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RETINAL DISORDERS

The effect of nondamaging subthreshold laser therapy in patients with chronic central serous chorioretinopathy

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Abstract

Purpose To evaluate the efficacy of nondamaging subthreshold laser therapy in Korean patients with chronic central serous chorioretinopathy (cCSC).

Methods This retrospective interventional case series included 31 patients (31 eyes) with cCSC who underwent nondamaging laser therapy using Endpoint Management (EpM) software. Since a barely visible burn of the test spot was defined as 100% pulse energy, 30% pulse energy with a 200-μm spot was titrated to treat the macular area based on EpM settings. A 30% pulse laser with a spacing of 0.25-beam diameter was applied to cover the macular area where hyperfluorescent leaks were observed on fluorescein angiography. Changes in central macular thickness (CMT), subretinal fluid (SRF) height, subfoveal choroidal thickness (SCT), and logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA) were measured at baseline and after 3 and 6 months. If the subretinal fluid persisted for 3 months, retreatment was performed.

Results At 6 months post-treatment, the complete SRF resolution rate was 48.39% (15/31 eyes), and the partial SRF resolution rate was 12.90% (4/31 eyes). The change in mean BCVA (logMAR) was not significant (0.31 ± 0.29 at the baseline and 0.31 ± 0.40 at month 6) ($p = 0.943$). At the baseline, the mean CMT (μm) decreased from 350.74 ± 112.76 at baseline to 239.71 ± 130.25 at month 6 ($p < 0.001$), and the mean SRF height (μm) decreased from 193.16 ± 90.69 at baseline to 70.58 ± 100.00 at month 6 ($p < 0.001$). However, the change in SCT was not statistically significant ($p = 0.516$). In 15 patients who were retreated at month 3, the mean SRF height (μm) decreased significantly from 144.67 ± 74.01 at month 3 to 77.13 ± 63.77 at month 6 ($p = 0.002$). No side effects associated with laser therapy were observed during the 6-month follow-up.

Conclusions Nondamaging laser therapy with a modified macular treatment was effective in reducing CMT and SRF and showed favorable visual and anatomical outcomes in patients with cCSC.

Keywords Chronic central serous chorioretinopathy · Nondamaging laser therapy · Subretinal fluid · Subthreshold laser

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Key messages

What is known

- Various laser treatments,including nondamaging laser and subthreshold micropulse laser,have been used for patients with chronic central serous chorioretinopathy.

What is new

- This study demonstrates that nondamaging laser therapy with a modified macular treatment has a favorable effect in reducing subretinal fluid in Asian patientswith chronic central serous chorioretinopathy.
- Since the mean pulse energy of nondamaging laser therapy in our study was different from the values reported previously, a pretreatment procedure for titration is necessary to define the margin of safety.

Introduction

Central serous chorioretinopathy (CSC), which is characterized by the accumulation of idiopathic serous retinal fluid (SRF) at the macula with or without accompanying pigment epithelial detachment (PED), has been reported as the fourth most common non-surgical retinopathy after macular degeneration, diabetic retinopathy, and branch retinal vein occlusion [1, 2]. It is mostly idiopathic and occurs primarily in young or middle-aged men, or during the working age, in which good visual acuity is required [3]. Symptoms due to SRF include metamorphopsia, micropsia, and central scotomas. SRF often resolves spontaneously within 3 months without treatment, and the visual prognosis is good. However, if it persists for 3 or more months, complications including retinal pigment epithelial (RPE) atrophy, cystic macular degeneration, and choroidal neovascularization (CNV) may occur, affecting visual acuity [4]. Moreover, almost one-half of patients with CSC experience a lifetime risk of recurrence, and 5% of patients experience serious visual impairment [5].

Although the pathogenesis of CSC is still not completely understood, previous studies have shown that extensive hyperdynamic and hyperpermeable choroidal circulation and dysfunction of the RPE play a significant role in the development of subretinal fluid (SRF) and PED [6–8]. Moreover, dye leakage at a single or multiple sites in the RPE layer is observed in fundus fluorescein angiography (FFA), and indocyanine green (ICG) angiography shows choroidal hyperpermeability at the site of RPE leakage, especially in chronic cases. In optical coherence tomography (OCT), various anatomical changes, such as SRF or PED, can be observed alone or simultaneously [9–11]. Acute CSC often presents as a single subretinal detachment and resolves spontaneously with a relatively favorable prognosis and minimal visual sequelae. However, chronic cases are associated with poor visual prognosis, since persistent and recurrent SRF progresses to extensive RPE atrophy and photoreceptor damage [12].

Although there is no standard treatment for CSC, several options have been utilized, including conventional laser photocoagulation, photodynamic therapy (PDT), and anti-vascular endothelial growth factor (anti-VEGF) injection. The mechanism of conventional laser photocoagulation is unknown, but it may induce scar formation at the leakage site and block local RPE leakage. However, laser photocoagulation can cause irreversible central scotomas and loss of contrast sensitivity due to photoreceptor damage and CNV [13, 14]. PDT using verteporfin can induce the contraction of exudative choroidal capillaries by lowering vascular permeability and causing temporary hypoperfusion. Although PDT shows good results in terms of structural and visual function, some complications, including RPE atrophy, ischemic changes in choroidal capillaries, and secondary choroidal neovascularization, have been reported [11, 15]. Although anti-VEGF injection has been frequently used for CSC recently, the efficacy of anti-VEGF for chronic CSC (cCSC) is limited. Since frequent recurrences have been observed after anti-VEGF treatment, repeated anti-VEGF injections can increase the risk of ocular inflammation [16, 17].

