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ORIGINAL ARTICLE

A pilot prospective study of 577-nm yellow subthreshold micropulse laser treatment with two different power settings for acute central serous chorioretinopathy

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Abstract

To compare the efficacy of 50% threshold power with 25% threshold power of 577-nm subthreshold micropulse laser (SMPL) for acute central serous chorioretinopathy (CSC). Prospective, interventional, non-randomized, comparative case series. A total of 54 patients (54 eyes) with acute CSC were enrolled. Twenty-four eyes received 25% threshold power and 30 eyes received 50% threshold power of 577-nm SMPL. Best-corrected visual acuity (BCVA), central macular thickness (CMT), and complete absorption of subretinal fluid (SRF) were evaluated at 1 month and 3 months. The complete absorption rate of SRF in the 50% power group was significantly greater than that in the 25% power group at 1 month (70.0% vs 25.0%, $p < 0.001$) and at 3 months (83.3% vs 54.2%, $p < 0.001$). Mean BCVA improved from 0.34 ± 0.20 LogMAR to 0.02 ± 0.13 LogMAR in the 50% power group and from 0.27 ± 0.15 LogMAR to 0.14 ± 0.21 LogMAR in the 25% power group with a significant difference between the two groups after 3 months ($p = 0.027$). In the 50% power group, the CMT decreased from 491.6 ± 154.8 μm at baseline to 231.3 ± 92.3 μm at 1 month and 228.2 ± 88.1 μm at 3 months, and in the 25% power group, the CMT decreased from 444.9 ± 164.1 to 306.8 ± 102.6 μm at 1 month and 254.5 ± 101.7 μm at 3 months. There was statistical difference of CMT at 1 month ($p = 0.009$) but no significant difference at 3 months between the two groups ($p = 0.232$). SMPL with 50% threshold power may be more effective than 25% threshold power for acute CSC.

Keywords Subthreshold micropulse laser · Acute central serous chorioretinopathy · Titration power

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Introduction

Central serous chorioretinopathy (CSC) is a common macular disorder characterized by serous detachment of the neurosensory retina with or without pigment epithelium detachment in adults, especially in men. Patients with CSC often suffer from decreased vision, metamorphopsia, and central scotoma during the disease duration [1]. CSC can be divided into acute and chronic form (more than 6 months) based on the duration of the disease [2]. It is generally regarded that acute CSC is a self-limiting disease with spontaneous resolution within 3–4 months for most patients [3].

It has been reported that CSC was associated with stress, type "A" personality pattern, sleep disturbances, and others. However, pathogenesis of CSC is poorly understood [4]. There is no standard treatment for acute CSC [2]; observation is commonly recommended [5]. However, 30–50% of patients suffer from recurrence, and 5–10% develop chronic CSC that can lead to permanent visual impairment [6–8]. Early intervention to acute CSC might accelerate the resolution of subretinal fluid (SRF), shortening the disease duration and recovering visual acuity more quickly [9]. Treatments, such as laser photocoagulation and photodynamic therapy (PDT) for acute CSC, were previously reported [9–11]. Conventional thermal laser photocoagulation can cause retinal pigment epithelium (RPE) damage, paracentral scotomas, and choroidal neovascularization (CNV) [10, 12]. Hence, it is inappropriate to use conventional laser for subfoveal or juxtafoveal lesions. PDT with half power or half dose of verteporfin (Novartis, Basel) has been used as treatment of CSC. However, choroidal ischemia and RPE atrophy have been reported [13, 14]. Furthermore, verteporfin is not approved for CSC and expensive for many patients with CSC.

Subthreshold micropulse laser (SMPL) has been used in the treatment of retinal diseases [15–18]. In micropulse laser mode, instead of laser energy delivered in a continuous wave, laser is delivered in a series of energy burst of very short duration allowing heat dissipation between the bursts of laser power. Using the right titration of power, no visible retinal damage can be observed in fundal photography, angiogram, and OCT [15, 18]. Although the exact mechanism of action is unclear, micropulse laser beams were delivered to the leakage area of retinal pigmented epithelium (RPE) in multiple dense spot pattern to induce a biological response to activate and repair the RPE cells [18].

