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# Subthreshold micropulse laser photocoagulation versus half-dose photodynamic therapy for acute central serous chorioretinopathy

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## Abstract

**Purpose:** To compare the efficacy and safety of subthreshold micropulse (STMP) laser photocoagulation and half-dose photodynamic therapy (PDT) in the treatment of acute central serous chorioretinopathy (CSC).

**Methods:** A total of 39 acute CSC patients were included. 18 patients were treated with STMP laser and 21 patients were treated with half-dose PDT. The main outcome measures were best-corrected visual acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) chart, the proportion of eyes with complete resolution of subretinal fluid, the number of treatments, and the retinal sensitivity by microperimetry during the 12-month study period.

**Results:** The mean number of treatments during the 12-month period was 1.6 in STMP group and 1.3 in half-dose PDT group, respectively ( $P=0.174$ ). The proportion of eyes with complete resolution of subretinal fluid was 83.3% in STMP group compared with 90.5% in half-dose PDT group at 12-month ( $P=0.647$ ). The mean BCVA at 12-month after treatment was  $75.28 \pm 12.58$  for STMP group and  $76.62 \pm 11.57$  for half-dose PDT group, respectively ( $P=0.731$ ). No statistically significant difference was found in the mean retinal sensitivity between the two groups during the 12 months follow-up ( $P=0.701$  at 3 months;  $P=0.725$  at 6 months;  $P=0.695$  at 12 months).

**Conclusions:** Subthreshold micropulse Laser Photocoagulation is as effective as half-dose PDT for acute CSC, while minimizing the damage effect on retinal.

**Keywords:** Central serous chorioretinopathy, Subthreshold micropulse, Laser photocoagulation, Photodynamic therapy

## Introduction

Central serous chorioretinopathy (CSC) is a common ocular disease characterized by a serous neurosensory retinal detachment in the posterior pole, often accompanied with retinal pigment epithelial (RPE) detachment [1]. Currently, the pathogenesis of CSC is still unclear [2]. Benefit from the widespread use of indocyanine

green angiography (ICGA) in ocular fundus disease, we can further understand the pathogenesis of CSC. Base on ICGA findings, several studies demonstrate the evidences of choroidal circulation abnormalities in addition to RPE in CSC, leading to multifocal areas of choroidal vascular hyperpermeability [3–8]. Patients with CSC usually experience some visual symptoms such as visual acuity decreased, metamorphopsia, micropsia, dyschromatopsia and relative central scotoma [8]. Most cases of acute CSC are self-limiting with spontaneous resolution of subretinal fluid within 3–4 months [9]. However, up to

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30–50% of patients, symptoms of serous retinal detachment may remain or recur within the first year [10]. Furthermore, a few of patients may suffer visual loss because the development of RPE atrophy or choroidal neovascularizations (CNV) [11].

The most usually performed treatments for CSC are photodynamic therapy (PDT) with verteporfin and sub-threshold micropulse laser (STMP) treatment. Nevertheless, PDT may increase the risk of RPE atrophy, choroidal ischemia, and secondary CNV [12–14]. These adverse effects may restrict the use of PDT for acute CSC. In the past few years, several studies had reported that half-dose photodynamic therapy (PDT) with verteporfin were effective for the treatment of acute CSC by reducing sub-retinal fluid and increasing visual acuity in most patients, while minimizing side effects [9, 15], however, it was expensive and unavailable in some regions.

Subthreshold micropulse (STMP) is a laser emission technique which is made up of trains of repetitive ultrashort laser pulses. It creates sublethal cellular thermal effect at the RPE without heat conduction to surrounding retinal tissue [16], and therefore it diminishes the risk of iatrogenic thermal damage. STMP laser therapy for acute CSC has been previously described [17, 18]. These studies have reported that STMP laser is effective for acute CSC, while few side effects occurred. Compared with PDT, the costs of STMP laser therapy are much lower for patients. However, until now there are few studies focused on comparing the results of STMP laser treatment and PDT treatment for acute CSC.