Unlike conventional laser photocoagulation, which can cause irreversible RPE and photoreceptor damage, a subthreshold micropulse laser can minimize damage to the RPE and surrounding neurosensory retinal tissue from harmful thermal effects using various titration strategies. Recently, a new titration method, the Endpoint Management™ (EpM), for a 577-nm subthreshold laser (PASCAL laser, Topcon Medical Laser Systems, Santa Clara, CA) was introduced [17]. Although the wavelength of the PASCAL laser was also 577 nm, it is a continuous wave laser. By evaluating tissue response in animal models and combining the

mathematical models of thermal damage, the EpM algorithm was developed to optimize therapeutic laser settings for clinical usage [18]. The laser strategy using nondamaging laser therapy (NLT) with EpM was originally suggested to cover both the thickened and non-thickened retina. The use of a 577-nm subthreshold micropulse laser has been reported in several studies [19–22]. In addition, few studies have reported the use of NLT with EpM for cCSC [23, 24]. Although previous studies did not report any complications after NLT, considering that the new titration using EpM has rarely been applied in an Asian population with different RPE pigmentation to date, the modified laser application of the irradiation confined to the thickened retina with hyperfluorescent leakages area was used in this study.

The current study aimed to evaluate the efficacy of NLT using EpM in Asian patients with cCSC.

Methods

The medical records of 31 patients (31 eyes) who underwent NLT with EpM for the treatment of cCSC between November 2019 and January 2021 were retrospectively reviewed. This study adhered to the principles of the Declaration of Helsinki, and data collection was compliant with and approved by the Institutional Review Board of Yeouido St. Mary's Hospital of the Catholic University of Korea (approval number: SC21RISI0066). Written informed consent was obtained from all patients in this study after informing them of the possible risks and benefits of NLT with EpM.

The inclusion criteria were as follows: (1) presence of SRF involving the fovea in OCT images for ≥ 3 months, (2) follow-up performed for ≥ 6 months as documented by clinical examination, and (3) presence of focal or diffuse leakages on FFA caused by CSC and not CNV or other diseases. Eyes with pathologic myopia, age-related macular degeneration, polypoidal choroidal vasculopathy, diabetic macular edema, retinal vascular diseases, epiretinal membrane, tilted disc syndrome, or a history of conventional laser photocoagulation, PDT, local steroid treatment, uveitis, trauma, or intraocular ophthalmic surgery were excluded. In addition, eyes with a history of intravitreal anti-VEGF injection ≤ 3 months prior to NLT were excluded. However, eyes with a history of cataract surgery ≥ 1 year prior to NLT were included.

Multimodal imaging studies, including color fundus photography using a fundus camera (Optos P200TDX, Optos PLC, Dunfermline, Scotland, UK), swept-source OCT (DRI OCT Triton, Topcon, Tokyo, Japan), and fundus autofluorescence (FAF) (Heidelberg Retina Angiograph 2 [HRA2]; Heidelberg Engineering, Heidelberg, Germany), were conducted for all patients after appropriate dilatation at baseline and at 3- and 6-months post-NLT. OCT was used to measure central macular thickness (CMT), SRF height, and subfoveal choroidal thickness (SCT) by macular scan in a 7 × 7 mm area using the macular cube 512 × 256 scan protocol.

FFA (HRA2) or ultra-widefield FFA was used at baseline and on the treatment day for all patients. Visual acuity was estimated using a standard Snellen chart and converted to the logarithm of the minimum angle of resolution (logMAR) at each visit. Partial SRF resolution was defined as a ≥ 50% decrease in the SRF height compared with the SRF height at baseline in the foveal area. Complete SRF resolution was defined as complete resolution of SRF in the macular area. Non-resolution of SRF was defined as an increase or < 50% decrease in the SRF height. Recurrence was defined as recurrence after complete resolution of SRF.

NLT was performed by a single surgeon (YJR). Laser therapy was applied to cover the hyperfluorescent leakage points using a Volk lens (SuperQuad 160, Volk Optical, Inc., Mentor, OH, USA). After ensuring that the 3 × 3 grid pattern test spots were irradiated around the temporal major arcade vessels using EpM, pretreatment FFA for titration was performed to evaluate retinal damage from the laser before irradiating treatment spots. Titration was performed by adjusting the laser power to produce a barely visible lesion (defined as a faintly visible gray-white spot within 3 s after lasering) at a 20-ms pulse duration, which is defined as the nominal (100%) pulse energy level. The pulse energy was set to 100% on the EpM scale. Subsequently, the pulse energy for the treatment spot was reduced to 30% on the EpM scale using the implemented software, as previously described [21, 25]. After ensuring that the NLT lesions were not shown on FFA, 200-μm diameter treatment spots were applied to cover the hyperfluorescent area using 3 × 3 or 2 × 2 patterns with landmarks off, using 0.25 disc diameter spacings between the spots (Fig. 1). According to the EpM protocol provided by the device, the areas of 3 × 3 patterns with nine spots and 2 × 2 patterns with four spots were 0.49 mm^2 and 0.20 mm^2, respectively. If the SRF height at month 3 remained > 50% of the baseline SRF height, retreatment was performed. For the subgroup analysis, the patients were divided into single-NLT and retreatment groups.

