleeding, resulting in irreversible visual impairment induced by vitreous hemorrhage and tractional retinal detachment [4-6].

Intravitreal anti-VEGF injection has been established as the first-line therapy for BRVO-related ME, which rapidly suppresses vascular leakage and resolves macular edema to improve central vision. Nevertheless, this regimen fails to ameliorate underlying retinal ischemia and cannot fundamentally block neovascular formation, requiring repeated intravitreal injections and increasing medical cost and complication risks. Focal retinal photocoagulation effectively occludes ischemic lesions, alleviates ischemic stimulation and lowers the incidence of neovascularization and secondary hemorrhage, yet monotherapy with laser tends to aggravate pre-existing macular edema. Combined therapy has gained clinical consensus currently, while uniform criteria regarding the optimal timing of photocoagulation after anti-VEGF injection remain absent. Some clinicians recommend deferred laser after neovascular development, whereas others advocate early intervention at non-perfusion stage, lacking high-quality clinical evidence to support either viewpoint [7-8].

This retrospective controlled study compared therapeutic outcomes between photocoagulation administered at non-perfusion phase versus neovascularization phase, aiming to identify optimal laser timing and provide clinical evidence for individualized BRVO treatment.

2. Materials and Methods

2.1 General Clinical Data

A total of 65 patients (67 eyes) with BRVO complicated with ME hospitalized in Inner Mongolia Forest General Hospital between January 2020 and December 2022 were retrospectively enrolled. Based on FFA results, subjects were stratified into two groups: non-perfusion zone group (34 patients, 36 eyes with non-perfusion area ≥5 DD without neovascularization) and neovascularization group (31 patients, 31 eyes complicated with retinal neovascularization).

Baseline characteristics: Non-perfusion zone group included 14 males and 20 females with mean age of (62.56±11.65) years; neovascularization group consisted of 15 males and 16 females aged (61.74±10.61) years old. No statistically significant intergroup differences were found in age, gender, baseline BCVA, baseline CRT and intraocular pressure (IOP) (all P>0.05), indicating comparable baseline demographics.

2.2 Inclusion Criteria

1) Definite diagnosis of BRVO confirmed by fundus examination, FFA and spectral-domain optical coherence tomography (SD-OCT);

2) Clinically significant ME with baseline CRT>250 μm measured via SD-OCT;

3) FFA-verified retinal non-perfusion area ≥5 DD or retinal neovascularization;

4) Clear refractive media allowing complete fundus photography, FFA and SD-OCT examinations;

5) Signed informed consent from all patients and complete 3-month follow-up availability.

2.3 Exclusion Criteria

1) Prior history of intravitreal anti-VEGF/corticosteroid injection, retinal photocoagulation or vitreoretinal surgery;

2) Combined other fundus diseases including diabetic retinopathy, uveitis, primary glaucoma, epiretinal membrane and retinal detachment;

3) Severe opacification of refractive media (advanced cataract, massive pre-existing vitreous hemorrhage) precluding standard ophthalmic examinations;

4) Severe cardio-cerebrovascular disease, hepatic/renal dysfunction or mental disorders interfering with treatment and follow-up;

5) Incomplete clinical data or lost to follow-up during observation.

2.4 Therapeutic Regimens

2.4.1 Intravitreal Anti-VEGF Injection with Ranibizumab

Preoperative preparation: Levofloxacin eye drops were administered topically four times daily for 3 consecutive days preoperatively to prevent infectious complications.

Intraoperative manipulation: Topical ocular anesthesia combined with routine disinfection and eyelid speculum placement; intravitreal injection of 0.05 mL ranibizumab via 30-gauge needle at 3.5–4.0 mm posterior to corneal limbus; puncture site compressed with sterile cotton swab for 30 seconds post-injection.

Postoperative management: Continuous topical levofloxacin eye drops for 3–4 days with routine outpatient recheck at 1 week after injection.

2.4.2 Focal Retinal Photocoagulation

Focal laser photocoagulation was performed 7 days after anti-VEGF injection.

Preoperative preparation: Full mydriasis with tropicamide phenylephrine eye drops to achieve pupil diameter>7 mm under topical anesthesia.

