Clinical Observation of Micropulse Laser Combined with Conbercept in the Treatment of Neovascular Age-related Macular Degeneration with Pigment Epithelial Detachment (PED)

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DOI: 10.32629/jcmr.v5i3.2636

Abstract: The aim of this study is to observe the efficacy of micropulse laser combined with Conbercept in the treatment of neovascular age-related macular degeneration (nAMD) complicated with PED. Thirty patients (30 eyes) diagnosed with nAMD and PED at our hospital in 2023 were randomly divided into two groups: the Conbercept treatment (IVC) group with 15 cases (15 eyes) and the Conbercept combined with 577 nm threshold micropulse laser treatment (IVC+SMLP) group with 15 cases (15 eyes). Anti-VEGF treatment was administered according to the 3+PRN regimen, and the combined treatment group received 577 nm threshold micropulse laser treatment within 2 weeks after anti-VEGF injection. Follow-up observed the best-corrected visual acuity (BCVA), central macular thickness (CMT), PED height (PEDH), number of injections, and related complications at 1 month, 3 months, 6 months, and 12 months after Conbercept intravitreal injection. The average BCVA, CMT, and PEDH in both groups improved significantly from baseline at all time points ($P < 0.05$). At 12 months of follow-up, PEDH in the IVC+SMLP group decreased significantly from baseline (293.57±82.59 vs 184.84±33.95) and was significantly lower than in the IVC group ($P < 0.05$). The number of IVC injections in the IVC group was significantly higher than in the IVC+SMLP group (8.04±0.3 vs 5.29±1.26) with a significant difference ($t=4.290$, $P=0.016$). No treatment-related adverse events were observed during the study. The 577 nm threshold micropulse laser combined with Conbercept effectively improves or stabilizes visual function and anatomical morphology in nAMD with PED, reduces the number of intravitreal injections, and alleviates the patient's economic burden to some extent.
***Keywords*:** neovascular age-related macular degeneration; intravitreal Conbercept (IVC); threshold micropulse laser photocoagulation (SMLP); pigment epithelial detachment height (PEDH)

1. Introduction

Wet age-related macular degeneration (AMD) is characterized by the formation of choroidal neovascularization in the macular region, affecting central vision in the elderly, and this vision impairment is irreversible [1]. Neovascular AMD with pigment epithelial detachment (PED) causes more severe visual function damage. Clinical studies have confirmed that intravitreal injection of anti-vascular endothelial growth factor (VEGF) can improve or maintain vision in wet AMD patients [2,3]. Conbercept inhibits VEGF-A and PIGF, providing a multi-target anti-inflammatory effect. As a fusion protein drug, it can stabilize macular structure and improve vision in wet AMD patients. Anti-VEGF treatment is the standard therapy for wet AMD but has limitations, including a drug effect duration of 4-8 weeks, requiring repeated or multiple injections, high treatment costs, and significant economic and psychological burdens for patients. Threshold micropulse laser photocoagulation (SMLP) is a non-invasive laser treatment technique. Clinical research has confirmed its efficacy in treating various retinal diseases, such as dry AMD, retinal vein occlusion macular edema (RVO-ME), diabetic macular edema (DME), and central serous chorioretinopathy (CSC). SMLP is effective in treating PED without damage to the macular area and is currently a hot topic in retinal disease treatment [4-8]. This study explores the therapeutic effect of SMLP combined with Conbercept in treating neovascular AMD complicated with PED, which severely impacts vision.

2. Materials and Methods

2.1 General Information

A total of 30 patients (30 eyes) diagnosed with neovascular age-related macular degeneration (nAMD) complicated with pigment epithelial detachment (PED) at our outpatient department from January to December 2023 were selected for the study. Inclusion criteria were as follows: (1) Clear diagnosis of neovascularization confirmed by FFA and OCT,

meeting the diagnostic criteria for neovascular AMD as outlined in the "Clinical Diagnosis and Treatment Pathway for Age-Related Macular Degeneration in China" [9]; (2) Clinical diagnosis of nAMD with PED, with best-corrected visual acuity (BCVA) ≥ 0.05; able to complete 12 months of follow-up. Exclusion criteria were: (1) Previous intravitreal injection treatment in the affected eye, including anti-VEGF agents or corticosteroids; previous micropulse laser photocoagulation treatment in the macular area of the affected eye; (2) Severe cataracts, vitreous hemorrhage, or other factors affecting FFA and OCT examinations, or affecting the retina and treatment with SMLP; (3) Presence of vitreoretinal diseases such as high myopia, macular hole, or macular pucker; (4) Systemic diseases such as new-onset cerebral infarction or poorly controlled hypertension that could hinder cooperation with FFA, OCT, and IVC and SMLP treatments. Patients (eyes) meeting the inclusion and exclusion criteria were randomly divided into two groups using a random number table: the Conbercept treatment group (IVC) and the Conbercept combined with 577 nm threshold micropulse laser treatment group (IVC+SMLP). There were no statistically significant differences in the general data between the two groups (all $P > 0.05$), but there were statistically significant differences in the number of injections between the two groups ($P < 0.05$) (Table 1). This study is a prospective randomized controlled trial and adheres to the Declaration of Helsinki. It was reviewed and approved by the Ethics Committee of Heilongjiang Provincial Ophthalmic Hospital (Approval No. 2023-Ethics Review-06). Patients and their families were informed about the treatment for eye diseases and agreed to the treatment plan, and they signed the informed consent form for eye disease treatment.