The Snellen visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Repeated-measures analysis of variance with Greenhouse–Geisser correction was used to analyze the changes in logMAR best-corrected visual acuity (BCVA), CMT, SRF height, and SCT from baseline to months 3 and 6 after the initial SRT. Post hoc tests using Bonferroni correction were performed to assess changes between the baseline and each follow-up visit. Comparisons between the single-NLT and retreatment groups were performed using Student's t-test for nominal variables (age, symptom duration, baseline BCVA, baseline CMT, baseline SRF height, and baseline

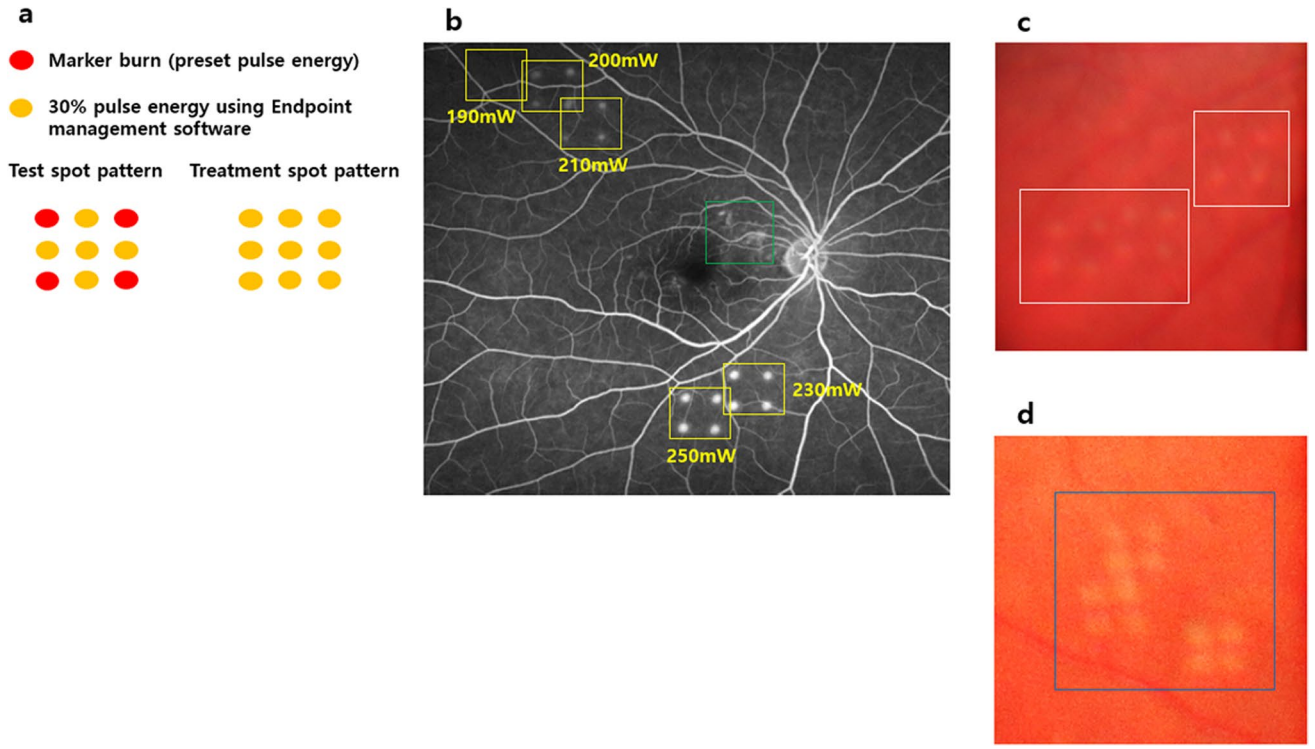

Fig. 1 Nondamaging subthreshold laser therapy (NLT) procedure. **a** 3×3 pattern test spots (yellow rectangular) with 190–250 mW preset pulse energy were irradiated around the major arcade vessels with 0.5 spot spacing. Apart from four marker burns (red dot), five out of nine treatment spots (yellow dot) were subjected to 30% pulse energy, which was set using Endpoint management software. For treatment spot irradiation, all nine spots with 3×3 pattern were set to 30% pulse energy. **b** The number of the 45 test spots (yellow boxes) was shown on fundus fluorescein angiography 1 h after irradiation. Barely visible test spots were observed at marker burns of 200 and 210 mW, while visible test spots were detected at marker burns of 230 and 250 mW. Ninety treatment spots (within green box) were irradiated confluently. However, no visible changes in test and treatment spots were detected at spots of 30% pulse energy during subthreshold laser therapy. **c** Barely visible spots (white boxes) and **d** visible spots (blue box) were observed at marker burns within 3 s after irradiation

SCT) and chi-square test for categorical variables (sex, type of leakage, PED type, and history of anti-VEGF injection). Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) and R Statistical Software v3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