This study attempted to evaluate the effect of STMP laser and half-dose photodynamic therapy (PDT) for acute CSC, and to analyze whether there are differences in efficacy between STMP laser and PDT in the treatment of acute CSC.

## Materials and methods

This study was a retrospective, nonrandomized, controlled clinical study on 39 patients with acute CSC. It was conducted at the Department of Ophthalmology, General Hospital of Central Theater Command of PLA. This study was approved by the Institutional Review Boards of General Hospital of Central Theater Command of PLA. The research adhered to the tenets of Declaration of Helsinki. Informed consents were obtained from all subjects, when informed about the risk of complications. Patients were divided into two groups according to the treatment.

All patients with acute CSC were enrolled from June 2017 to April 2019. Inclusion criteria included: (1) patient age  $\geq 18$  years; (2) the symptoms of CSC for 3 months or less; (3) presence of subretinal fluid involving the fovea, with or without RPE detachment

on optical coherence tomography (OCT); (4) presence of active angiographic leakage in fundus fluorescein angiography (FFA) caused by CSC. The following were exclusion criteria: (1) any evidence of choroidal neovascularization on FFA and ICGA; (2) any other associated ocular and macular disease influencing visual acuity; (3) history of any intraocular surgery; (4) received previous treatments including PDT, focal thermal laser photocoagulation, intravitreal injection of steroid or anti-VEGF agent.

The baseline ophthalmologic examination was performed in each patient, including best-corrected visual acuity (BCVA) by the standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart, slit-lamp examination, indirect funduscopy, color fundus photography (TRC-NW7SF; Topcon, Japan), OCT (3D OCT-2000; Topcon, Japan), microperimetry (MP-1; Nidek Italy), FFA and ICGA (Heidelberg Engineering, Heidelberg, Germany). Diagnosis of acute CSC was based on findings on indirect ophthalmoscopy, FFA, ICGA, and OCT. Central foveal thickness (CFT) was defined as the distance between the inner neurosensory retinal surface and the inner border of the RPE at the central foveal. Retinal sensitivity was performed using microperimetry within 12 degrees of the retinal central in a dark room. The mean retinal sensitivity was evaluated.

PDT was performed using the half-dose of verteporfin (Visudyne; Novartis, Basel, Switzerland), which is 3 mg/m<sup>2</sup> verteporfin. Verteporfin was infused over 10 min, followed by laser delivery at 15 min from the start of infusion. The laser light at 689 nm was delivered to the area of choroidal hyperperfusion as observed in ICGA for 83 s with an energy of 50 J/cm<sup>2</sup>. The laser spot size was set at a smallest size of covering the whole area of choroidal hyperperfusion. After treatment, the patients were instructed to avoid strong light for 3 days.

STMP photocoagulation treatment was performed with an 810-nm diode laser (OcuLight SLx; Iridex Corp, USA), and laser light was delivered via a slit-lamp adapter though an Area Centralis Laser contact lens (Volk Optical Inc, Mentor, USA). The laser power was determined in each patient by creating a threshold burn with the lowest energy required to make a visible “test burn” at the nasal mid periphery of retina. Then the laser was applied at a lower energy level and changed to the micropulse mode. The laser apparatus were: 125μm spot, 0.2-s exposure duration, 15% duty cycle. About 100 pulse envelope were applied at each leakage site identified by FFA [16].

Repeated treatment was performed at least 3 months later from baseline if the subretinal fluid of CSC was not or incompletely resolved 3 months after treatments. During follow-up, patients were not allowed to change groups.

Follow-up examinations with BCVA, slit-lamp, indirect funduscopy, OCT were performed at baseline and each monthly visit. FFA, ICGA, and microperimetry were performed at baseline and control visit at month 3, 6, 9, and 12.

The primary outcome measure of the study was the proportion of eyes with complete absorption of the macular subretinal fluid (SRF) at 12 months. Secondary outcome measures were the numbers of treatments and the serial changes in BCVA, CFT, and retinal sensitivity.