There are three kinds of primary pigments in the macula: xanthophylls (420–500 nm), melanin (400–1000 nm), and hemoglobin (450–550 nm). Five hundred seventy-seven–nanometer laser light has a higher absorption rate of oxyhemoglobin and melanin. Besides, it is beyond the absorption spectrum of xanthophyll, which can be used in proximity to the fovea [18, 19]. The 577-nm micropulse laser has shown efficacy in the treatment of chronic CSC with 50% threshold energy [19–21]. However, there have been no studies reported the efficacy of 577-nm SMPL in the treatment of acute CSC. Furthermore, diffuse RPE damage is commonly seen in chronic CSC, which may influence the laser absorption and need greater laser power compared with acute CSC. Thus we hypothesized that the laser energy needed for acute CSC might be less than that in chronic CSC. In this pilot study, we compared 50% threshold power with 25% threshold energy, in the short-term efficacy of 577-nm SMPL on the treatment of acute CSC.

Methods

Subjects

This was a prospective, interventional, nonrandomized, comparative clinical study about SMPL with 25% threshold power versus 50% threshold power for the treatment of acute CSC, which was performed at Zhongshan Ophthalmic Center (ZOC) between December 2015 and December 2016. A total of 54 eyes (54 patients) enrolled in the study; 24 eyes received SMPL with 25% threshold power and 30 eyes received SMPL with 50% threshold power. The study adhered to the tenets of the Declaration of Helsinki, and approval for the study protocol was obtained from ethics committees of ZOC.

Inclusion criteria were as follows: (1) patients aged between 18 and 55 years; (2) first onset with disease duration less than 6 months; (3) no history of any treatment for CSC in the past; (4) presence of active leakage in fluorescein angiography caused by CSC but not CNV or other diseases; (5) presence of SRF involving the macula on optical coherence tomography (OCT). Exclusion criteria were as follows: (1) previous treatment of PDT, focal photocoagulation and intravitreal injections of anti-vascular endothelial growth factor for any other retinal conditions; (2) use of steroid systemically; (3) other retinal diseases such as pathological myopia, CNV, and polypoidal choroidal vasculopathy; (4) pregnancy.

Examinations

All patients received comprehensive ophthalmic examination after enrollment. Best-corrected visual acuity (BCVA) was examined using a decimal visual acuity chart. Color fundus photography (Visucam Carl Zeiss Meditec, Jena, Germany, or TRC-50DX Topcon Optical Company, Tokyo, Japan), fundus fluorescein angiography (FFA), fundus autofluorescence (FAF), and spectral domain OCT (Spectralis HRA; Heidelberg Engineering; Heidelberg, Germany) were performed at baseline. Central macular thickness (CMT) was defined as the distance between the internal limiting membrane and the inner border of the RPE by the OCT. The RPE changes observed on the FAF were analyzed at 3-month

follow-up after treatment. They were categorized as no RPE damage, mild RPE damage, and obvious RPE damage. No RPE damage was defined as the absence of changes at the treatment area, mild RPE damage was defined as the focally rough RPE but no obvious laser spot, and obvious RPE damage was defined as the presence of clear laser spots. All patients were reviewed at 1 month and 3 months after the laser treatment. At follow-up visits, OCT, FAF, and BCVA were performed.