Results

Overall, 31 eyes of 31 patients with cCSC (21 men and 10 women) who underwent NLT with EpM were included in this study. The mean age ± standard deviation was 53.19 ± 8.99 years (range 41–85), and the mean CSC episode before NLT was 2.60 ± 1.09. The mean duration of symptoms was 10.65 ± 3.55 months (Table 1). The mean number of test spots was 16.95 ± 12.11 (range 4–48), and the mean number of treatment spots was 33.29 ± 26.05 (range 16–99). The range of preset pulse energy used for each patient was 150–250 μJ (mean preset pulse energy: 173.39 ± 19.20). The complete SRF resolution rate increased from 25.81% (8/31 eyes) at month 3 to 48.39% (15/31 eyes) at month 6. The SRF non-resolution rate decreased from 48.39% (15/31 eyes) at month 3 to 38.71% (12/31 eyes) at month 6 (Fig. 2). The mean number of NLT sessions was 1.71 ± 0.86, and retreatment was performed in 15 patients. In the retreatment group, the range of preset pulse energy was 150–250 μJ (mean preset pulse energy: 185.0 ± 12.68), and the mean number of treatment spots was 34.06 ± 18.14 (range 16–63). The mean BCVA (logMAR) of 31 eyes did not change significantly from 0.31 ± 0.29 at baseline to 0.31 ± 0.40 logMAR at month 6 ($p = 0.943$). The mean CMT decreased from 350.74 ± 112.76 μm at baseline to 239.71 ± 130.25 μm at month 6 ($p < 0.001$). The mean SRF height decreased from 193.16 ± 90.69 μm at baseline to 70.58 ± 100.00 μm at month 6 ($p < 0.001$). Significant differences were observed in the mean SRF heights between baseline and month 3 ($p = 0.001$) and months 3 and 6 ($p = 0.007$). The change in mean SCT was not significant from 385.48 ± 65.48 μm at baseline to 381.16 ± 65.86 μm at month 6 ($p = 0.516$) (Table 2). Visible changes in the treatment spot in the macula were not observed during 6-month follow-up.

Table 1 Baseline demographics and clinical findings of all patients with chronic central serous chorioretinopathy (cCSC) who were treated with nondamaging laser therapy

Patients' characteristics	Values
Number of patients (eyes)	31 (31)
Age, years, mean ± SD (range)	53.19 ± 8.99
Gender (Male/Female)	21/10
Eye (OD/OS)	14/17
Number of patients who received IVB injection, *n* (%)	23 (74.19)
Number of previous CSC episode, mean ± SD	2.60 ± 1.09
Type of leakages	
Focal, *n* (%)	21 (67.74)
Diffuse, *n* (%)	10 (32.26)
Presence of PED	
no PED or RPE bumps, *n* (%)	13 (41.94)
PED (dome, flat irregular), *n* (%)	18 (58.06)
Baseline BCVA (LogMAR), mean ± SD (range)	0.31 ± 0.29
Baseline CMT, μm, mean ± SD (range)	350.74 ± 112.76
Baseline SRF height, μm, mean ± SD (range)	193.16 ± 90.69
Symptom duration in months, mean ± SD	10.65 ± 3.55
Follow-up duration in months, mean ± SD	8.77 ± 4.95

SD standard deviation, *IVB* intravitreal bevacizumab, *PED* pigment epithelial detachment, *RPE* retinal pigment epithelium, *BCVA* best-corrected visual acuity, *LogMAR* logarithm of the minimum angle of resolution, *CMT* central macular thickness, *SRF* subretinal fluid

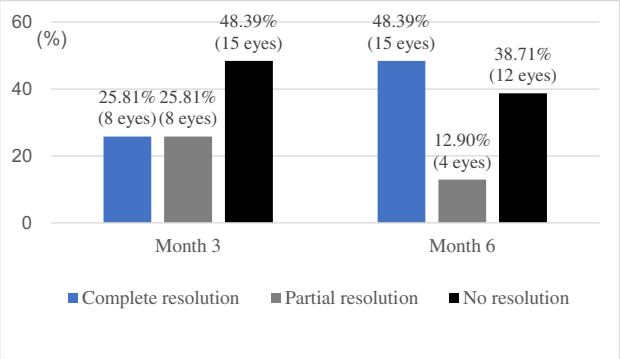

Fig. 2 The percentage of subretinal fluid height resolution in 31 eyes of 31 chronic central serous chorioretinopathy patients at months 3 and 6 after nondamaging laser therapy

Subgroup analysis

A comparison of the baseline characteristics between the complete SRF resolution and remnant SRF groups is shown in Table 3. Fifteen eyes with SRF non-resolution were retreated with NLT at month 3. In the single-NLT-treated group (16 eyes), the change in mean CMT and SRF height between months 3 and 6 was not significant ($p = 0.248$ and $p = 0.141$, respectively) (Fig. 3). In the retreatment group, although the reduction in mean CMT from 280.40 ± 69.43 μm at month 3 to 243.00 ± 71.87 μm at month 6 was not significant ($p = 0.131$), the mean SRF height decreased significantly from 144.67 ± 74.01 μm at month 3 to 77.13 ± 63.77 μm ($p = 0.008$) (Table 4). In the single-NLT group, an additional three eyes with partial resolution at month 3 showed complete resolution at month 6. In the retreatment group, four eyes showed complete SRF resolution (Fig. 4). No recurrence was observed during the 6-month follow-up. In the multiple logistic regression analysis, the presence of PED resulted in a 2.78 odds ratio, but the difference was not statistically significant ($p = 0.208$). No other predictive factors influenced the initial response to NLT (Table 5).