Laser parameters: IRIDEX semiconductor laser system (USA); spot diameter: 200–500 μm, exposure duration: 0.3 seconds, one-spot interval between adjacent laser lesions.

Operational specifications: Sector-scattered photocoagulation targeting non-perfusion or neovascular lesions with grade II~III gray-white retinal coagulation spots; macular area strictly avoided to preserve central visual function.

2.5 Observation Indicators

All patients were followed up for 3 months with recorded parameters listed below:

- BCVA: decimal visual acuity assessed at baseline, 1 week, 1 month and 3 months after combined therapy;
- CRT: central macular thickness measured via SD-OCT;
- Retinal hemorrhage absorption: graded as complete absorption, most absorption, partial absorption and no absorption according to fundus photographs;
- Adverse events: incidence of vitreous hemorrhage, elevated IOP and retinal detachment documented throughout follow-up.

2.6 Statistical Analysis

Statistical analyses were conducted using SPSS 25.0 software. Measurement data were expressed as mean ± standard deviation (x±s); intra-group before-after comparisons adopted paired t-test and intergroup comparisons used analysis of variance. Enumeration data were presented as constituent ratio (%) and compared via Chi-square test. P<0.05 indicated statistically significant difference.

3. Results

Table 1: Baseline demographic and ocular parameters of two groups

Items	Non-perfusion zone group (36 eyes)	Neovascularization group (31 eyes)	P value
Age (years)	62.56±11.65	61.74±10.61	>0.05
Male/Female (cases)	14/20	15/16	>0.05
Baseline BCVA	0.19±0.11	0.18±0.13	>0.05
Baseline CRT (μm)	432.83±103.13	438.03±128.48	>0.05

3.1 Changes in BCVA

BCVA improved significantly at all post-treatment timepoints versus baseline in both groups (all P<0.05). Non-perfusion zone group: baseline (0.19±0.11), 1 week post-treatment (0.41±0.21), 1 month post-treatment (0.60±0.21), 3 months post-treatment (0.64±0.22); Neovascularization group: baseline (0.18±0.13), 1 week post-treatment (0.31±0.21), 1 month post-treatment (0.44±0.24), 3 months post-treatment (0.57±0.23).

Intergroup comparison revealed significantly higher BCVA in non-perfusion zone group at 1 month after treatment (P<0.05), whereas no statistical differences existed at 1 week and 3 months post-treatment (P>0.05).

Table 2: Serial changes of BCVA in two groups

Timepoint	Non-perfusion zone group	Neovascularization group	P value
Pretreatment	0.19±0.11	0.18±0.13	>0.05
1 week postoperatively	0.41±0.21	0.31±0.21	> 0.05
1 month postoperatively	0.60±0.21	0.44±0.24	<0.05
3 months postoperatively	0.64±0.22	0.57±0.23	>0.05

3.2 Changes in CRT

CRT was remarkably reduced at all follow-up timepoints compared with baseline for both cohorts (P<0.05). Non-perfusion zone group: baseline (432.83±103.13) μm, 1 week (277.33±77.84) μm, 1 month (234.75±54.75) μm, 3 months (221.78±42.58) μm; Neovascularization group: baseline (438.03±128.48) μm, 1 week (307.35±72.92) μm, 1 month (282.13±92.24) μm, 3 months (256.42±85.80) μm.

CRT was statistically lower in non-perfusion zone group at 1 and 3 months post-treatment (P<0.05), with comparable CRT between groups at postoperative week 1 (P>0.05).

Table 3: Serial changes of CRT (μm) in two groups

Timepoint	Non-perfusion zone group	Neovascularization group	P value
Pretreatment	432.83±103.13	438.03±128.48	>0.05
1 week postoperatively	277.33±77.84	307.35±72.92	>0.05
1 month postoperatively	234.75±54.75	282.13±92.24	<0.05
3 months postoperatively	221.78±42.58	256.42±85.80	<0.05

3.3 Retinal Hemorrhage Absorption Rate

Non-perfusion zone group: complete absorption in 27 eyes, major absorption in 7 eyes, partial absorption in 2 eyes; Neovascularization group: complete absorption in 26 eyes, major absorption in 4 eyes, partial absorption in 1 eye. No significant between-group difference in hemorrhage absorption (P>0.05).