577-nm micropulse laser treatment

The 577-nm yellow laser system (Supra 577Y Laser System; Quantel Medical, Clermont-Ferrand, France) was used with the Mainster contact lens (Ocular Instruments, Bellevue, WA). The micropulse treatment parameters were standardized for all patients, with 100-μm spot size and 200-ms duration with 5% duty cycle (0.1 ms ON and 1.9 ms OFF). The power was individualized in every patient after energy titration before treatment in a normal area of retina away from the lesion. The power titration was started at 600 mW power with monospot micropulse model and a just visible minimal graying reaction on the retina served as the threshold burn. At this threshold, the laser power was reduced to 50% (Fig. 1) or 25% (Fig. 2) for the SMPL treatment. No visual endpoints were made in the retina during treatment. Titration power was ranged from 800 to 1200 mW; hence, the treatment power of the 50% groups was between 400 and 600 mW while the treatment power of the 25% groups was between 200 and 300 mW. The micropulse laser in a multiple dense spot pattern was delivered to the leakage area, and the number of spots was limited to 50 in one session.

Outcome measures

The primary outcome measure was the proportion of complete absorption of SRF on OCT images at 3 months. The secondary outcome measures were the mean change of BCVA and CMT and the changes of RPE at 3 months.

Statistical analyses

All statistical analyses were performed using SPSS version 22.0 for Windows software (SPSS, Chicago, IL). BCVA was converted to the logarithm of the minimal angle of resolution (LogMAR) before statistical analyses. Data were presented as "mean ± standard deviation." The complete absorption rate of SRF and the changes of RPE were analyzed by the Pearson χ^2 test or the Fisher exact test between the two groups. Continuous variables were compared using a two-tailed T test (parametric data distributions) or the Mann–Whitney U test (non-parametric data distributions). A p value of < 0.05 was considered statistically significant.

Results

Baseline demographic and clinical characteristics

There were 24 patients (21 males) included in the 25% power group and 30 patients (24 males) included in the 50% power groups as consecutive case series. The baseline demographic and clinical characteristics of patients in the two study groups are shown in Table 1. There are no significant differences between the two groups with respect to the sex, age, duration of symptoms, BCVA, and CRT (all $p > 0.05$).

Resolution of subretinal fluid

At 1 month, the complete resolution rate of SRF was significantly higher in the 50% power group compared with that of the 25% power group (70.0% vs 30.0%, $p = 0.001$, chi-square test). At 3 months, the number of eyes with complete absorption of SRF increased in both groups. The resolution rate of SRF was still significantly higher in the 50% power group than that in the 25% power group (83.3% vs 54.2%, $p = 0.001$, chi-square test).

The changes in visual acuity

The changes of BCVA before and after the treatment in the two groups were shown in Fig. 3. The mean value of BCVA was 0.27 ± 0.15 (range 0.0 to 1.0) LogMAR and 0.34 ± 0.20 (range − 0.1 to 1.0) LogMAR, respectively, in the 50% power group and 25% power group at baseline. At 1 month, visual acuity improved significantly in both groups, but in the 50% power group, BCVA was better than that in the 25% power group ($p = 0.008$, Mann–Whitney U test). At 3 months, visual acuity continued to improve in both groups, and the BCVA in the 50% power group was 0.02 ± 0.13 LogMAR, which was still significantly better than that in the 25% power group with 0.14 ± 0.21 LogMAR ($p = 0.027$, Mann–Whitney U test).

The changes in central macular thickness

Figure 4 shows the changes in CMT after the treatment. In the 50% power group, the mean CMT decreased from 491.6 ± 154.8 μm at baseline to 231.3 ± 92.3 μm at 1 month, and in the 25% power group, the mean CMT decreased from 444.9 ± 164.1 μm at baseline to 306.8 ± 102.6 μm at 1 month. There was statistical difference of CMT between the two groups at 1 month ($p = 0.009$, Mann–Whitney U test). At 3 months, in 50% power group, CMT was 228.2 ± 88.1 μm which was nearly the same as that at 1 month, while the CMT continued to decrease to 254.5 ± 101.7 μm in the 25% power group. Thus, at 3 months, the difference of CMT between the two groups was not significant ($p = 0.232$, Mann–Whitney U test).