Discussion

To our knowledge, this is the first study to evaluate the efficacy of NLT with EpM in Asian patients with cCSC. Our results showed that NLT using EpM was effective in reducing CMT and SRF heights in patients with cCSC. Retreatment was also helpful for additional SRF reductions.

Since conventional laser photocoagulation is limited for treating macular areas because of potential complications, including central scotoma, secondary choroidal neovascularization, and retinal hemorrhages, nondamaging 577-nm subthreshold micropulse laser (SML) has been investigated in several clinical studies. Yadav et al. [25] reported that 40% of 13 patients with CSC (15 eyes) showed complete resolution at 2 months after 577-nm yellow SML. Gawecki et al. [26] reported a complete SRF resolution rate of 70.6% in 51 patients with cCSC 2 months after SML. Scholz et al. [22] reported a complete resolution rate of 61% with SML in patients with cCSC who were not responsive to PDT. In the PLACE trial, the efficacy and safety of half-dose PDT and high-density SML with a wavelength of 810 nm for cCSC were compared. The results demonstrated that 67.2% of PDT-treated and 28.8% of SML-treated patients showed complete SRF resolution at 8 months [27]. Since different laser parameters, including wavelength, pulse power, and titration methods, are used in SML, the outcomes are different from those of NLT. In the PLACE trial, when a 5% duty cycle was used, the reduction in the laser power was titrated based on visible retinal discoloration in the test spots. In contrast to SML, NLT titration was performed using the implemented EpM software. Considering that NLT is a continuous wave laser and clinical reports with NLT are few, potential adverse events can be expected due to different retinal tissue responses to NLT due to ethnic variance in the fundus pigmentation of Asian patients. Therefore, in

Table 2 Best-corrected visual acuity, central macular thickness, subretinal fluid height, and submacular choroidal thickness change during follow-up of 31 patients with chronic central serous chorioretinopathy treated by nondamaging laser therapy

	Baseline	Month 3	Month 6	*p*-value *	*p*-value **	*p*-value ***
Best-corrected visual acuity, LogMAR, mean ± SD	0.31 ± 0.29	0.31 ± 0.29	0.31 ± 0.40	0.943	0.975	0.946
Central macular thickness, µm, mean ± SD	350.74 ± 112.76	262.32 ± 129.75	239.71 ± 130.25	< 0.001	< 0.001	0.068
Subretinal fluid height, µm, mean ± SD	193.16 ± 90.69	117.32 ± 106.67	70.85 ± 100.00	< 0.001	0.001	0.004
Submacular choroidal thickness, µm, mean ± SD	385.48 ± 65.48	383.65 ± 64.10	381.16 ± 65.86	0.516	0.731	0.526

SD standard deviation, *LogMAR* logarithm of the minimum angle of resolution

*, comparison between baseline and month 6;

**, comparison between baseline and month 3;

***, comparison between month 3 and 6; post hoc test using Bonferroni correction

Table 3 Comparison of baseline characteristics between the single-NLT and retreatment groups

Patients' characteristics	Single-NLT group	Retreatment group	*p*-value
Number of eyes	16	15	
Age, years, mean ± SD (range)	53.44 ± 7.36	52.93 ± 10.72	0.879
Gender, *n* (%)	Male 12 (75%) / Female 4 (25%)	Male 9 (60%) / Female 6 (40%)	0.389
Symptom duration in months, mean ± SD	10.69 ± 3.26	10.6 ± 3.94	0.947
Previous treatments Patients who received intravitreal bevacizumab injection, *n* (%)	12 (75%)	11 (73.3%)	0.919
Type of leakages			0.535
Focal, *n* (%)	10 (62.5%)	11 (73.3%)	
Diffuse, *n* (%)	6 (37.5%)	4 (26.7%)	
Presence of PED			0.224
no PED or RPE bumps, *n* (%)	10 (62.5%)	6 (40%)	
PED (dome, flat irregular), *n* (%)	6 (37.5%)	9 (60%)	
Baseline BCVA (LogMAR), mean ± SD	0.32 ± 0.26	0.29 ± 0.33	0.737
Baseline CMT, µm, mean ± SD	349.69 ± 124.08	351.87 ± 103.68	0.958
Baseline SRF height, µm, mean ± SD	190.75 ± 92.53	195.73 ± 91.86	0.882
Baseline SCT, µm, mean ± SD	386.63 ± 84.78	384.27 ± 38.52	0.922

NLT non-damaging laser therapy, *SD* standard deviation, *IVB* intravitreal bevacizumab, *PED* pigment epithelial detachment, *RPE* retinal pigment epithelium, *BCVA* best-corrected visual acuity, *LogMAR* logarithm of the minimum angle of resolution, *CMT* central macular thickness, *SRF* subretinal fluid

addition to observing the visible change in the test spots, FFA was used to confirm the extent of retinal tissue damage before irradiating the treatment spots in this study. No NLT-related adverse events were observed during the 6-month follow-up.