Table 1. Comparison of general information between two groups

Group	Number of Eyes	Age	Gender	BCVA	CMT	PEDH	Injection Frequency
			(M/F)	($\bar{x}$±s, logMAR)	($\bar{x}$±s, μm)	($\bar{x}$±s, μm)	($\bar{x}$±s)
IVC	15	60.34±11.20	6/9	0.78±0.21	520.72±80.40	312.17±80.71	8.04±0.3
IVC+SMLP	15	56.08±9.10	7/8	0.72±0.18	498.45±91.2	293.57±82.59	5.29 ±1.26
Test Value		t=0.135	χ^2=3.108	t=1.621	t=0.521	t=1.956	t=4.290
p-value		0.612	0.162	0.301	0.631	0.438	0.016

Note: IVC: intravitreal injection of Conbercept; SMLP: Micro pulse laser photocoagulation under threshold; BCVA: Best corrected visual acuity; LogMAR: The logarithm of the minimum resolution angle; CMT: thickness of macular fovea; PEDH: Height of pigment epithelial layer protrusion

2.2 Methods

2.2.1 Ophthalmic Examination

Patients (eyes) in the study were evaluated for best-corrected visual acuity (BCVA), central macular thickness (CMT), and height of pigment epithelial detachment (PEDH). BCVA was measured using the international standard logarithmic visual acuity chart and converted to LogMAR for statistical analysis. Fluorescein angiography and/or indocyanine green angiography were performed using a Heidelberg Engineering machine to determine neovascularization in the macular region. CMT and PEDH were measured using the Topcon 3D-OCT2000 machine, with PEDH measured manually from OCT scans of the macular area.

2.2.2 Treatment Methods

In the IVC group, only intravitreal injections of Conbercept were administered, following the 3+PRN treatment regimen. In the IVC+SMLP group, Conbercept was injected intravitreally first, followed by SMLP treatment within 2 weeks, with a time interval of ≥3 months between the two SMLP treatments. All treatments during the study were administered by the same experienced physician at our hospital. The IVC procedure was strictly conducted according to the intravitreal injection guidelines, with a Conbercept dose of 0.5 mg/0.05 ml. For the macular SMLP treatment: micro-pulse laser therapy used the IQ577nm IRIDEX device for yellow micro-pulse laser. First, threshold energy was measured and set as P value, then the machine was switched to micro-pulse mode with the energy set to 4-6 times the threshold energy P value, laser duty cycle at 5%-10%, spot diameter at 200 μm, scanning grid in "7*7" mode, spot spacing at 0, exposure time of 200 ms, covering the macular lesion area and its surroundings (including the macular fovea). Clinical practice has confirmed that parameters for micro-pulse laser treatment at threshold energy can vary based on the location and extent of the macular lesion for different eye diseases.

Re-treatment Criteria:

(1) New bleeding lesions in the macular area detected by OCT.

(2) A decrease of 1 line in Best Corrected Visual Acuity (BCVA).

(3) OCT and Fluorescein Fundus Angiography (FFA) indicating active lesions in the macular area (subretinal or intraretinal hemorrhage or fluid).

Criteria to Pause Treatment: If BCVA does not show significant changes in three consecutive follow-ups, or if there is no significant change in macular lesions (CMT, PEDH).

2.2.3 Follow-up and Evaluation Indicators

The study included 30 patients (30 eyes), aged 50 to 77 years, with an average age of 59.24 ± 15.14 years and no significant gender difference. All patients were followed up regularly and completed 12 months of follow-up, with an average follow-up time of 10.11 ± 2.5 months. Anti-VEGF treatment followed the 3+PRN regimen, and the combined treatment group received SMLP within 2 weeks after anti-VEGF injection. Follow-up observations included BCVA, CMT, PEDH, number of injections, and treatment-related adverse events before anti-VEGF treatment and 1 month, 3 months, 6 months, and 12 months after the first intravitreal injection. Treatment-related adverse events included systemic adverse events (cardiovascular accidents) and ocular adverse events (subconjunctival hemorrhage, anterior chamber inflammatory reaction, elevated intraocular pressure, retinal hemorrhage, endophthalmitis) following intravitreal injection. Adverse events from micro-pulse laser treatment included macular laser spot scarring.