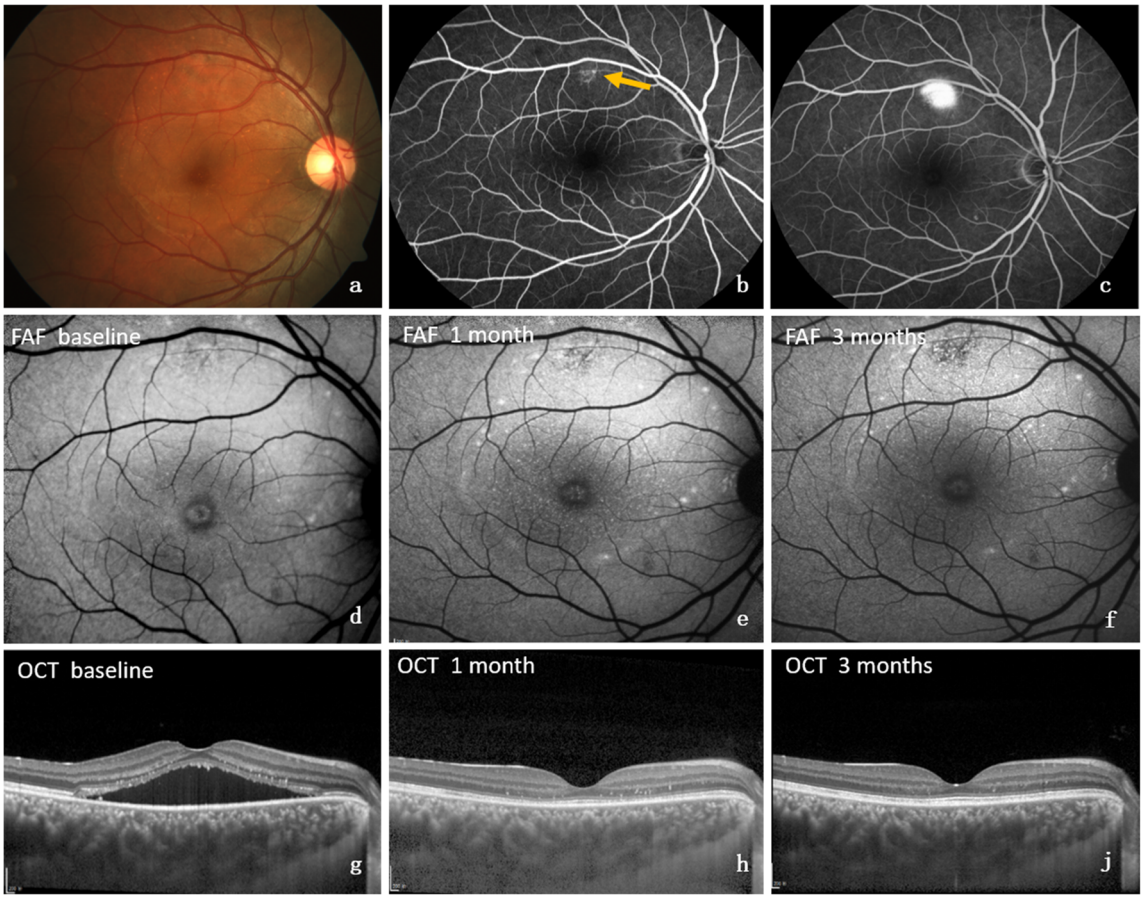

Fig. 1 The patient with CSC received 577-nm SMPL with 50% titration power. Retinal neuroepithelium detachment of the macula in fundus photography (**a**). FFA revealed dye leakage located just above the macula in the early phase in **b** (yellow arrows) and subsequent pooling involving the macula in **c**. After treatment, mild RPE damage was seen in the image of FAF at 1 month (**e**) and 3 months (**f**), compared with that before treatment (**d**). OCT showed subretinal fluid was absorbed completely at 1 month (**h**) and 3 months (**j**), compared with that at baseline (**g**). **b** represented the location of treatment with SMPL

Safety

In the 25% threshold power group, no RPE damage was observed in 87.5% (21/24) patients, mild RPE damage was observed in 12.5% (3/24), and obvious RPE damage was not observed. The corresponding data in the 50% group were 70% (21/30), 26.7% (8/30), and 3.3% (1/30), respectively. There was no significant difference in the RPE changes between the two groups ($p = 0.267$, chi-square test).