In a previous study using NLT with EpM for cCSC, Lavinsky et al. [18] reported that SRF in 21 eyes resolved completely in 81% of eyes 12 months after NLT. Although the rate (48.4%) of complete SRF resolution in the present study was lower than in the previous study, the reduction (111 µm) in mean CMT from 350.74 ± 112.76 µm to 239.71 ± 130.25 µm in this study was higher than the reduction (79 µm) in CMT in the study by Lavinsky et al. (406,362 ± 13,611 µm to 297,283 ± 789 µm). While the gain in visual acuity was 12.5 ± 4 ETDRS letters in the previous study, there was no improvement in BCVA in the current study. In addition to the different baseline characteristics of the enrolled patients, the cause of the dissimilar results could be explained by different treatment methods and laser powers. Although the same titration method using EpM was applied in the current study, in the report by Lavinsky, a standardized macular grid pattern consisting of 400 spots in total that covered the macular area with an outer diameter of 3000 µm and an inner diameter of 500 µm, which allowed for sparing of the fovea, was used. Since a modified treatment pattern that covers the hyperfluorescent area was applied in the current study, the mean of treatment spots in our study was lower (33.3 spots vs. 400 spots), and the mean titrated treatment power was higher (173.4 ± 19.2 mW vs 126 ± 14 mW) than that of Lavinsky et al. The therapeutic range of

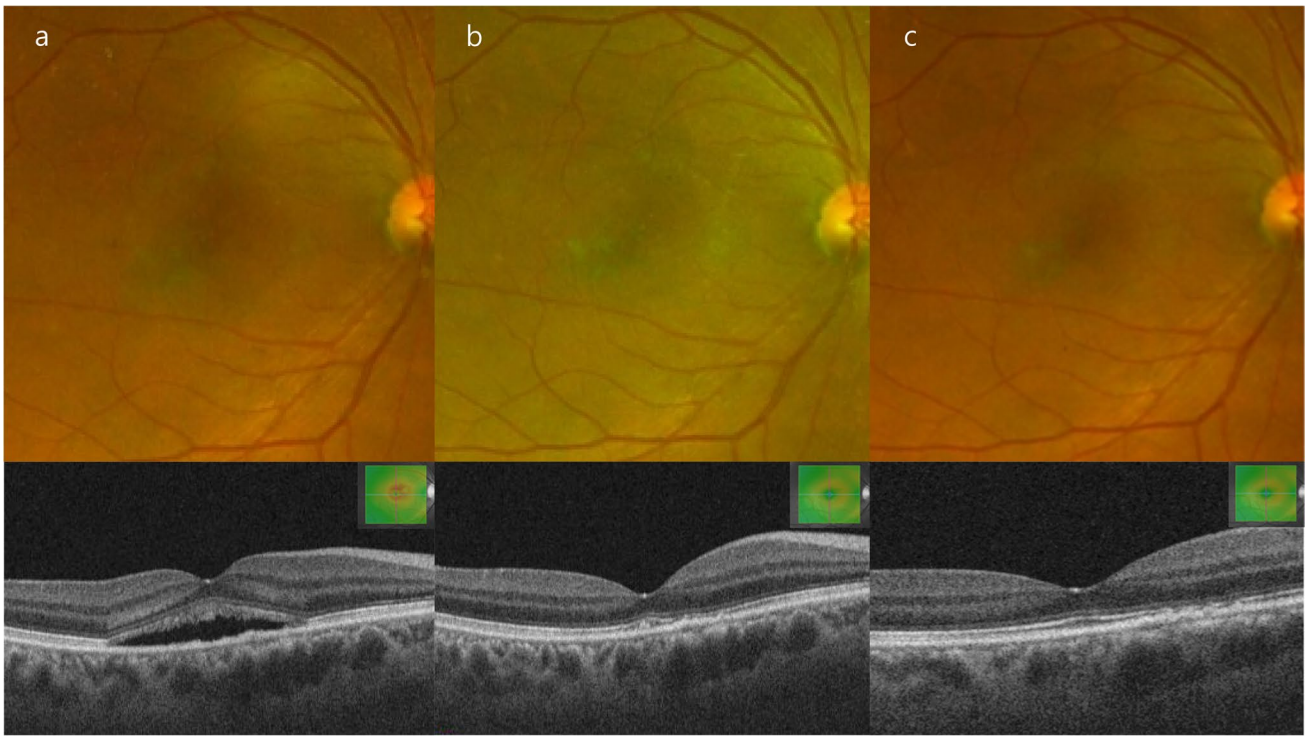

Fig. 3 Case 15. A 44-year-old man who presented with a 4-month history of subretinal fluid (SRF) in the right eye. **a** SRF was observed on optical coherence tomography at initial presentation. At months 3 (**b**) and 6 (**c**) after nondamaging subthreshold laser therapy, SRF was completely resolved

Table 4 Comparison of main outcomes between the single-NLT and retreatment groups based on initial nondamaging laser therapy

Single-NLT group (N = 16)	Baseline	Month 3	Month 6	*p*-value *	*p*-value **	*p*-value ***
Best-corrected visual acuity, LogMAR, mean ± SD	0.32 ± 0.26	0.31 ± 0.25	0.30 ± 0.30	0.547	0.758	0.534
Central macular thickness, µm, mean ± SD	349.69 ± 124.08	245.38 ± 168.93	236.63 ± 170.55	0.007	0.007	0.248
Subretinal fluid height, µm, mean ± SD	190.75 ± 92.53	77.50 ± 123.78	64.44 ± 126.97	0.003	0.003	0.141
Submacular choroidal thickness, µm, mean ± SD	386.63 ± 84.75	387.06 ± 79.77	384.00 ± 75.65	0.757	0.951	0.551
Retreatment group (N = 15)	Baseline	Month 3	Month 6	*p*-value *	*p*-value **	*p*-value ***
Best-corrected visual acuity, LogMAR, mean ± SD	0.29 ± 0.33	0.30 ± 0.33	0.32 ± 0.49	0.609	0.688	0.714
Central macular thickness, µm, mean ± SD	351.87 ± 103.68	280.40 ± 69.43	243.00 ± 71.87	0.002	0.032	0.131
Subretinal fluid height, µm, mean ± SD	195.73 ± 91.86	144.67 ± 74.01	77.13 ± 63.77	< 0.001	0.148	0.008
Submacular choroidal thickness, µm, mean ± SD	384.27 ± 38.52	380.00 ± 44.27	378.13 ± 56.10	0.571	0.615	0.765