2.3 Statistical Methods

Data were processed using SPSS 23.0 statistical software. Measurement data for BCVA, CMT, PEDH, and number of injections from both groups were confirmed to follow a normal distribution and were described using mean ± standard deviation. Independent samples t-test was used to compare data between groups. Repeated measures two-way ANOVA was used to compare overall differences at different time points between groups, with multiple comparisons performed using LSD-t test. Counting data were expressed as frequency and percentage, with differences between groups compared using $\chi 2$ test. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1 Comparison of BCVA After Initial Intravitreal Injection of Conbercept

There was no significant overall difference in BCVA between the two groups ($F_{group} = 0.286$, $p = 0.659$). However, there were significant differences in BCVA at different time points after the first injection ($F_{time} = 11.601$, $p = 0.001$). BCVA improved at 1 month, 3 months, 6 months, and 12 months compared to baseline, with all differences being statistically significant ($p < 0.05$) (Table 2).

3.2 Comparison of CMT After Initial Intravitreal Injection of Conbercept

There were significant differences in CMT at different time points after the first injection between the two groups ($F_{group} = 8.104$, $p = 0.029$; $F_{time} = 48.621$, $p = 0.001$). Both groups showed a decrease in CMT compared to baseline, with significant differences ($p < 0.05$), particularly at 12 months. At 3 months post-injection, the CMT in the IVC+SMLP group was significantly lower than that in the IVC group, with a significant difference ($p < 0.05$) (Table 3).

3.3 Comparison of PEDH After Initial Intravitreal Injection of Conbercept

There was no significant overall difference in PEDH between the two groups ($F_{group} = 0.291$, $p = 0.694$). However, there were significant differences in PEDH at different time points after the first injection ($F_{time} = 16.952$, $p = 0.012$). PEDH decreased at different time points compared to baseline in both groups, with significant differences ($p < 0.05$), and the IVC+SMLP group showed a notable reduction in PEDH at 12 months, with 2 eyes having PED resolved (Table 4).

3.4 Number of Injections

During the study, the average number of injections in the IVC group was 8.04 ± 0.3. In the IVC+SMLP group, patients received 2.12 ± 0.35 micro-pulse laser treatments and 5.29 ± 1.26 injections. The total number of injections in the IVC+SMLP group was lower than that in the IVC group, with a significant difference ($t = 4.290$, $p = 0.016$). Throughout the follow-up period, no significant vision loss was observed in any patient, and no treatment-related adverse events were reported from Conbercept injections or laser treatments.

Table 2. Comparison of BCVA between two groups at various time points ($\bar{x}\pm s$)

	Pre-treatment	Post-treatment 1m	Post-treatment 3m	Post-treatment 6m	Post-treatment 12m	Pre-treatment
IVC	0.78±0.21		0.67±0.12	0.59±0.15	0.45±0.13	0.30±0.11
IVC+SMLP	0.72±0.18		0.61±0.15	0.45±0.12	0.39±0.11	0.27±0.14

Note: F_{group}=0.286, P=0.659; F_{time}=11.601, P=0.001; $F_{interaction}$=0.841, P=0.147. Compared with respective preoperative, P<0.05 (Two-way repeated measures ANOVA, LSD-t test) BCVA: Best corrected visual acuity

Table 3. Comparison of CMT between two groups at various time points ($\bar{x}$±s) μm

	Pre-treatment	Post-treatment 1m	Post-treatment 3m	Post-treatment 6m	Post-treatment 12m
IVC	520.72±80.40	410.86±80.59	390.42±60.38	300.24±61.95	278.81±30.08
IVC+SMLP	498.45±91.27	420.12±89.12	312.42±30.69	263.22±63.15	266.84±40.95

Note: F_{group}=8.104, P=0.029; F_{time}=48.621, P=0.001; $F_{interaction}$=1.107, P=0.154. Compared with respective preoperative, P<0.05 (Two-way repeated measures ANOVA, LSD-t test) CMT: Thickness of macular fovea

Table 4. Comparison of PEDH between two groups at various time points ($\bar{x}$±s)μm

	Pre-treatment	Post-treatment 1m	Post-treatment 3m	Post-treatment 6m	Post-treatment 12m
IVC	312.17±80.71	282.86±77.59	241.96±61.98	236.24±61.95	230.71±42.08
IVC+SMLP	293.57±82.59	270.75±89.14	231.45±78.91	221.33±35.83	184.84±33.95

Note: F_{group}=0.291, P=0.694; F_{time}=16.952, P=0.012; $F_{interaction}$=2.057, P=1.702. Compared with respective preoperative, P<0.05 (Two-way repeated measures ANOVA, LSD-t test) PEDH: Height of pigment epithelial layer protrusion