Discussion

Although acute CSC is commonly considered a self-limiting disease, some patients with CSC could go on to the chronic stage accompanied with persistent neurosensory retinal detachment, which would lead to permanent visual acuity loss. In addition, as most patients are of working age, they often need fast resolution of visual function. If there was a safe, effective, and economical intervention for CSC, it would be valuable. This pilot study applied the subthreshold 577-nm micropulse laser, which has been used in treating chronic CSC and DME [16, 19–21], for treating acute CSC. It found 25% and 50% power of SMPL could effectively achieve significant absorption of SRF and improve BCVA. Both power settings were safe, and the 50% threshold power setting was more effective compared with the 25% threshold power setting in terms of visual acuity improvement and absorption of subretinal fluid.

Laser power is a critical parameter in the treatment. In most previous clinical studies using SMPL for chronic CSC and DME, 50% threshold power was the most commonly used. Using the 50% threshold power for the treatment of chronic CSC, several clinical studies showed good results without apparent retinal damage. Kim analyzed the short-term efficacy of subthreshold micropulse yellow laser with the 50% threshold power for chronic CSC in a retrospective study, and the results showed BCVA in LogMAR was improved from 0.21 ± 0.21 at baseline to 0.06 ± 0.09 at 3 months [21]. In a prospective randomized controlled pilot trial study, patients with