Statistical analysis was performed using SPSS 13.0. Comparisons of mean BCVA, CFT and central retinal sensitivity before and after treatment within each group were conducted using the repeated measure ANOVA. All the numerical variables were tested for normality. The student *t*-test or Mann–Whitney *U* test was used for comparison of the numerical variables between the two groups. The Mann–Whitney *U* test was used for comparison of the ordinal variables between the two groups. The Fisher exact test was used to compare the categorical variables. A *P* value of < 0.05 was considered to be statistically significant.

## Results

The average age was  $43.4 \pm 9.8$  years. 27 patients were male (69.2%), and 12 patients were female (30.8%). The mean follow-up period was  $16.4 \pm 3.8$  months. 18 eyes were included in the STMP group, 21 eyes were included in the half-dose PDT group. No patients were lost to follow-up in the study. Baseline characteristics of the two groups are detailed in Table 1.

In the STMP group, the resorption of the macular SRF was complete in 11 eyes (61.1%) at 1 month, 15 eyes (83.3%) at 3 months, 12 eyes (66.7%) at 6 months, 16 eyes (88.89%) at 9 months, and 15 eyes (83.3%) at 12 months. During the 12-month follow-up period, the macular SRF had recurred in three patients, and persisted in two patients. The mean times of STMP laser were 1.6 times. In the half-dose PDT group, complete absorption of the macular SRF was achieved in 17 eyes (81.0%) at 1 month, 20 eyes (95.2%) at 3 months, 19 eyes (90.5%) at 6 months, 18 eyes (85.71%) at 9 months, and 19 eyes (90.5%) at 12 months. The macular SRF had recurred in two patients, and persisted in one patient during the 12-month period. The mean times of half-dose PDT were 1.3 times. The proportion of eyes with complete absorption of the macular SRF and the number of treatments

**Table 1** Baseline characteristics and demographics of patients with acute CSC

	STMP Group	Half-dose PDT Group	<i>P</i> value
Variables	( <i>n</i> = 18)	( <i>n</i> = 21)	
Age, mean $\pm$ SD, (years)	37.22 $\pm$ 7.83	38.76 $\pm$ 8.08	0.582
Gender, (n)			
Male	13	14	
Female	5	7	0.742
Duration of symptoms, mean $\pm$ SD, (days)	25.06 $\pm$ 16.09	21.33 $\pm$ 15.63	0.359
Baseline BCVA, mean $\pm$ SD, (ETDRS)	63.67 $\pm$ 9.79	62.81 $\pm$ 8.52	0.772
Baseline CFT, mean $\pm$ SD, ( $\mu$ m)	427.28 $\pm$ 52.23	423.38 $\pm$ 47.39	0.808
Baseline retinal sensitivity, mean $\pm$ SD, (dB)	12.29 $\pm$ 1.88	12.61 $\pm$ 1.95	0.601
Presence of macular PED, (n)	3(16.7%)	5(23.8%)	0.702
Location of leakage site, (n)			
Subfoveal	2	4	
Juxtafoveal	14	15	
Extrafoveal	2	2	0.789
Number of leakage point, (n)			
1	15	16	
2	3	4	
3	0	1	0.622

CSC central serous chorioretinopathy, STMP subthreshold micropulse, PDT photodynamic therapy, SD standard deviation, BCVA best-corrected visual acuity, ETDRS Early Treatment Diabetic Retinopathy Study, CFT central foveal thickness, PED pigment epithelial detachment

between the two groups were no significant difference ( $P=0.647$ , Fisher exact test;  $P=0.174$ , Mann–Whitney U test, respectively).