NLT non-damaging laser therapy, *SD* standard deviation, *LogMAR* logarithm of the minimum angle of resolution;

*, comparison between baseline and month 6;

**, comparison between baseline and month 3;

***, comparison between months 3 and 6; post hoc test using Bonferroni correction

the 577-nm micropulse laser starts from the reset power (160 mW) to the death power (450 mW), as previously reported [28]. Since pulse duration differs between the continuous wave (20 ms) and the 577-nm micropulse laser (duty cycle 5%), the therapeutic range of power for the 577-nm micropulse laser cannot be directly applied to the 577-nm continuous laser. Unlike in the 577-nm micropulse laser, the preset laser power and the actually applied power differ in the 577-nm continuous laser with EpM. Considering that the preset energy (range: 150–250 mW) was reduced to 30% on the EpM scale in our study, the mean actually applied power was approximately 52 mW (range: 45–75 mW). Therefore, the actual therapeutic power of the 577-nm continuous laser was lower than 577-nm. Since we selected the treatment power just below the angiographic threshold after pretreatment FFA, the actually applied power seems close to the

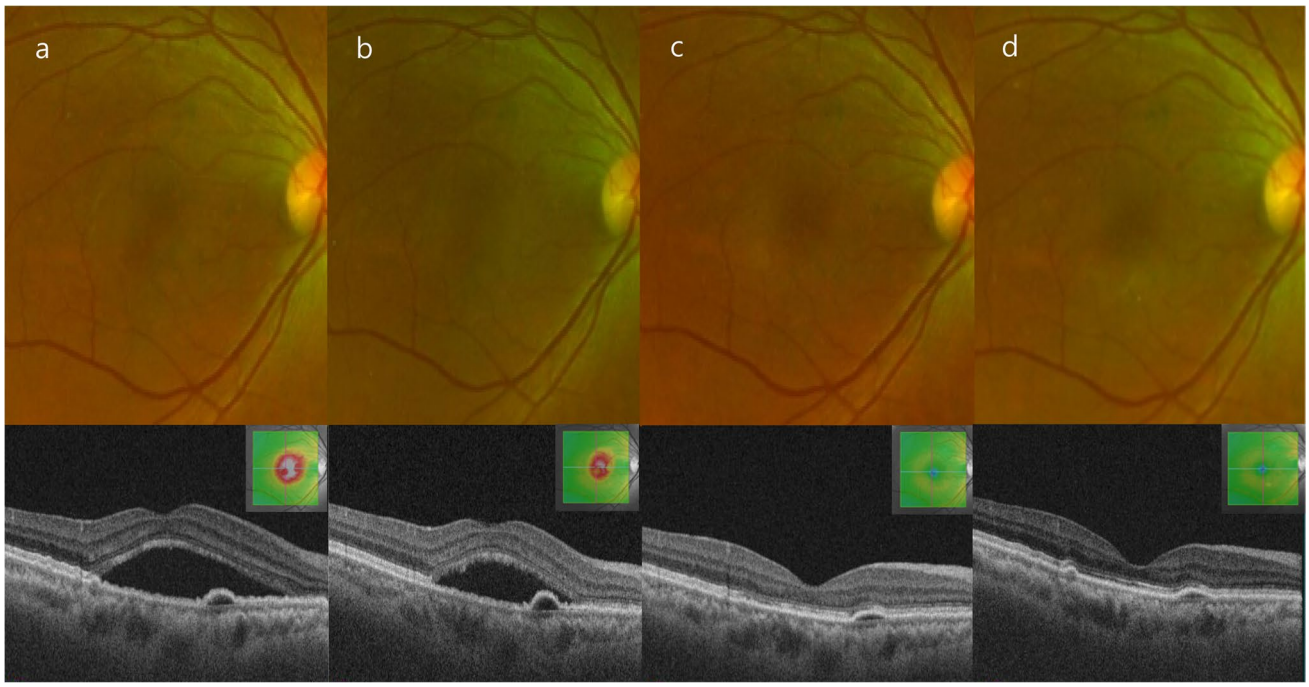

Fig. 4 Case 29. A 59-year-old woman who presented with a 9-month history of subretinal fluid (SRF) in the right eye. **a** SRF with pigment epithelial detachment was observed on optical coherence tomography (OCT) at initial presentation. **b** At month 3 after initial nondamaging subthreshold laser therapy (NLT), remnant SRF persisted, and a second NLT was performed. Complete SRF resolution was revealed on OCT 3 months (**c**) and 6 months (**d**) after the second NLT

Table 5 Multiple logistic regression analysis of factors associated with the need for NLT retreatment in patients with chronic central serous chorioretinopathy