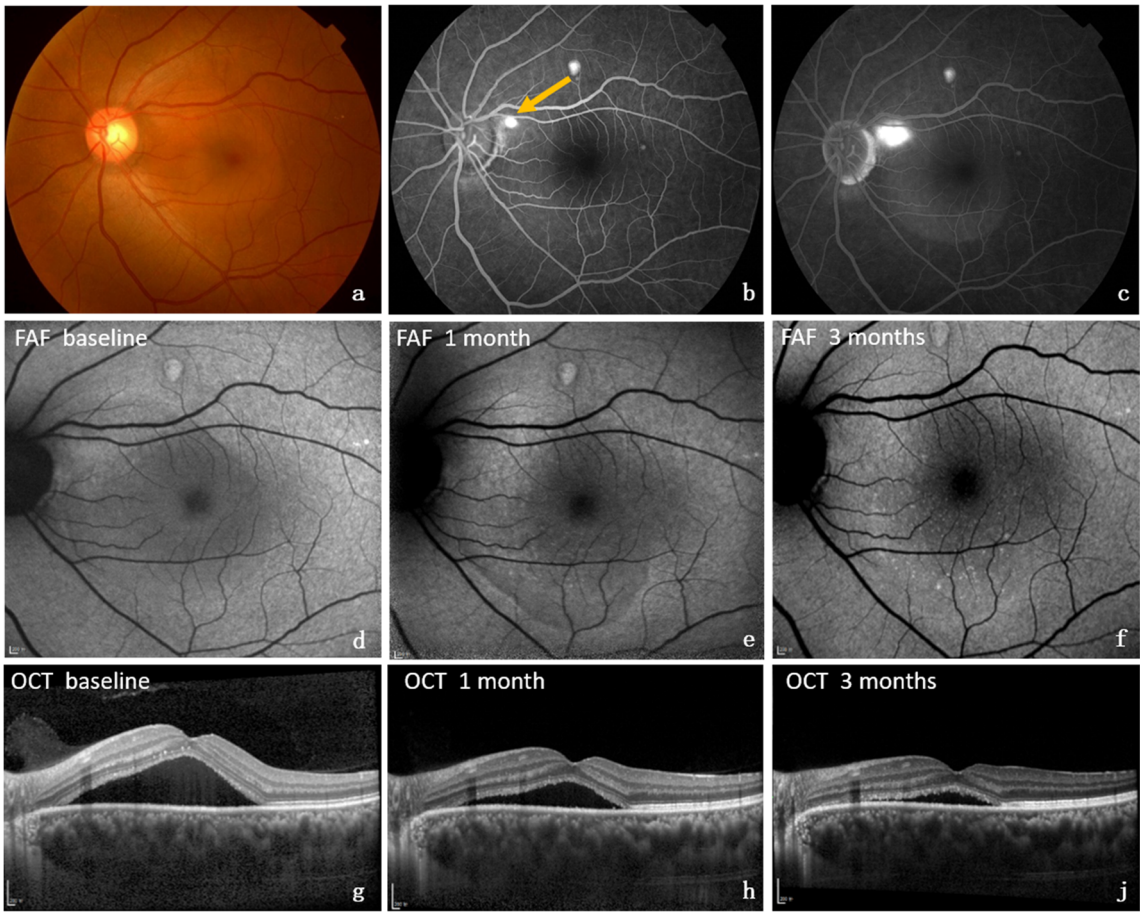

Fig. 2 The patient with CSC received 577-nm SMPL with 25% titration power. Retinal neuroepithelium detachment in fundus photography (**a**). FFA revealed dye leakage next to optic disk in the early phase and subsequent pooling involving the macula in **b** and **c**. After treatment, no RPE damage was seen in the image of FAF at 1 month (**e**) and 3 months (**f**), compared with that before treatment (**d**). OCT showed gradually decreased subretinal fluid (**h**) but remained little fluid at 3 months (**j**) compared with that at baseline (**g**). The yellow arrows (**b**) represented the location of treatment with SMPL

chronic CSC were randomized to subthreshold diode micropulse laser group and sham group. At 3 months after treatment, BCVA was significantly better in the treated group compared with that in the sham group [22]. Our study showed that 70% and 83.3% of patients reached complete absorption of SRF at 1 month and 3 months, respectively, in the 50%

Table 1 Baseline clinical data of 25% SMPL group and 50% SMPL group

	25% SMPL group ($n = 24$)	50% SMPL group ($n = 30$)	p value
Gender, male (%)	21/24 (87.5%)	24/30 (80.0%)	0.72*
Age (years) Range	42.4 ± 4.3 27~50	39.9 ± 6.4 28~53	0.12†
Duration of symptoms (months) Range	1.9 ± 1.0 1~5	2.3 ± 1.6 1~6	0.37†
CMT (μm) Range	444.9 ± 164.1 160~854	491.6 ± 154.8 194~846	0.29‡
BCVA (LogMAR) Range	0.34 ± 0.20 − 0.1~1.0	0.27 ± 0.15 0.0~1.0	0.12‡

CMT central macular thickness, *OCT* optical coherence tomography, *BCVA* best-corrected visual acuity, *LogMAR* logarithm of the minimum angle of resolution

*Determined by the use of Fisher's exact test

† Determined by the use of the Mann–Whitney *U* test

‡ Determined by the use of independent-samples *T* test

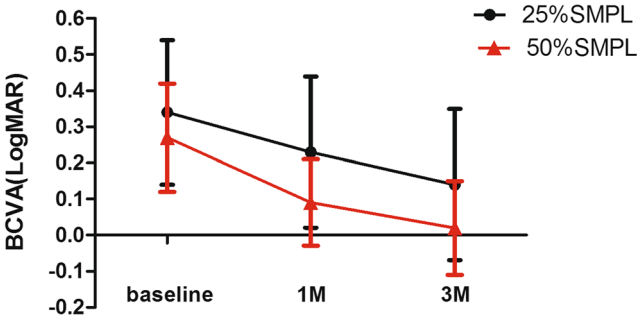

Fig. 3 The improvements in best-corrected visual acuity (BCVA) from baseline in the two groups at each follow-up