3.4 Adverse Event Profiles

Non-perfusion zone group: 2 cases of transient elevated IOP without vitreous hemorrhage or retinal detachment; Neovascularization group: 5 cases of vitreous hemorrhage (16.1%), 4 cases of increased IOP and 1 case of retinal detachment. Vitreous hemorrhage rate was significantly higher in neovascularization group (P<0.05).

4. Discussion

4.1 Pathogenesis and Current Therapeutic Status of BRVO

A vicious pathological cascade is formed in BRVO: retinal ischemia secondary to venous occlusion upregulates VEGF overexpression, inducing ME; persistent capillary occlusion forms extensive non-perfusion area which further boosts VEGF secretion and accelerates pathological neovascularization. Immature neovessels lack intact basement membrane and are susceptible to spontaneous rupture leading to vitreous hemorrhage and tractional retinal detachment with permanent visual loss.

Anti-VEGF agents rapidly inhibit VEGF-mediated vascular leakage and resolve ME to improve visual acuity yet cannot reverse intrinsic retinal ischemia, leading to repeated reinjection requirement. Conversely, focal retinal photocoagulation eliminates ischemic retinal tissue to reduce endogenous VEGF production and inhibit neovascular progression. Combined therapy complements advantages of two modalities and interrupts the above-mentioned pathological cycle, having become mainstream treatment for BRVO-ME with ischemic lesions; however, optimal timing of laser intervention remains controversial worldwide [9].

4.2 Correlation Between Photocoagulation Timing and Visual Recovery

Our study demonstrated superior BCVA and CRT improvement at postoperative month 1 in patients receiving early laser at non-perfusion stage, indicating earlier intervention facilitates accelerated early visual rehabilitation. Possible explanations are as follows: non-perfusion phase is featured by pure ischemic change without neovascular formation and milder retinal structural damage; timely photocoagulation blocks the transition from chronic ischemia to pathological neovascularization, suppresses sustained VEGF release and reduces recurrent ME risk. By contrast, patients with established neovascularization suffer longer-standing ischemic injury and fragile newly formed vessels; laser irritation easily triggers intraocular bleeding with delayed ME regression and slower visual recovery.

No significant intergroup disparity in BCVA and CRT was observed at 3-month follow-up, implying delayed laser intervention could also achieve satisfactory long-term

therapeutic effect, whereas early photocoagulation accelerates recovery course, decreases ME recurrence and cuts long-term medical expenditure [10].

4.3 Safety Profile Related to Laser Timing

Higher vitreous hemorrhage incidence in neovascularization cohort confirmed early-stage laser significantly reduces severe ocular complications. Advanced ischemic status accompanied by elevated intraocular VEGF level and fragile neovasculature in neovascular phase raises bleeding risk upon laser stimulation; early photocoagulation at non-perfusion stage fundamentally prevents pathological neovascularization and subsequent severe complications including vitreous hemorrhage and retinal detachment. Comparable transient IOP elevation rate between two groups with normalized IOP after symptomatic treatment verified the overall safety of combined anti-VEGF plus photocoagulation regimen.

4.4 Clinical Significance and Study Limitations

This clinical research validates photocoagulation performed at non-perfusion stage (non-perfusion area ≥5 DD) as preferred intervention timing for combined BRVO therapy balancing efficacy and safety, providing practical reference for individualized clinical management. Limitations of this study include single-center retrospective design, limited sample size and relatively short follow-up period. Further multicenter prospective large-cohort trials with prolonged observation are required to validate present findings and explore long-term clinical outcomes and late complications.

5. Conclusion

Combined anti-VEGF intravitreal injection and focal retinal photocoagulation is safe and effective for BRVO complicated with ME. For BRVO patients presenting with ≥5 DD retinal non-perfusion area, focal photocoagulation administered one week after anti-VEGF injection optimizes early visual function restoration and minimizes the risk of severe complications such as vitreous hemorrhage, which deserves wide clinical promotion.

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