In the STMP groups, the mean ETDRS BCVA was  $63.67 \pm 9.79$  at baseline, and improved to  $71.78 \pm 12.23$  at 1 month,  $74.22 \pm 11.66$  at 3 months,  $73.00 \pm 13.73$  at 6 months,  $74.89 \pm 12.42$  at 9 months,  $75.28 \pm 12.58$  at 12 months, respectively. The improvement of mean BCVA was significant over the 12-month period ( $F=2.311$   $P=0.049$ , ANOVA). Multiple comparison analysis indicated that the mean BCVA improved significantly during follow-up compared with the baseline values ( $P=0.047$  at 1 month;  $P=0.01$  at 3 months;  $P=0.023$  at 6 months;  $P=0.007$  at 9 months;  $P=0.005$  at 12 months, ANOVA). At 12 months, the ETDRS BCVA was improved by  $\geq 5$  letters in 15 eyes, improved by  $\geq 15$  letters in 6 eyes, remained unchanged (increased or decreased less than 5 letters) in 3 eyes, none of eyes worsened  $\geq 5$  letters (Table 2). In the half-dose PDT group, the BCVA improved significantly over the 12-month period ( $F=5.696$   $P<0.001$ , ANOVA). The mean BCVA was  $62.81 \pm 8.52$  at baseline,  $73.62 \pm 10.10$  at 1 month,  $76.43 \pm 10.46$  at 3 months,  $77.10 \pm 10.79$  at 6 months,  $74.86 \pm 10.83$  at 9 months,  $76.62 \pm 11.57$  at 12 months. The mean BCVA improved significantly during follow-up compared with the baseline values ( $P=0.001$  at 1 month;  $P<0.001$  at 3 months;  $P<0.001$  at 6 months;  $P<0.001$  at 9 months;  $P<0.001$  at 12 months, ANOVA).

**Table 2** Proportion of complete absorption of macular SRF, change in BCVA, and number of treatment over the 12-month period both the STMP group and the half-dose PDT group