power group. The BCVA was also significantly improved compared with that at baseline. To minimize the damage to the retina while retaining the effect, we need to consider a lower threshold power. But to our knowledge, there was no study reported the use of less than 50% of threshold power in micropulse laser for the treatment of CSC. In the 25% power group in our study, 30% and 54.2% of patients with complete absorption of SRF were observed at 1 and 3 months, respectively. Because of the lack of an observational group, we cannot be sure whether 25% of the threshold power in micropulse laser could promote the SRF absorption. But a small sample clinical study about acute central serous chorioretinopathy showed that in the observation group, complete resolution of SRF was achieved in 8.3% (1/12) of the eyes at the 2-month follow-up [23]. Our study revealed that the complete resolution rate of SRF in the 25% power group was higher than that report. Thus, we believe that the treatment of 25% power may be advantageous in the recovery of acute CSC.

Subthreshold micropulse laser could be considered a safe and effective method because it reduced damage to the retina [17, 24, 25]. A recently retrospective study demonstrated that the 577-nm SMPL can achieve an equivalent effect as conventional laser but without RPE damage [26]. In our study, there was no apparent RPE damage observed in the 25% group and only 1 case with obvious RPE damage was seen on the FAF imaging in the 50% group. Thus, we think that it is necessary to be careful with the use of SMLP when the leakage is close to the fovea. As the amount of pigmentation may

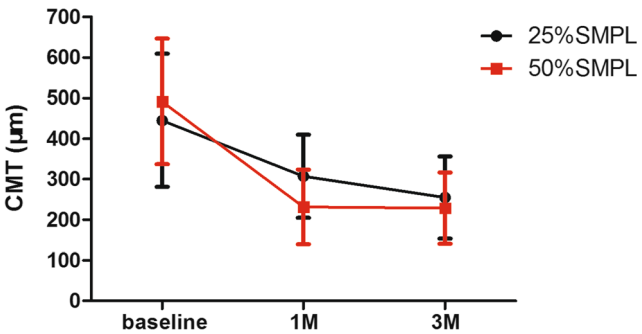

Fig. 4 The changes in mean central macular thickness (CMT) from baseline in the two groups at each follow-up

be variable at different retinal points, titration power may be different at different areas of the retina. So in order to decrease the injury of RPE during micropulse treatment, we can make power titration at more than one site, then calculate the mean value of power titration in different sites as the final threshold power.

There are several limitations to the study. One is the design of the trial, which is not randomized and the sample size is relatively small. Another limitation is the short term of follow-up, which might preclude the observation of recurrence. There was no observation group, so it is unclear whether the 25% power group is just reflecting the natural history of the disease. So a prospective, randomized clinical trial with longer observation may provide further information on the SMPL treatment for acute CSC.

In summary, the 50% threshold power of 577-nm yellow micropulse laser can accelerate the resolution of SRF and improve visual acuity in patients with acute CSC without causing apparent retinal damage at 1 month and 3 months even if the 25% threshold power was considered to have no treatment effect and just be reflecting natural history. This study demonstrates that the 577-nm yellow SMPL at 50% threshold power is a low-cost and safe option for treating acute CSC.

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Compliance with ethical standards

Conflict of interest All authors have no financial or other conflicts of interest concerning this study. VC is a consultant of Quantel Medical and an employee of Boehringer Ingelheim.

Informed consent Written informed consents were obtained from the patients before treatment.

Ethical approval This study was approved by the Ethics Committee of Zhongshan Ophthalmic Center of Sun Yat-Sen University and was conducted in adherence with the tenets of the Declaration of Helsinki.

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