Patients' characteristics	OR	95% CI	*p*-value
Age	1.03	0.934–1.136	0.551
Gender	0.317	0.035–2.900	0.309
Symptom duration	0.914	0.713–1.172	0.478
Previous history of IVB	0.917	0.142–5.896	0.927
Type of leakages	0.915	0.109–7.657	0.935
Presence of PED	2.777	0.566–13.614	0.208
Baseline BCVA	1.50	0.034–67.032	0.834
Baseline SRF height	0.994	0.970–1.018	0.625
Baseline CMT	1.004	0.986–1.021	0.671
Baseline SCT	0.998	0.986–1.011	0.796

NLT non-damaging laser therapy, *OR* odds ratio, *CI* confidence interval, *IVB* intravitreal bevacizumab, *PED* pigment epithelial detachment, *BCVA* best-corrected visual acuity, *SRF* subretinal fluid, *CMT* central macular thickness, *SCT* submacular choroidal thickness

death power. Based on the EpM protocol, laser power can be set after observing the visible changes of marker burns. Although the therapeutic range of the preset power was broad in this study (150–250 mW), the death power would just be above the therapeutic range. Therefore, our results suggest the need for careful observation of the discoloration of laser spots even when the preset laser power using NRT with EpM is within the therapeutic range for Asian patients.

In a previous study, the number of treatments per eye ranged from 1 to 4 depending on the response to the laser during the 12-month follow-up. Considering that the mean treatment during the 6-month follow-up period was lower (1.71 vs 2.2 per eye) in this study compared to the report of Lavinsky et al., a lower number of retreatments and mean treatment spots might negatively affect our clinical outcomes.

Similar to the complete SRF resolution rate (48.39%) in our study, Schworm et al. [24]. demonstrated that 42.9% (18 of 42) of eyes showed complete resolution by 6 months. Since the complete resolution increased to 53.8% of eyes by 12 months after repeated treatments (from one to four sessions) in the previous report, we deduced that our clinical outcomes could also be improved depending on the number of treatments. As the beneficial effect of NLT is associated with the upregulation of heat shock protein (HSP) [12], a wider standardized treatment with a circular pattern could be effective in inducing the increased expression of HSP. HSP is known to have anti-apoptotic functions through intracellular pathways and participates in protein homeostasis, all of which lead to the improved pumping capacity of RPE [18]. Furthermore, the similar complete resolution rates support the idea that the modified treatment covering the fovea could be an alternative treatment option if the appropriate titration was sufficient to ensure safety in Asian patients with ethical differences in fundus pigmentation.

Subgroup analysis was performed to evaluate the predictive factors influencing the initial response to NLT. Although there were no statistically significant predictive factors influencing the initial response to NLT, the presence of PED tended to negatively influence the resolution of SRF in this study.

Based on the imaging features of thickened choroid and abnormally dilated Haller layer vessels in patients with CSC [29], CSC has been regarded as a pachychoroid disease spectrum. The treatment targets focused on choroidal changes. Although PDT induced a reduction in choroidal thickness in a previous report [30], choroidal changes after NLT have not yet been confirmed. While Lavinsky et al. [18] reported a reduction (56 μm) in mean SCT, Schworm et al. [24] demonstrated a lower reduction (19 μm) in SCT. In this study, the reduction (4.3 μm) in mean SCT was not statistically significant ($p = 0.516$). As the effect of NLT seems to be confined to the RPE layer because RPE cells are solely influenced by non-lethal thermal stress, subtle changes in the choroid after NLT suggest that the therapeutic mechanism of NLT is mostly related to the RPE layer rather than the choroid.

Nevertheless, our study has several limitations, including the retrospective and non-randomized study design, short-term follow-up period, and small number of patients. In addition, 74% of the patients were not treatment-naïve, as they had a history of intravitreal bevacizumab injection for ≥ 3 months prior to NLT. However, the previous bevacizumab treatment may not have affected our clinical outcomes, given the pharmacokinetics of bevacizumab. Moreover, among the predictive factors influencing the initial response to laser therapy between the single-laser and retreatment groups, prior history of anti-VEGF injections showed no statistically significant difference ($p = 0.919$). Despite the limitations, we demonstrated for the first time that NLT with modified irradiation could be effective in resolving SRF in cCSC.

In conclusion, NLT with a modified macular treatment showed a favorable effect in reducing SRF in patients with cCSC during the 6-month follow-up. Although NLT with EpM did not produce any adverse events, a pretreatment titration procedure for obtaining an appropriate pulse power is still mandatory, especially for Asian patients with variable fundus pigmentation. Moreover, further randomized studies are necessary to confirm the efficacy and safety of NLT with EpM for cCSC.

Author contribution Conceived and designed the study: Young-Jung Roh; Performed the treatment: Young-Jung Roh; Analyzed the data: Seung Hoon Lee, Jiyoung Lee, Minhee Kim, Young-Jung Roh; Wrote the paper: Seung Hoon Lee, Young-Jung Roh; Approved final version of the manuscript: Seung Hoon Lee, Jiyoung Lee, Minhee Kim, Young-Jung Roh.

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Declarations

Ethics approval This study was approved by the Institutional Review Board of Yeouido St. Mary's Hospital of the Catholic University of Korea (approval number: SC21RISI0066) and adhered to the declarations of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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