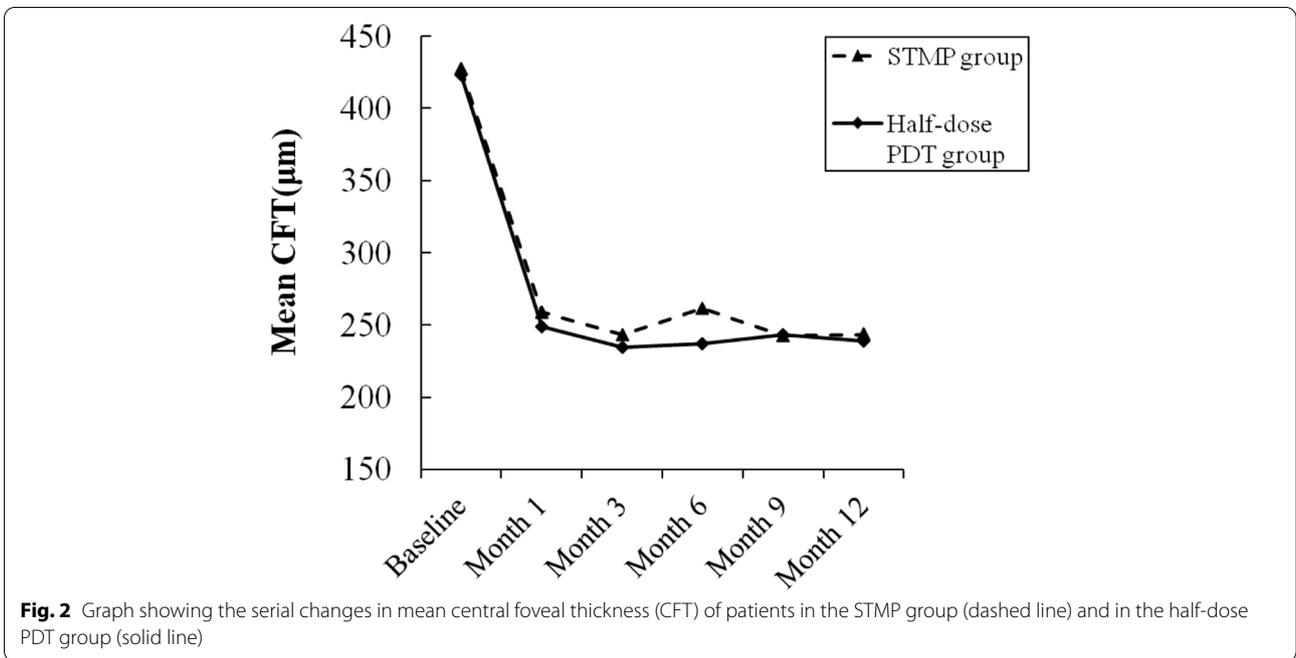
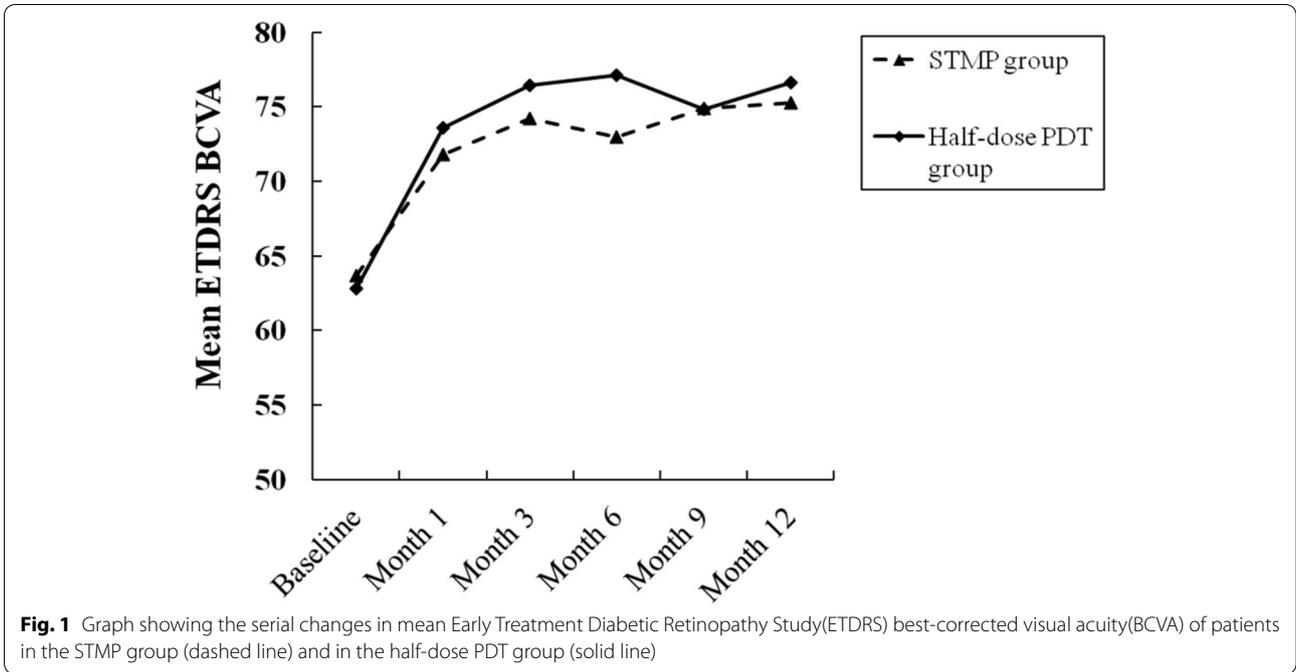
STMP Group	Half-dose PDT Group	P value	
Variables	(n = 18)	(n = 21)	
Complete absorption of macular SRF at month 12, (n)	15(83.3%)	19(90.5%)	0.647
Change in BCVA at month 12, (n), (ETDRS)			
Gained $\geq 15$ letters	6 (33.3%)	8(38.1%)	0.757
Gained $\geq 5$ letters	15(83.3%)	19(90.5%)	
No change	3(16.7%)	2(9.5%)	0.506
Lost $\geq 5$ letters	0	0	
Number of treatment over the 12-month period, (n)			
1	11	17	
2	5	3	
3	0	0	
4	2	1	0.174

SRF subretinal fluid, BCVA best-corrected visual acuity, STMP subthreshold micropulse, PDT photodynamic therapy, ETDRS Early Treatment Diabetic Retinopathy Study

At 12 months, the BCVA increased at least 5 letters in 19 eyes, improved by  $\geq 15$  letters in 8 eyes, unchanged in 2 eyes, and none of eyes decreased  $\geq 5$  letters (Table 2). There was no significant statistical difference in the mean BCVA between the two groups during follow-up ( $P=0.610$  at 1 month;  $P=0.537$  at 3 months;  $P=0.304$  at 6 months;  $P=0.993$  at 9 months,  $P=0.731$  at 12 months,  $t$ -test). The changes in BCVA over the 12-month study period are shown in Fig. 1.