4. Discussion

Neovascular age-related macular degeneration (nAMD) is a complex, multifactorial disease associated with factors such as dyslipidemia, age, genetics, cardiovascular diseases, smoking, and unhealthy diet. Retinal pigment epithelium (RPE) degeneration is linked to the development and progression of AMD. These factors lead to oxidative stress, mitochondrial dysfunction, and reduced autophagy in RPE cells, causing damage to photoreceptors and retinal nerve fibers, including RPE degeneration, loss of photoreceptors, Bruch's membrane thickening, choroidal capillary degeneration, inflammation, and fibrosis. PED formation involves abnormal macular neovascularization breaking the blood-retinal barrier, leading to bleeding and exudation between the RPE and Bruch's membrane. Prolonged PED can cause irreversible damage to photoreceptor cells.[10]

Anti-VEGF therapy is the primary strategy for nAMD, aiming to eliminate macular bleeding, edema, and exudation, thus slowing or halting disease progression.[11] However, repeated treatments are often required due to the limited duration of intraocular drug action, increasing treatment costs and risk of intraocular infection, thereby adding to patient economic burden and psychological stress.[12] Hence, reducing injection frequency while maximizing vision benefits is increasingly emphasized. Subthreshold micropulse laser photocoagulation (SMLP) is a new approach that does not cause trauma to the tissue like traditional laser photocoagulation, promoting tissue repair. It acts directly on RPE cells, inducing heat shock protein expression, activating autoimmune activity, downregulating VEGF levels, and upregulating pigment epithelial-derived factor expression to improve or restore RPE function.[13,15] Several clinical studies have confirmed SMLP's effectiveness in various retinal diseases without causing visible damage to retinal tissue. Li Hong et al.[14] found that SMLP effectively reduced vitreous membrane warts and PED height, stabilizing vision and allowing for repeat treatments safely. Li Wenqing et al.[15] reported that combining anti-VEGF drugs with SMLP improved macular thickness and visual quality in diabetic macular edema (DME) while reducing the number of intraocular injections and alleviating patient economic burden and psychological stress.

Our study indicates that both IVC and IVC+SMLP groups showed improved BCVA and reduced CMT (PEDH) at 1, 3, 6, and 12 months post-treatment compared to baseline values, with no significant differences between the two groups. Both treatments improved visual acuity and macular structure, but IVC+SMLP showed a more significant reduction in PEDH, with PED disappearing in two cases. This suggests that while both methods are similarly effective for nAMD with PED, IVC combined with SMLP may be more effective in reducing PEDH. Patients in the IVC+SMLP group required fewer injections (5.29 ±1.26 vs 8.04±0.3) and fewer SMLP treatments (2.12±0.35), indicating that SMLP combined with IVC can effectively reduce injection frequency, lower the risk of intraocular inflammation, and alleviate economic burden. A study by Terashima et al.[16] found better visual outcomes and lower CME incidence with SMLP combination therapy compared to monotherapy. Our findings suggest that there is no significant difference in treatment results between the IVC+SMLP and IVC groups, which may be related to the number of patients and disease duration.

The study used SMLP treatment within 2 weeks of IVC treatment, with an interval of ≥3 months. In the IVC+SMLP group, anti-VEGF treatment was administered first, followed by SMLP after structural improvement. Literature indicates that the effectiveness of micropulse laser treatment is closely related to macular thickness; CMT ≥400μm may alter laser energy distribution in the retina and RPE, leading to uneven energy distribution and poor treatment response.[17,18]

PED involves the accumulation of blood and exudate between the RPE and Bruch's membrane, with prolonged PED

causing irreversible damage to photoreceptor cells. For nAMD with PED, IVC reduces intraocular VEGF and inflammatory factors[19], inhibiting abnormal neovascularization and stabilizing PED structure. Subthreshold micropulse laser directly acts on RPE cells, activating autoimmune activity, downregulating VEGF, upregulating pigment epithelial-derived factor, and improving RPE drainage function[13]. SMLP combined with anti-VEGF treatment can effectively reduce injection frequency, enhance visual acuity, lower PED height, stabilize macular structure, and alleviate economic and psychological burdens on patients.

This study has limitations: small sample size and short follow-up time. Larger sample sizes, longer follow-up, and more detailed statistical analysis are needed to further explore and confirm the long-term efficacy and safety of SMLP combined with anti-VEGF treatment for nAMD with PED, to provide better treatment outcomes and reduce economic burden for more patients.

Acknowledgments

This work was supported by the following funding project: Heilongjiang Provincial Research Project (CZKYF2023-1-C048).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Mingming Jiang: Contributed to study design, data collection and analysis, and manuscript writing and revision. Zhidan Ren and Jiaqi Xu: Case observation, data collection, and analysis. Guanghong Li: Manuscript review, revision, and finalization.

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