The mean CFT in the STMP group was  $427.28 \pm 52.23$   $\mu\text{m}$  at baseline, and decreased to  $259.06 \pm 50.46$   $\mu\text{m}$  at 1 month,  $243.17 \pm 30.95$   $\mu\text{m}$  at 3 months,  $261.56 \pm 49.13$   $\mu\text{m}$  at 6 months,  $242.72 \pm 33.27$   $\mu\text{m}$  at 9 months,  $243.67 \pm 39.46$   $\mu\text{m}$  at 12 months (Fig. 2). The mean CFT was decreased significantly over the 12-month period ( $F=50.680$   $P<0.001$ , ANOVA). The CFT decreased significantly during follow-up compared with the baseline values ( $P<0.001$ , ANOVA). In the half-dose group, the mean CFT was  $423.38 \pm 47.39$   $\mu\text{m}$  at baseline,  $249.10 \pm 52.36$   $\mu\text{m}$  at 1 month,  $234.86 \pm 31.31$   $\mu\text{m}$  at 3 months,  $237.05 \pm 41.10$   $\mu\text{m}$  at 6 months,  $243.62 \pm 43.89$   $\mu\text{m}$  at 9 months,  $238.95 \pm 34.12$   $\mu\text{m}$  at 12 months (Fig. 2). The mean CFT was decreased significantly over the 12-month period ( $F=65.503$   $P<0.001$ , ANOVA). The CFT decreased significantly during follow-up compared with the baseline values ( $P<0.001$ , ANOVA). There was no statistically significant difference in the mean CFT reduction between the two groups during follow-up ( $P=0.551$  at 1 month;  $P=0.412$  at 3 months;  $P=0.098$  at 6 months;  $P=0.944$  at 9 months;  $P=0.691$  at 12 months,  $t$ -test).

The mean retinal sensitivity in the STMP group was significantly improved during the 12-month period ( $F=5.042$   $P<0.001$ , ANOVA). It was  $12.29 \pm 1.88$  dB at baseline, and improved to  $14.21 \pm 2.19$  dB at 1 months ( $P=0.011$ , ANOVA),  $15.43 \pm 2.16$  dB at 3 months ( $P<0.001$ , ANOVA),  $14.72 \pm 2.57$  dB at 6 months ( $P=0.001$ , ANOVA),  $15.13 \pm 2.23$  dB at 9 months ( $P<0.001$ , ANOVA),  $15.26 \pm 2.22$  dB at 12 months ( $P<0.001$ , ANOVA) (Fig. 3). In the half-dose group, the mean retinal sensitivity was improved during the study period ( $F=6.254$   $P<0.001$ , ANOVA). It was  $12.61 \pm 1.95$  dB at baseline, and improved to  $14.09 \pm 1.80$  dB at 1 months ( $P=0.018$ , ANOVA),  $15.17 \pm 1.97$  dB at 3 months ( $P<0.001$ , ANOVA),  $14.98 \pm 2.09$  dB at 6 months ( $P<0.001$ , ANOVA),  $15.23 \pm 2.15$  dB at 9 months ( $P<0.001$ , ANOVA),  $15.53 \pm 2.01$  dB at 12 months ( $P<0.001$ , ANOVA) (Fig. 3). There was no statistical difference in retinal sensitivity between the two groups ( $P=0.850$  at 1 months;  $P=0.701$  at 3 months;  $P=0.725$  at 6 months;  $P=0.887$  at 9 months;  $P=0.695$  at 12 months,  $t$ -test).

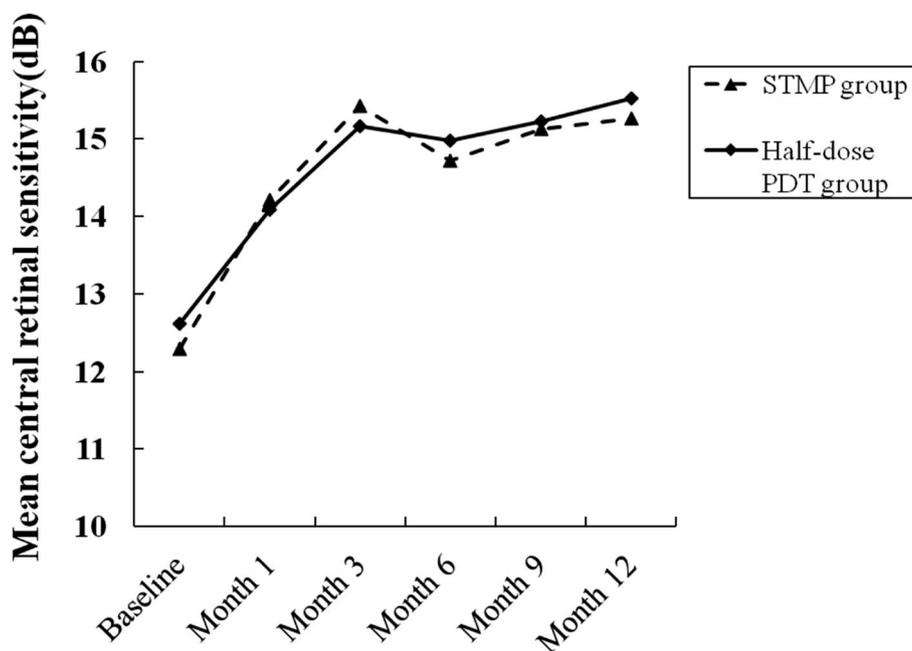


No systemic or ocular side effects associated with treatment were observed in any of the cases during the follow-up period.

**Discussion**

STMP laser is designed to target the RPE cells while minimizing the negative thermal effects on the neural retina and deeper structures [19]. STMP laser treated for

CSC was first reported by Bandello et al. in 2003 (Invest Ophthalmol Vis Sci ARVO E-Abstract, 2003). The mechanisms of action of STMP laser in CSC is not clearly understood. It seems that STMP laser induces the production of intracellular biological factors that stimulate PRE function and speeds up absorption of the SRF which in turn leads to less photoreceptor damage [20]. Although several studies have confirmed the efficacy and safety of



**Fig. 3** Graph showing the serial changes in mean central retinal sensitivity of patients in the STMP group (dashed line) and in the half-dose PDT group (solid line)

half-dose PDT and STMP laser in treating acute CSC [17, 18, 21, 22]. the clinical results compared between the two therapeutic methods have not been reported. In this retrospective study, we evaluate the changes in SRF, CFT, BCVA and central retinal sensitivity of acute CSC after treated by these two modalities respectively. In our study, we found that the anatomic success rates were slightly higher in half-dose PDT group compared with STMP group at 12-month, but there was no statistically significant difference between the two groups. However, at 1 month, the rate of resorption of SRF was significantly higher in half-dose PDT group (81.0%) than in STMP group (61.1%). The better anatomic outcomes after half-dose PDT treatment at short-term may be attributed to the fact that PDT targets the choroidal tissue, in contrast, STMP laser is thought to primarily produce an effect on the RPE. Chan et al. reported that the proportion was 79.5% at 1 month in acute CSC after treated by half-dose PDT [9], there results were consistent with our study. Kross et al. showed that the proportion of eyes with complete resolution of SRF was 37.5% at 6 weeks in CSC after treated by STMP laser [23]. the proportion was significantly lower than our results. We speculate that the different results may be due to the duration of CSC patients in their study was longer than ours. Our study showed that the proportion of eyes with recurrence of SRF was no significant difference in STMP group compared with half-dose PDT group during the 12-month follow-up

period. Three eyes (16.7%) had recurred in STMP group versus 2 eyes (9.5%) in half-dose group, the proportion of recurrence was significantly higher in STMP group than half-dose PDT group. It could be due to the larger extent of PDT taking effect on choroid than STMP laser. In CSC, more extensive choroidal lesions could be exist, not limited to the area of leakage on FA [24]. The proportion of recurrence was higher compared with the results of other studies [9, 15, 18], however, the reason of the difference was unknown. Recurrence of SRF was occurred mainly between the 3-month and 9-month follow-up visits in most of those eyes. Until now, it remains controversial that STMP laser has the benefit of reducing recurrence of CSC. Some researchers demonstrated STMP laser could reduce the recurrence rate of eyes with CSC [16, 18], however, some other researchers deemed that STMP laser could not prevent the recurrence of CSC [25].

In this study, we found the mean BCVA was significantly improved compared with baseline in both groups at 12-month visit, and there were no statistical differences in the increase of letters between the two groups. Similar findings were observed in other studies on acute CSC patients who had received the treatments by half-dose PDT or STMP laser [9, 15, 17, 18]. However, some studies show a better result in visual acuity after half-dose PDT and STMP at the last follow-up compared with our study [15, 17, 18, 21]. It could be due to the worse visual acuity in our study at baseline. In this study, the improvement in

BCVA fluctuated with a little drop at months 6 in STMP group and at months 9 in half-dose PDT group, which was accompanied by a small increase in CFT. It might be the result of recurrence of macular SRF at that time. A significant reduction of mean CFT was observed at each month after treatment in both groups. No significant difference in the mean CFT was found between the two groups. Compared with other studies [26], we found the CFT decreased faster in our patients treated with STMP laser. The reason for difference in speed of CFT recovery was unclear.

Compared with visual acuity, the retinal sensitivity is a more reliable index in evaluation of the function of more extensive macular area, including juxtafoveal and extrafoveal. Kim et al. demonstrated that the mean retinal sensitivity improved significantly after treated by half-dose PDT in acute CSC patients [15]. Fujita et al. performed half-dose PDT in 16 eyes with CSC and found that the mean retinal sensitivities at month 1 and month 3 after treatment had a great improvements compared with pretreatment [27]. Currently, there were few researches reported the changes in retinal sensitivity after treated by STMP laser in patients with acute CSC. Our study showed the mean retinal sensitivity improved significantly at each visit after treatment compared with baseline in both groups, and the retinal sensitivity was slight better in half-PDT group than STMP group at final visit, however, there was no statistical difference between the two groups. We speculated that the slight difference in retinal sensitivity was due to the higher absorption rate of SRF at early time after treatment in half-dose PDT group, which led to less photoreceptor damage.

The limitations of this study include the retrospective and nonrandomized design, the small sample size, a short follow-up period and the lack of an untreated control group for the assessment of the effect of each therapeutic method. Furthermore, some patients of acute CSC have a natural good prognosis, which might have created a bias in terms of anatomical outcomes. A randomized, placebo-controlled, long-term, large sample size clinical trial is necessary to ascertain the efficacy and safety of both STMP laser and half-dose PDT in acute CSC.

In conclusion, STMP laser and half-dose PDT can accelerate the absorption of SRF, improve visual acuity and central retinal sensitivity in patients with acute CSC without causing obvious retinal damage. Our study shows that STMP laser is a low-cost, effective and safe treatment for patients with acute CSC.

#### Acknowledgements

We would like to thank all of the participants involved in this study.

#### Authors' contributions

MZ analyzed the data and wrote the manuscript. XC conceived and designed the study. YPS performed the study and acquired the data. CYC contributed

to manuscript review. The final version of the manuscript has been read and approved by all authors.

#### Funding

No funding was received.

#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Declarations

##### Ethics approval and consent to participate

This study was approved by the ethics committee of Central Theater Command General Hospital and conducted in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all patients.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare that they have no competing interests.

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Received: 2 December 2021 Accepted: 25 February 2022

Published online: 08 March 2022

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